Special Collection

Science's Response to CoVID-19

Marcus J. C. Long[b] and Yimon Aye*[a]

CoVID-19 is a multi-symptomatic disease which has made a global impact due to its ability to spread rapidly, and its relatively high mortality rate. Beyond the heroic efforts to develop vaccines, which we do not discuss herein, the response of scientists and clinicians to this complex problem has reflected the need to detect CoVID-19 rapidly, to diagnose patients likely to show adverse symptoms, and to treat severe and critical CoVID-19. Here we aim to encapsulate these varied and sometimes conflicting approaches and the resulting data in terms of chemistry and biology. In the process we highlight emerging concepts, and potential future applications that may arise out of this immense effort.

Introduction

Between the dawn of the new millennium and today, several viral diseases have emerged due to zoonotic processes. Such events occur when a virus that infects an animal becomes able to infect humans. Until recently, the most well-known of these diseases were: Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV; arrived in the Middle East circa 2012), with a mortality of ~35%; and Sudden Acute Respiratory Syndrome coronavirus (SARS-CoV; arrived circa 2002 from Guangdong, China), which had a mortality of ~15%.[1] Such mortality data are a function of ability to precisely assign the number of people infected and those that died from the disease, both of which can be underestimated. The number infected is often a severe underestimate: e.g., during the CoVID-19 pandemic, 10-times more people were infected than the number of people formally declared as suffers in the USA.[2] Thus, these and similar mortalities are approximations, and often overestimates. Nevertheless, in the case of MERS-CoV, mortality lies close to that of the bubonic plague.[3] Other milder diseases, such as HCoV-229E, likely arose via a similar route. More intriguingly, all these events have actually been linked, to some extent, to coronaviruses (CoVs; principally the β- and α-variants) endemic to bats.

Indeed, bats may be a common link to all zoonotic CoV events.[4] In the case of MERS-CoV and SARS-CoV, these diseases have been principally ascribed to β-CoVs from horseshoe bats, of the genus *Rhinolophus*. This group of sedentary bats (i.e., bats that do not stray far from their roosts)[5] is widely distributed across temperate and tropical areas, including China, and other parts of Eurasia all the way to Africa. As a result of MERS- and SARS-CoVs, zoonosis from bats was perceived as a clear and present threat to global health in the early years of the new millennium.[6] Further stoking these worries, our understanding of CoVs endemic in bats was, and remains, overall poor. Thousands of endemic CoVs are hitherto unknown. Thus, several initiatives were established to understand and map CoVs in bats since 2000. These efforts were enacted most extensively in bats in China,[7] but also in other groups of bats in Asia[8] and Africa.[9] This research unearthed numerous new CoVs,[10] several of which appear to be pathogenic to humans. Despite remonstrations, many of these initiatives were either halted or coming to an end as of 2019.

In December 2019, almost a year to the day of writing this piece, a new respiratory virus surfaced in Wuhan, the capital city of Hubei province, China. This virus can spread between humans and is also believed to have derived from transfer from β-CoVs in horseshoe bats,[11] although the precise route is disputed. Estimates have varied, but the currently quoted mortality of this virus, that came to be known as SARS-CoV-2, causing a disease/pandemic referred to as CoVID-19, is ~0.5–2%.[12] CoVID-19's mortality is significantly less than MERS-CoV and SARS-CoV; nonetheless, the mortality of CoVID-19 is significantly higher than common flu, and at the low end of estimates of the mortality of the Spanish flu of 1918, which killed ~50 million people worldwide[13] (equivalent to quadruple that number in today's figures).[14] SARS-CoV-2 shows a reproductivity (R) number ~3,[15] although estimates vary considerably[16] and interpretation of R needs careful consideration. Indeed, R values vary as a function of method and circumstances:[17] e.g., some methods show that the R value of CoVID-19 aboard the Diamond Princess cruise ship was ~15. Nevertheless, the average R value for CoVID-19 is significantly higher than MERS-CoV[18] (R 0.9, for most estimates[19]) but is quite similar[20] to that of SARS-CoV.[21] Critically, SARS-CoV is spread most effectively when patients are manifesting symptoms,[22] which made management/containment of SARS-CoV relatively simple. By contrast, CoVID-19-infected people are infectious prior to onset of symptoms.[23] Most studies agree that asymptomatic CoVID-19 patients (1 in 5 of those infected)[24] can spread the disease.[25] However, estimates vary as to the importance of spreading by totally asymptomatic people.[26]

Although this is not uncommon for viral infections,[27] CoVID-19 presents an astounding number of pathologies, with growing evidence that there are specific phenotypes associated

[a] *Prof. Y. Aye*
Swiss Federal Institute of Technology in Lausanne (EPFL)
1015 Lausanne (Switzerland)
E-mail: yimon.aye@epfl.ch
[b] *Dr. M. J. C. Long*
University of Lausanne
1015 Lausanne (Switzerland)

Special Collection *This article belongs to the Early-Career Special Collection, "EuroMedChem Talents".*

with severity[28] and timing post infection/progression (Figure 1). Many symptoms are related to respiratory issues and lung damage.[29] Consistent with these observations, viral proteins bind host proteins abundant in the lungs. Many other reported CoVID-19-associated pathologies are associated with the immune response and blood clotting: cytokine storms leading to hyperinflammation (elevated inflammatory markers including ferritin, interleukins 1 and 6, and C-reactive protein have been reported);[30] oxidative stress, potentially leading to ferroptosis in several tissues;[31] changes[32] in immune cells;[33] thrombic microangiopathy (blood clots forming in capillaries and arterioles);[34] and a host of other issues, including neurological problems.[35] Immune evasion is one of the hallmarks separating CoVID-19 from SARS-CoV, although how these observations link to the clinical outcomes is unclear. Intriguingly, reports of self-harm in infected patients, due to, e.g., consumption of ethanol-based hand cleaners have also surfaced. This has also been met with a general increase in calls to poison control centers concerning ingestion of household cleaners.[36]

After early reports from China, the Western world watched as daily news updates surfaced of the escalating troubles that began to permeate from the epicenter of this crisis to other parts of China and later reverberate to the rest of the world. This spread was doubtless fanned by the frequency of global travel, and the season during which these events occurred, among other variables. Due to an unprecedented response, China started to flatten the progression of the disease in the proceeding months. Huge hospitals were built in days; whole cities were locked down; mandatory quarantine was introduced;[37] and interaction between people/towns/cities was minimized. However, it would not be until April of 2020 that Wuhan would be lifted from lockdown.[38] By February 2020, the first CoVID-19-related death was recorded in Europe. Shockingly, despite advanced warning, by March, hospitals in many Western countries were overrun, leading to mass shutdowns of government and businesses as well as border closures. By June 2020, almost half of the global population had experienced quarantine/confinement of some description,[39] including in India,[40] and Africa.[41] However, the global response was overall quite varied.[42] Over the summer of 2020, many countries that had instigated lockdown measures reopened and a semblance of normality returned in much of the Western world, at least. However, this hiatus was in turn met with an autumn and winter in which the number of cases spiked again, spurring "new waves" of CoVID-19. More recently and into 2021, new strains of the virus have been identified which are more infectious than the original strain(s), including the UK strain,[43] and the South African strain.[44] These have started to dominate in some populations. Thus, blanket lockdown procedures and curfews have been reinstated in numerous countries. Intriguingly, in China, and even Wuhan, SARS-CoV-2 was almost totally under control by September 2020. This reflects differences in the ways governments dealt with the crisis,[45] but likely also cultural differences in the ways governments and citizens interact.[46]

All the above responses were taken from a playbook dating at least as far back as the 12th–16th centuries.[47] Indeed, the word quarantine derives from "quaranta" referring to the 40 day isolation imposed on outsiders wishing to enter European cities during the plague around that period.[48] Bolstering this tried-and-tested response, were novel technological approaches that reflect a modern intervention to a disease presenting myriad symptoms and with an unnerving ability to spread. These approaches constitute two different aspects: (i) initiatives aimed at diagnosing infected people, which required rapid, reliable and innovative testing initiatives and

Marcus J. C. Long was born in Yorkshire, UK. He was a chemistry scholar at Oxford University, and performed his PhD thesis research at Brandeis University, USA. He subsequently performed postdoctoral research in the Aye research group.

Born and raised in Burma, Yimon Aye read chemistry at the University of Oxford (UK) (2000-04), and achieved her PhD degree in organic chemistry with Prof. David Evans at Harvard University (USA) (2004–09). She then switched research discipline and pursued her postdoctoral training in life sciences with Prof. JoAnne Stubbe. As a Damon Runyon cancer research fellow at MIT (USA) (2009–12), she established the mechanisms-of-action of therapeutics targeting the enzyme ribonucleotide reductase. In her independent career that began mid-2012, Yimon Aye set out to understand the detailed mechanisms of electrophile signaling. This impetus culminated in the development of "REX" technologies (T-REX™ delivery and G-REX™ profiling). In a parallel research program, she studies pathways involved in genome maintenance and nucleotide signaling, including the mechanisms of anticancer drugs in clinical use. In Autumn 2018, she and her team members established the Laboratory of Electrophiles and Genome Operation (LEAGO) at EPFL https://leago.epfl.ch/

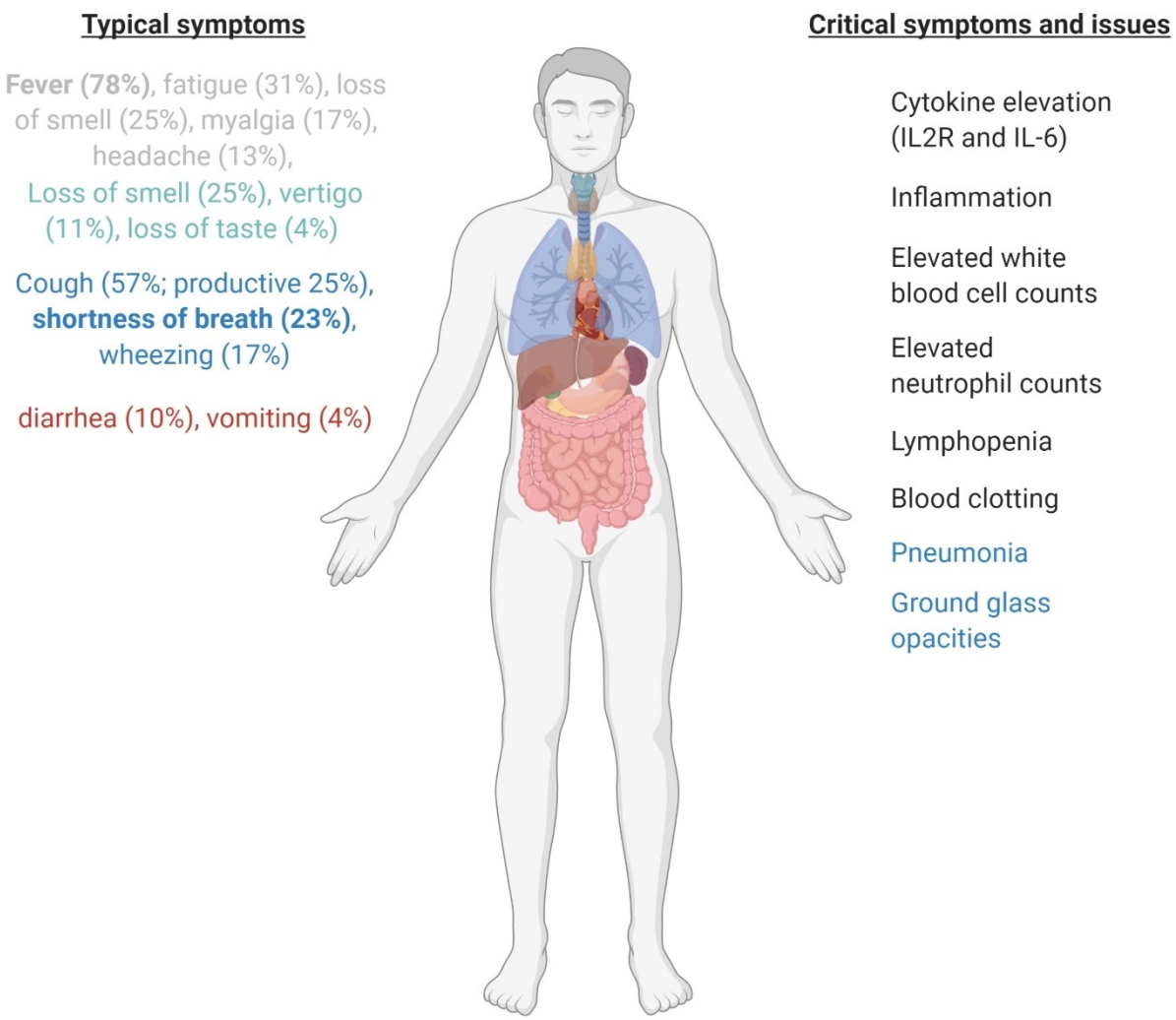

Figure 1. Some of the most common symptoms of CoVID-19, grouped by typical, i.e. less severe (on left) and critical (on right). For typical symptoms parenthesis indicates percentages in one reported study of >24000 people;[368] bolding indicates that these are associated with more severe CoVID-19, if symptoms are particularly severe. Severe symptoms[369] taken from several sources.[370]

protocols to be developed that could be field (and even "home") ready; (ii) continuations of huge chemical and biological counteroffensive that was launched to identify and exploit weak points in SARS-CoV-2. Arguably, this two-pronged response represents a focused and coordinated effort across a huge number of disciplines, perhaps rivaling the war on cancer and the space program. The current apogee of this drive is the record-breaking approval of several SARS-CoV-2 vaccines, including those from Pfizer and Moderna that were approved for use in the USA before 2021. Work toward vaccine development was backed up by doctors globally developing new treatment regimens in real-time, investigations of new medications, and basic science approaches aimed at identifying chemical weak points in the virus' armor and in the patients' themselves. Many reviews have covered in depth deployment and development of advanced technical paraphernalia. However, it is crucial to note that one of the largest divergences between the response to the plague in the 12th–16th centuries and SARS-CoV-2 today is that the latter leveraged global communications that allowed the passage of data, personnel, and equipment to guide and coordinate responses. In the wake of CoVID-19, maintaining,[49] and honing this network will be crucial.[50] Of course, the human, economic, and social impact of this epidemic cannot be understated. More than 2 million people have died; falls in GDP, e.g., in the UK, have been the highest since records were maintained; numerous patients with non-CoVID-19-related diseases have suffered,[51] either indirectly and/or due to be sensitized to the disease;[52] and the mental and physical health of the population will have been impacted for years to come.[53]

Our review specifically focuses on knowledge and ideas that arose out of the two forementioned scientific responses to the disease, and how that knowledge-base can be deployed for our future benefit. We discuss some take home lessons that the community could draw from this difficult period, and suggest some improvements. Likely both the issues raised and their remedies we discuss will require refining through individual reflection and also debate. Finally, although our review

encompasses most of the key emerging concepts, the rapidity of changes in treatments, screens, etc., effectively prohibits being able to include all relevant work; we thus apologize to everyone whose work is not covered by this piece.

A brief guided tour of SARS-CoV-2

A brief outline of what the virus is and how it enters the cell is clearly important for understanding and treating the disease. Much of this information is derived from analogy to previous CoV's, but also through the use of innovative work based around reverse genetics,[54] viral genome sequencing strategies,[55] as well as multi-omics.[56] We will also refer to many of these aspects in subsequent sections. SARS-CoV2 contains a 30 kbp RNA genome (Figure 2A). This is very large by virus standards.[57] SARS-CoV2's genome has high (>87%) identity with three SARS-like bat viruses BatCoV-RaTG13, Bat-SL-CoV-ZC45 and Bat-SL-CoV-ZXC21.[58] It also has ~80% pairwise identity to SARS-CoV[59] and 50% identity to MERS-CoV (Figure 2B).[60] The amino acid sequence of the largest ORF, ORF1ab, in SARS-CoV and SARS-CoV-2 are ~95% identical, indicating that these viruses belong to the same species. The SARS-CoV-2 genome is unusually AT rich in protein-coding regions and contains CG-rich internal ribosomal entry sites in the 5'-UTRs of several genes, both of which may promote viral replication.[61]

At the 5'-end of the genome lies the largest ORF, comprising ORF1a and ORF1b, which is two-thirds the length of the whole genome (Figure 2A).[61] This ORF encodes 16 proteins, called non-structural proteins (NSPs1–16), comprising two cysteine proteases [NSP3, also known as (aka) papain-like protease, PL^{PRO}; and NSP5, aka 3-chymotrypsin-like, $3CL^{PRO}$], an endonuclease (NSP15),[62] an exonuclease[63]/N7-methyltransferase[64] (NSP14) that bolsters fidelity of the relatively-inaccurate RNA-dependent RNA polymerase (RdRp),[65] a 2'O-methyltransferase (NSP16),[66] a helicase (NSP13), and RdRp (NSP12).[67] All the above proteins have clear (and likely essential) roles in the viral lifecycle.[68] Compromising function of many of these gene products can strongly lower virulence and elevate sensitivity to antiviral drugs:[69] mutations in some of these proteins in SARS-CoV-2 may be important for virulence.[70]

Interspersed across the 3'-end of the genome, SARS-CoV-2 contains several structural genes. Arguably the most commonly discussed is the spike protein (S) that is a transmembrane glycoprotein required for host-cell entry. This is a site of relatively high mutational frequency[71] and several high throughput methods have mapped sites essential for/enhancing function on this protein.[72] There are also the envelope (E) and membrane (M) proteins, that along with the S-protein form the viral envelope. Finally, there is the nucleocapsid protein (N), aka ORF9a, that encases the genome in the mature virus.

The 3'-region contains several ancillary proteins, whose encoding genes sometimes overlap with structural proteins or each other (Table 1, Figure 2). These proteins are overall less well understood than the other protein components of the virus, and seem to be mostly virulence factors whose require-

Table 1. Accessory proteins and their roles in SARS-CoV and SARS-CoV-2.

Name	Protein identity with SARS-CoV (Frankfurt 1)	Function in SARS-CoV-2
ORF3a	73% identity (divergence in N-terminus)	ion channel activity; inflammasome activation; replication and pathogeneses; possible links to cell death.[91]
		Viruses lacking ORF3a (but not ORF8a) and E are not viable.[92]
ORF3b	Minimal (ORF3b is located in different regions of Orf3a in SARS-CoV1 and 2)	Not necessarily a genuine ORF.[93] Potential interferon antagonist.[94] Lost in population.[88]
ORF3c	Not present in SARS-CoV	Predicted to be a transmembrane protein.[74]
ORF3d	Not present in SARS-CoV	A potential novel gene product that is poorly characterized (overlaps partly with ORF3c).[95]
ORF6	69% (variation in body and C terminus)	Antagonizes interferon signaling.[75]
ORF7a	85%	Deletions in the viral population have been identified.[96]
		This is a transmembrane protein regulating host/virus interplay.[97] May also regulate cell death.
ORF7b	81% (only 43 amino acids long)	May be incorporated into the virus; may suppress interferon signaling.[80]
ORF8	weak versus both ORF8a and ORF8b	SARS-CoV-2 ortholog can form high order oligomers that cannot occur in SARS-CoV.[98]
		Antagonizes interferon signaling,[99] and downregulates MHC-1.[100]
ORF8b	Not present in SARS-Cov-2	SARS-CoV protein is prone to aggregation. Can trigger cell death and activate inflammasome.
		Triggers ER stress and activates autophagy/lysosomes.[90]
ORF9b	72% (divergence mainly in N-terminus)	This is also a suppressor of interferon responses.[101] Antibodies have been detected in SARS-CoV-2 patients.[102]
ORF9c	Not present in SARS-CoV	Linked to avoiding the immune response. This is a transmembrane protein.[87]
ORF10	Not present in SARS-CoV	Unknown/potentially not translated

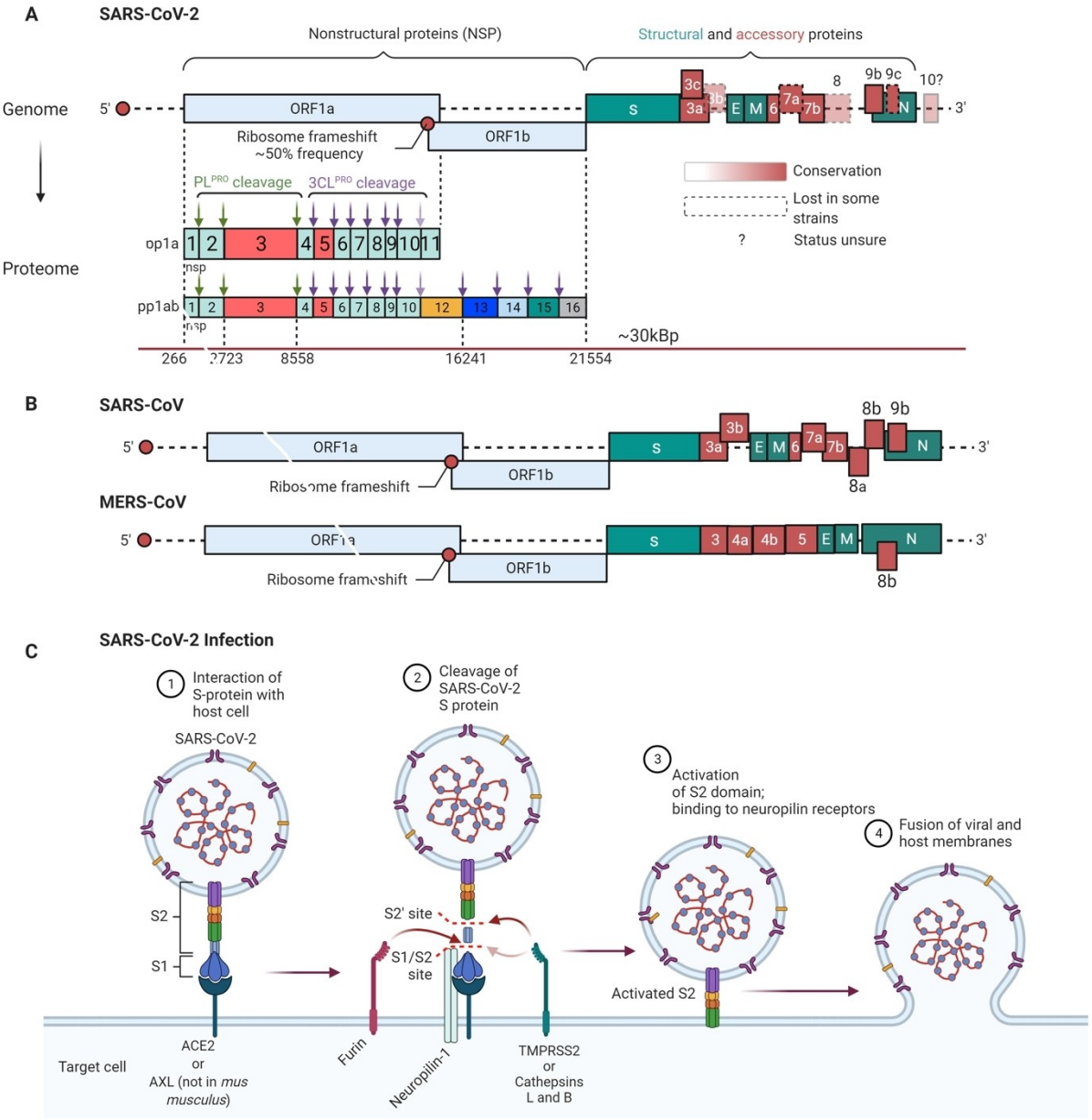

Figure 2. A brief guided tour of CoV biology. (A) SARS-CoV2 genome and proteolytic processing. In the genome, light blue denotes ORF1ab; green denotes structural proteins; red ancillary proteins. Shading denotes conservation; dotted borders indicates variants lacking this gene are known (truncations in ORF7b are known, but not shown here)[331]. In the protein, Pp1a and pp1ab denotes different gene products derived from ORF1ab. Height of boxes denotes translation rate. Note NSP11 is only 13 amino acids in length; other NSPs range from 180 amino acids (NSP1) to 1945 amino acids (NSP3).[371] For NSPs, red boxes indicate proteases; Green down arrow indicates a step catalyzed by PL^{PRO}; purple downwards arrow indicates cleavage by $3CL^{PRO}$ (faded arrows indicate not necessary for replication in some CoVs, but can lead to attenuation).[372] Red line indicates genomic positions. (B) Genomes of SARS-CoV and MERS-CoV for comparison. (C) SARS-CoV-2 infection occurs when the S-protein binds to an acceptor protein on the cell surface. This protein is believed to be ACE-2 or AXL (except in mice). Upon formation of the complex, the S-protein is cleaved by several different proteases (Furin and TMPRSS2 or cathepsins L or B). Other proteins, such as neuropilin-1 are required for viral entry. Upon cleavage the activated S-protein can orchestrate fusion with the plasma membrane and delivery of the genome to the cell.

ments for infectivity vary. The principal proteins are: ORF3a (a (largest) accessory protein that assists virus synthesis/escape also linked to cell death),[73] several other proteins have been proposed to lie in this ORF (in alternative reading frames);[74] ORF6,[75] involved in inhibiting type 1[77] interferon response;[78] ORF7a, a transmembrane protein that assists virulence;[79] ORF7b that localizes to the Golgi apparatus, may suppress interferon signaling,[80] and may be a structural component of the virion;[81] ORF8, likely defective in a strain from Singapore that eventually died out[82] and likely unnecessary for SARS-CoV-2 persistence,[83] (ORF8 is a known target of human antibodies, and evidence indicates selection against this protein as a function of disease progression from both SARS-CoV and CoVID-19);[84] ORF9b, a dimeric all β-sheet membrane protein

housing a tunnel that can incorporate hydrophobic molecules[85] (lies within ORF9a and is likely linked to evading the innate immune response);[86] and ORF9c, a transmembrane protein linked to impairing antiviral response.[87] These regions have high to moderate (in the case of ORF8) homology with SARS-CoV. Two other ORFs possess limited homology with SARS-CoV. The first is ORF3b is a suppressor of interferon activity that is more efficient than its SARS-CoV ortholog. More active versions of this protein are found in severe SARS-CoV-2 variants,[77] despite it being lost in some strains.[88] The second is ORF10. This protein is not necessary for infection in humans, [83] and likely not a bona fide protein. The SARS-CoV ORF8b protein (that triggers ER stress and autophagy, and stimulates cell death) is missing from SARS-CoV-2.[90]

SARS-CoV and SARS-CoV-2 (although not MERS-CoV and several other CoVs) enter cells via interaction with angiotensin-converting enzyme 2 (ACE2) (Figure 2C).[103] There is evidence that newly emerged SARS-CoV-2 strains show higher affinity between the S-protein and ACE2, testifying to the importance of this interaction.[104] Genomewide association (GWAS) analysis of 1980 Spanish and Italian severe CoVID-19 patients showed that a cluster of 6 genes on chromosome 3p21.31 is associated with genetic sensitivity to CoVID-19.[105] Among other interesting genes, this cluster includes SLC6A20, which functionally interacts with ACE2. These results have been backed up by other experiments.[106] The receptor tyrosine kinase, AXL, may also be involved in virus entry through a direct interaction with the S-protein; importantly these studies showed that mouse AXL did not bind CoVID-19 S-protein.[107] Such nuances are hugely important for planning and evaluating in vitro and cellular/animal model studies of infection.

Once anchored on the host cell, the virus requires S-protein cleavage at several sites (S1/S2/S2′) by host cell proteases (TMPRSS2,[108] a serine protease, the principal cleavage enzyme in some cell lines in the case of SARS-CoV-2, although cathepsin B and cathepsin L can also be significant players in these events in some cell lines). S-protein cleavage appears to be particularly critical for the virus lifecycle. Addition of external proteases (i.e., in trans to the viral proteome) is sufficient to allow some MERS-CoV-like viruses that can dock with the membrane, but otherwise cannot infect human cells, to become infective.[109] Additionally, unlike SARS-CoV,[58] the SARS-CoV-2 S-protein can also be cleaved by the serine protease furin, in what has been described as a preprocessing step that may aid virulence[110] through promoting the TMPRSS2 cleavage step.[111] It is possible that furin cleavage sites are positively selected in SARS-CoV-2.[112] Furin-mediated cleavage is inhibited by plasma from CoVID-19 sufferers.[113]

Upon entry to the cell, the viral genome needs to be translated.[114] ORF1a/b is translated to give ORF1a (~500 kDa, comprising NSPs1–11). A −1 frameshift can occur during translation to give a longer polypeptide ORF1ab (800 kDa, comprising NSPs1-10 *and* 12–16). This frameshift is not 100% efficient, giving rise to different expression levels of gene products derived from ORF1a and ORF1ab (the amount of ORF1b-derived protein is ~50% of ORF1a-derived protein). Notably, subsequent proteolysis-mediated processing creates 16 proteins in total. This proteolysis is executed by the two viral cysteine proteases (PL^{PRO} and $3CL^{PRO}$) (similar to how linear polyubiquitin is cleaved to ubiquitin monomers, for instance).[115] $3CL^{PRO}$ (aka main protease, M^{PRO}) performs the bulk of this work, leading to M^{PRO} being proposed as a drug target (Figure 2A).[116] These proteases also cleave human proteins, potentially aiding virulence.[117] The cleaved proteins so produced start to generate the viral genome. This process requires making a minus strand (reverse complement of the virus genome) to serve as a template to make copies of the coding RNA. These processes are performed by two different RNA-synthesis complexes.[118] Once viruses are assembled, β-CoVs use an Arl8-dependent lysosome pathway to exit the cell. Intriguingly, lysosomes appear to be deacidified during coronavirus infection, perhaps to prevent protease cleavage (reported to be reduced by 40% in infected cells) that could occur during egress. This altering of lysosomal function also affects antigen presentation.[119]

New CoVID-19 diagnostic methods

One of the significant issues promoting spread of CoVID-19 has been the virus's prolonged incubation time, with often ~2 weeks post exposure being required to display symptoms coupled with a relatively early infective period.[120] Thus, rapid development of sensitive and diagnostic testing[121] has been necessary to quell local eruptions of the disease and focus confinement, e.g., in the tier system introduced in the UK. Clearly how infected people were dealt with, and how this response was organized, has differed greatly amongst countries, and is in part responsible for differences in spread and management of the virus across different continents,[122] which makes a general discussion difficult. This review will not dwell on those issues here. Instead, we will outline the technological approaches and how they differ. Numerous sampling regions on the patient are of course possible, including nasopharyngeal areas, eyes,[123] and saliva.[124] The sampling region can affect fidelity of results, as a function of different testing strategies, and manifest different likelihoods of detection based on the stage of infection, and impinge on administration of the test. The choice of sampling region can in turn bring additional discomfort to patients, and change the resulting danger to healthcare workers who may be needed to take the samples.[125] Thus, when evaluating diagnostic methodologies, such factors must be taken into consideration.[126] Indeed, the end goal of testing, or use case, also needs to be considered.[127]

We will discuss each method based on typical parameters, e.g., cost, turnaround time, and accuracy (see below).[126] These variables provide numerical data that are deceptively easy to interpret: in terms of cost, the lower, the better; in terms of accuracy, the higher the better. However, it has been concluded that these arguments require contextualization. E.g., >90% accuracy may not be necessary for effective population-based screening when coupled with other active countermeasures, especially among predominantly younger populations.[128] Conversely, false positives can potentially have severe ramifications

for individual patients, e.g., mandatory hospitalization and potential exposure to CoVID-19 patients[129] in many Asian countries, and may convey other risks in terms of loss of capital and isolation elsewhere. On the other hand, simple probability laws have been used to show how tests with ~70% accuracy administered in series can lead to >90% accuracy when two such tests are run in series, and a patient is only considered negative if both tests give a negative result.[130] This sort of sequential amplification is known in numerous fields of science.[131] However, increasing sampling necessarily increases cost and time. Furthermore, given as this protocol mandates that we consider opposing outputs from the two tests as a negative by default, this strategy could lead to lowering confidence among the general public. Thus, from the perspective of an individual buying the test-kit(s), or a researcher trying to accurately understand the disease, it is critical that we seek optimal performance. Our review will thus discuss assays in terms of individual experiments, for standardization. We will not directly compare these procedures, as in effect, the different variables require different considerations for given purposes. However, this has been done elsewhere, and we refer readers to such papers.[132]

Reverse transcription polymerase chain reaction (RT-PCR)

Real time RT-PCR screening is the gold standard test for CoVID-19, and numerous other CoVs (Figure 3A).[133] The basic protocol is common to the majority of RT-PCR procedures. Critically, each step is an important variable, and can affect fidelity of testing. The general scheme involves, lysis, RNA purification, RT of the RNA, amplification of specific stretches of the product cDNA using carefully designed primers[134] by PCR, and detection of these DNA products by probes[135] (e.g., by TAQMAN, molecular beacon). Several amplification regions have been suggested for this procedure, including a two-step process that examines the E-gene as a screen, followed by the RdRp region of ORF1b as a second confirmatory step;[136] and a two-step RT-PCR analysis using RdRp and N-genes from Abbot that is approved for use on nasopharangeal and oropharangeal swabs. These two-step testing regimens can also be supplemented to include control sequences to account for competence or sample degradation.[127] Self-collected saliva and nasopharyngeal swabs are potentially viable for testing.[137] All RT-PCR methods have the benefit of testing based on the viral genome, and hence can show that a patient is presented with a viral load at the time of testing. RT-PCR also appears to be able

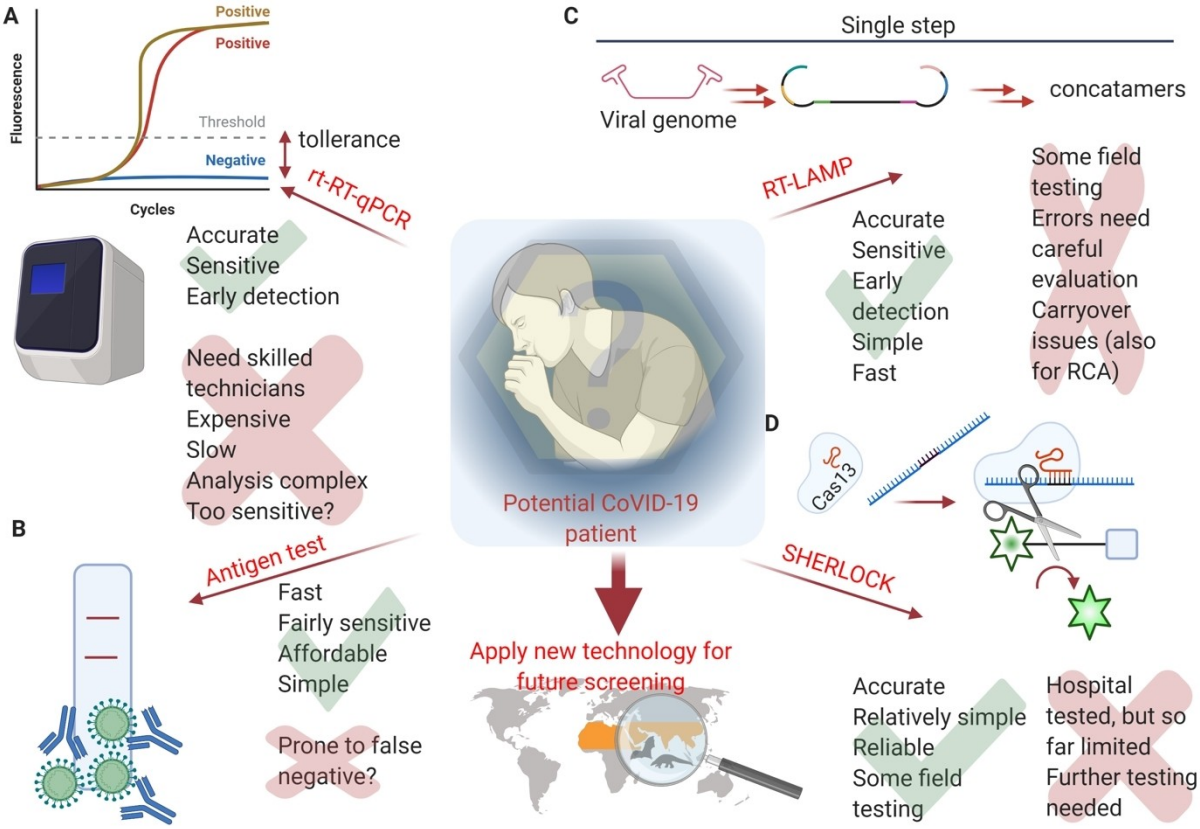

Figure 3. Detection strategies for CoVID-19. A. qRT-PCR, arguably the gold standard. B. Antigen testing, a rapid and cheap alternative, that is less sensitive than rt-RT-PCR. C. RT-LAMP, a modern method using multiple primers that generates concatenated products. D. SHERLOCK, another modern method using Cas enzymes (Cas13 is shown here) that gain activity dependent on a specific interaction with an amplicon derived from the viral genome. All methods could be harnessed for new screening technologies against zoonotic diseases; only some are apposite for deployment in at risk areas.

to detect viral loads the earliest out of the traditionally-used methods, and gives the highest accuracy.[138] Variants of RT-PCR, e.g., digital PCR, may be more sensitive[139] than RT-PCR with lower false-positive rates,[140] although such improvements, are likely not necessary for routine applications. Nevertheless, pooling of samples from different patients for mass testing has been suggested as an effective strategy to reduce workloads and increase efficiency. In this scenario, high accuracy and sensitivity[141] are critically important factors.[142]

Although deservedly often considered the gold standard, RT-PCR strategies suffer from several issues.[143] Perhaps the greatest issue with RT-PCR is data analysis itself, which can be subjective and requires experience and standardization.[144] There are various schools of thought to define if the products so derived are due to specific amplification or off target behaviors, and these are often not standardized.[145] Furthermore, the method is complex and prone to experimental-induced artifacts, particularly during collection and processing:[146] several steps are required, RNA extraction and handling steps are a must, specialized equipment is needed, and high technical skill is mandatory. Turnaround times can be long, mandating patient isolation. Mitigating some of these considerations, protocols side-stepping extraction and minimizing screening time are being optimized.[147] Perhaps counter-intuitively, the sensitivity of RT-PCR is, in some contexts, reportedly too high, meaning that this assay catches people who are not in the peak of infectivity. This could be an issue since SARS-CoV-2 viral load takes a long time to return to 0, post infection.[148] As with all homology-based amplification strategies, mutation to the priming sequences, or the detection sequences will hamper sensitivity and could lead to false negatives. Thus, it is important to choose loci with relatively low mutagenesis rates and it is preferable to screen several loci at a time. It is also important to note that although CoVs are considered relatively stable, potentially assuaging these worries, there are numerous circulating mutants although overall variation remains small.[149] It is likely that variation in SARS-CoV-2 strains will increase with the introduction of new vaccines and increasing deployment of CoVID-19-targeting drugs.[150]

RT-Loop-mediated isothermal amplification (LAMP) screening

LAMP[151] is a multiple primer/multi-homology strategy to perform PCR to generate multi-concatenated amplicons that can be detected by several simple methods (Figure 3C). This isothermal amplification method has been applied to detection of numerous viruses, including MERS-CoV.[152] It is noteworthy that other isothermal amplification techniques (some of which will be discussed below) are also in existence and have been used for viral detection, for instance: recombinase polymerase amplification (RPA);[153] rolling cycle amplification (RCA);[154] and nucleic acid sequence-based amplification (NASBA).[155] We will discuss LAMP as an exemplar. One key benefit of this method over traditional PCR is that it is an isothermal reaction, and hence can be run in simple setups without the need for a thermocycler. However, the use of isothermal conditions[156] may increase the chance of false positives.[157] Although LAMP requires multiple sequential PCR reactions, it is also reportedly of very high fidelity, low background and very sensitive: down to 6 copies of the target have been successfully detected, even when coupled to RT-PCR in mock blood samples.[158] It is particularly critical to ensure that a strand displacing polymerase be used for LAMP. Given the need for strand displacement, this method works best on short stretches of nucleic acid ($<$ 300 bp).[159]

RT-LAMP (where RT is coupled to LAMP, either separately, or in the same pot)[158] has proven to be a particularly versatile platform on which to build CoVID-19 testing. Indeed, this procedure is also believed to be particularly robust to inhibitors of the PCR process, rendering it ideal for field use/one-step procedures.[160] Protocols amplifying the N gene and the S-gene, or portions of ORF1ab have been reported.[161] These and similar methods take less than one hour.[162] Several of these have proven to be useful on primary clinical samples. This was also extended to a direct CoVID-19 test (i.e., that did not require prior RNA isolation: this was faster than RT-PCR, although less sensitive).[163] Barcoded LAMP reactions are also possible to allow multiplexing of samples with individual-level specificity.[164] Obviously, continued development of these processes will enable better evaluation of how RT-LAMP holds up relative to other strategies, but initial reports are encouraging.[165] However, the low technical requirements render this strategy applicable to low technology level areas that are in need of rapid and cheap tests that are simple to run. It should be noted that one issue with such strategies is product contamination across samples, although some approaches have been proposed to minimize this issue.[166]

Crispr-Cas-based screening

SHERLOCK screening

Cas-13 enzymes are RNA-guided RNA-cleaving proteins that show an unusual property often referred to as collateral activation (Figure 3D). This means that when a guide RNA is loaded into the Cas13 nuclease and that complex recognizes its target RNA, the activity of Cas13 to cleave RNA non-specifically is increased, leading to non-specific cleavage of nearby sequences (i.e., in a sequence-independent manner). This activity-amplification pathway could be linked to a bacterial cell-death pathway.[167] In vitro, this activity-promoting mechanism can be used for signal amplification, leading to sensitive sequence-detection strategies. This method is typically referred to as SHERLOCK, and has been applied to numerous virus detection stratagems.[167]

The basic steps of SHERLOCK involve, RT-PCA of the sequence to be detected; transcription, typically using an engineered T7 site; addition of Cas13 and an RNA sequence for detection and a self-quenched single-stranded RNA probe, that can be cleaved by activated Cas13. Sherlock-based methods

manifest attomolar sensitivity.[168] Readouts are made by measuring fluorescence increase, often in relation to positive and negative controls, and are applicable to test strips. Generally speaking, these assays are rapid, accurate, do not require complex equipment (e.g., thermocyclers), and are reliable. This reliability has been extended to the testing kit stage that has been trialed in hospitals. Single step assays have been reported.[169] Several loci within the SARS-CoV-2 genome have been tested and shown to function well; these include: Orf1ab;[170] S-protein;[171] and the N gene.[156] More recently massively multiplexed assays using Cas13 have also arisen.[172] A potential drawback of Cas13 methods is that they use RNA-based reporters. Clearly this renders adventitious cleavage and RNAase contamination a worry. The use of standards certainly help assuages these errors.[156]

Similar detection stratagems using Cas12 collateral activity[173] have also been reported.[174] In one instance, called "DETECTR" amplification of cDNA (encoding viral E- and N-genes) and human RNase P (included as a positive control) was performed using RT-LAMP (which has also been used for SHERLOCK).[175] Then a viral cDNA sequence was detected using a specific guide RNA that triggered cleavage of a self-quenched ssDNA fluorescent probe. Tests were rapid (~1 hour) and showed similar sensitivity to RT-PCR. One pot methods have been shown to work on limited numbers of patient samples with good accuracy.[157] A Cas12a-based approach has also been used to develop a glucose-meter-coupled SARS-CoV-2 assay for simple field use.[176]

Obviously, all the above methods require more field testing, larger scale manufacturing, and more robust evaluation, especially in challenging environments. Initial results are promising for high throughput applications in real-world settings[165] and they promise to be effective and accurate tests, which may come to maturity in the near future and even if not deployed directly against CoVID-19, could be useful in future applications as outlined below. One potential issue is that these tests are accurate down to the single-nucleotide level,[177] which means highly stable loci need to be taken. Developing several detection loci and methods to deal with conflicting results then becomes important.

Antigen testing

Antigen testing has been approved for use in the USA (Figure 3B). This has also been approved as the first over the counter CoVID-19 test in the USA;[178] data are reported to be available in as little as 20 minutes. This test directly detects a SARS-CoV-2 antigen (e.g., S-protein) using immunochromatography. Apparently, production test kit capacity will reach 50 million per month.[138] The Panbio version of this test has almost 90% accuracy, especially when nasopharengeal swabs are used. Throat and saliva samples are not as effective.[179]

Obviously, this test fares particularly well against others in terms of accessibility (no laboratory is required), rapidity, and affordability ($5). Such considerations are particularly important variables for deployment in developing countries. The accuracy and threshold of detection, are impressive and offer detection prior to onset of symptoms with good accuracy. However, they are not as accurate/sensitive as PCR-based strategies. Some studies indicate sensitivity of some kits may be prohibitively low.[180] Hence it is critical that users research the specific kit used and evaluate how those data were obtained. Nevertheless, it is still debated if the level of accuracy and sensitivity of RT-PCR is really necessary[148] so opinions on what constitutes "a good test" may change. As antigen testing requires detection of a viral gene product, this strategy is also susceptible to false negatives due to mutation. There is no hard and fast rule on how nucleic acid-based detection strategies versus antibody-based strategies differ in terms of their susceptibility to mutagenesis.

Antibody testing

This test detects whether a patient is producing antibodies to a specific viral protein. Presence of such antibodies are inferred to mean the patient has been exposed to the virus, although some patients do not mount a strong or persistent antibody response to SARS-CoV-2.[181] The antibody response to SARS-CoV is mediated principally IgM[102] production (for early stage) and IgG[182] production for later/post recovery stages. These can be detected by a range of methods including ELISA, immunofluorescence, and immunochromatographic assays. Numerous tests (probing for IgGs binding to either the N or S-proteins) have been given approval for use by the FDA;[183] other tests for IgM are available and several tests assay for both IgM[184] and IgG.[185] Although outputs are varied, these tests do seem to be rapid, accurate and sensitive.[186] Unlike RT-PCR and other virus detection methods, the antibody test has the added benefit in that it can indicate if a patient has been exposed to the virus, even if they have recovered. Antibodies have been detected circulating in CoVID-19 patients 8 months after infection.[186] Conversely, for this reason, the antibody test does not inform on whether a patient is infectious at the instance of testing.[187] It further has a relatively long latency (two commercially-available kits show positives 14–15[185] days post onset of symptoms), that could lead to the most infectious periods being missed.

As cases are typically significantly underestimated during outbreaks, the use of antibody testing can be important for population studies to inform on the actual spread of the virus. Such testing must be performed in a window where antibodies are present, although antibody production in patients is quite long lasting.[186] One potential use for antibody testing is to inform a patient on whether they *may* have acquired immunity. However, it is also not fully known how the presence of antibodies due to CoVID-19 infection confers protection against reinfection: both human IgG and IgM bind to important viral proteins including the N[188] and S1 proteins;[102] there is a statistically significant reduction (although not complete protection) in SARS-CoV-2 infection in people who have already suffered from CoVID-19 up to 6 months post infection:[189] comorbidities may promote reinfection.[190] Nevertheless, sec-

ond infections are known.[191] Furthermore, there are also no real indication as to whether second infections of SARS-CoV-2 are similar or worse than the first infections or how different mutants are able to evade an existing immune response due to exposure to an earlier strain. It should also be noted that high levels of IgG may indicate poor response to severe CoVID-19,[192] whereas asymptomatic patients tend to mount a poor antibody response.[181] Thus there are potential diagnostic uses of the antibody test. This method shows overall low accuracy to different CoV-based human infections (e.g. SARS-CoV and MERS-CoV).

One final note on immunity: the importance of antibodies has somewhat dwarfed the T-cell mediated response.[193] However, T-cell response in patients who had recovered from SARS-CoV almost 20 years ago, was strong against SARS-CoV-2.[27] Given the prevalence of CoVs in the broader population, it is likely that T-cell immunity to SARS-CoV-2 exists in fractions of the population through various routes. However, it is not entirely clear how such acquired immunity would affect CoVID-19 patients, and how effective it would be.[194] Significant careful research needs to be done in this area. Such research is particularly critical for the protection of young exposed to SARS-CoV-2 as we outline later.

Other diagnostic methods

Other methods have been used to detect SARS-CoV2. In many cases, these have been compared to other diagnostic procedures, typically RT-PCR. New molecular tests are in development, such as development of protein sensors[195] and direct RNA detection strategies,[196] as well as novel methods for product detection, such as through aptamers.[197] Screening for temperature, i.e., looking for signs of fever, is a common strategy deployed in shops and other commercial centers. This strategy is clearly not diagnostic for CoVID-19 and requires that the person be symptomatic at the time of screening. Thus, many people who are contagious will be missed. Other issues with this strategy have been reported, namely that faulty or poorly-designed equipment may be incapable of detecting fever.[198] Molecular noses, and dogs have also been proposed as a means to identify CoVID-19 sufferers, although these seem a long way off deployment.[199] Several nanotechnology-based strategies have also been reported,[200] although again these seem a long way from even entering trials. Chest computed tomography (CCT) procedures were shown to be 97% accurate, 56% specific and 72% accurate by a group from Italy,[201] which agrees with previous data from a group from China.[202] Some studies claim CTC procedures may be more accurate than RT-PCR.[203] These studies have also incorporated artificial intelligence to standardize and rigidify protocols.[204] Clearly these methods require specialized equipment and specialists to interpret, and are unlikely to be used as routine screening procedures.

Putting these Screening Methods into Action Post CoVID-19

Changing geopolitical profiles and climate variations are causing shifts in numerous animal habitats, including bats (horseshoe bats, are sedentary; disturbing their habitats is unduly stressful). Such stressors, in conjunction with increases in bat population densities, are often causes of viral outbreaks[205] and can promote virus mutations in bats, and cause human/bat conflicts. All these factors can elevate the threat of zoonotic events and are potentially relevant to former, current, and future zoonotic outbreaks. Given the unprecedented levels of SARS-CoV-2 in the community, we should further not underestimate the potential risk of spilling back of SARS-CoV-2 into bat and other animal populations,[206] which could introduce new complications[207]/mutations.

Fortunately, similarly to how the ramifications of efforts to respond to MERS-CoV and SARS-CoV facilitated development of vaccines,[208] as discussed above, there now exists an arsenal of accurate screening and rapid response tests for CoVID-19. Critically, due to the huge imperative set by CoVID-19, many of these tests function in clinical settings. To meet the demand and market competitiveness, the cost and intricacy of the technology has overall drastically fallen as well. Further consistent with a global disease, local knowledge and production ability of test kits have risen,[209] in many parts of the world.[210] In other words, we are once again "woke" to the dangers of zoonoses, while at the same time, we are globally in a better position than ever, to screen for CoV infection at point of care, or in the field, even in developing countries. It is vital that this confluence of awareness and technological advancement be harnessed to developing a screening net for understanding the movement and genetic changes of animal CoVs across areas believed to be at high risk of zoonotic events and to monitor their impact on human populations. Clearly such a mechanism needs to incorporate local farmers and laborers both in regular health checks, and in establishing a reporting system for potential dangers. Such a system thus mandates development of sustainable local involvement and education and building of trust between research scientists and people in the front line of animal/human contact, in a large part of Asia and Africa. It further mandates global collaboration between disease research laboratories and hospitals, which is important for future scientific development and pandemic detection. The varied needs and networks currently in place may necessitate several distinct (county/canton or state-localized) efforts in the early years post CoVID-19. However, these efforts should be encouraged to unite as early as possible: critically, this net, and subsequent screening efforts centered around early mapping of potential zoonotic events and characterization of associated strains, must strive to be externally coordinated, and run by an overseeing committee with rapid and equal access to all data.[22] Logistical, legal, and language barriers will all serve to mount huge obstacles to establishing such a system.

It is also critical to note that bats are of huge importance to all countries' economies (billions of dollars to the US economy

alone,[211] and proportionally more to developing nations).[212] Bat Guano is also a common commodity used and traded in Asia, and this is also a source of CoVs.[213] Thus, developing commitments between farmers and scientists to sustain bat populations in a healthy way are critical to reinitializing agribusiness post CoVID-19. It is certainly true that local bat populations have been targeted in numerous countries throughout the world[214] as a result of CoVID-19, meaning that screening, education, and improved local involvement/complicity (requiring close collaboration with and coordination by conservationists)[215] will be even more critical in years to come.

Research into CoVID-19 Treatments

In parallel to screening efforts, those who were diagnosed, especially patients showing severe symptoms, needed treatment. This was initially a difficult task, as no drugs were approved to treat CoVID-19 or other SARS-like infections. This led to a huge number of clinical and exploratory investigations that we outline below. In line with the broadening of drug-discovery platforms beyond traditional small-molecule-based therapies, a large number of therapeutic options have been and are being investigated to treat CoVID-19. Although we will discuss mainly small-molecule-based approaches in detail here, it is noteworthy that several other options have been investigated and may be effective. One of the early treatments was convalescent plasma, i.e., plasma from patients who had had CoVID-19. Such an approach is an established therapy that has been used for over 100 years to treat many infectious diseases,[216] and was the subject of the first Nobel Prize in Physiology and Medicine.[217] This approach for CoVID-19[218] has been met with checkered results,[219] although recent data indicate that high titers and early administration is important for efficacy, especially in older adults.[220] These observations underscore that context dependence – particularly in terms of timing post infection, but also in terms of symptom presentation – is a crucial factor determining success of trials and treatments.

Clinical (and clinically-orientated) research has focused on evaluating the efficacies of approved drugs against CoVID-19, in a bid to repurpose. We will evaluate this approach further subsequently. Given time constraints facing clinicians, and being met with what appeared to be at some stretches a losing battle, this approach was on the surface logical: it leverages known information on drug mechanism/targets, doses, contraindications and general toxicity to help pinpoint potential clinically-validated molecules. Conversely, reapplication of approved drugs brings several unknowns that were not well-controlled in early tests. These include effective doses, timing of administration, and how side effects can synergize with drug symptoms.

Assessment of clinical reports on potential CoVID-19-treatment options reveals that most data are often far from clear cut. The importance of side effects of administered drugs can also be subject to debate,[221] and how much drug-drug interactions were considered in planning is not always clear.[222] Dosing, and other simple factors are often not standardized.[223] This confusion is further hindered because especially in the early days of CoVID-19, investigations were not conducted with sufficient sample size (patient number) to achieve "statistical significance".[223] Given the many years spent carefully honing drug development, these loose ends may seem surprising. This is perhaps further disappointing as these investigations were often functioning as Phase-II trials, which routinely take hundreds of people precisely to ensure adequate statistical power. Nevertheless, such controversies are not uncommon,[224] even in data that have been contested for many years, especially among context-specific diseases. Indeed, efficacies of CoV treatments in general also seem to be somewhat prone to being controversial;[225] in the case of CoVID-19 perhaps even more controversy may be expected given the complex relation of mortality to age, and numerous unknown factors and the variations in pathophysiologies as a function of severity, and time post contraction (many of which may not have even been considered as variables in early studies). Coupling the disease complexity with the extreme circumstances under which the CoVID-19 clinical data have been collected, different practices across different countries, clinical standards/routines, and the rapidly-shifting circumstances that occurred during the months from February 2020 to even today, discrepancies were likely. Faced with such realities, interpretations of clinical data could change in the future. Deciding on treatment options requires discussion with an expert to make informed treatment decisions; as of today, there are around 3500 CoVID-19-associated clinical trials either underway or completed.

CoVID-19 Treatments

One of the early screens, performed in cell culture models of infection, published in March 2020 identified from a pool of approved drugs remdesivir[226] and chloroquine (both known antivirals)[227] as potential CoVID-19 therapeutics (Figure 4).[228] Notably, the SARS-CoV/MERS-CoV-active drug, ribiravirin, was very weakly effective in this assay (although it later reemerged as a molecule of interest); nafamostat, a potent MERS-CoV inhibitor[108] (likely through TMPRSS2 inhibition), was also only marginally effective (Figure 4). However, the efficacy of these drugs against SARS-CoV/MERS-CoV was not assessed, making the origins of these failures far from clear. We begin our discussion of clinical data on the hits that came out of this screen.

Targeting Transcription: Remdesivir

Remdesivir,[229] an ATP analog, is an inhibitor of viral RdRp, displaying activity against SARS-CoV, MERS-CoV and SARS-CoV-2.[230] It appears to be active in the regimen post viral entry, consistent with this mechanism. Numerous clinical trials have shown that this molecule is well tolerated in humans,[231] although some negative effects were reported.[232] A treatment regimen of 200 mg followed by daily 100 mg for up to 9 days is

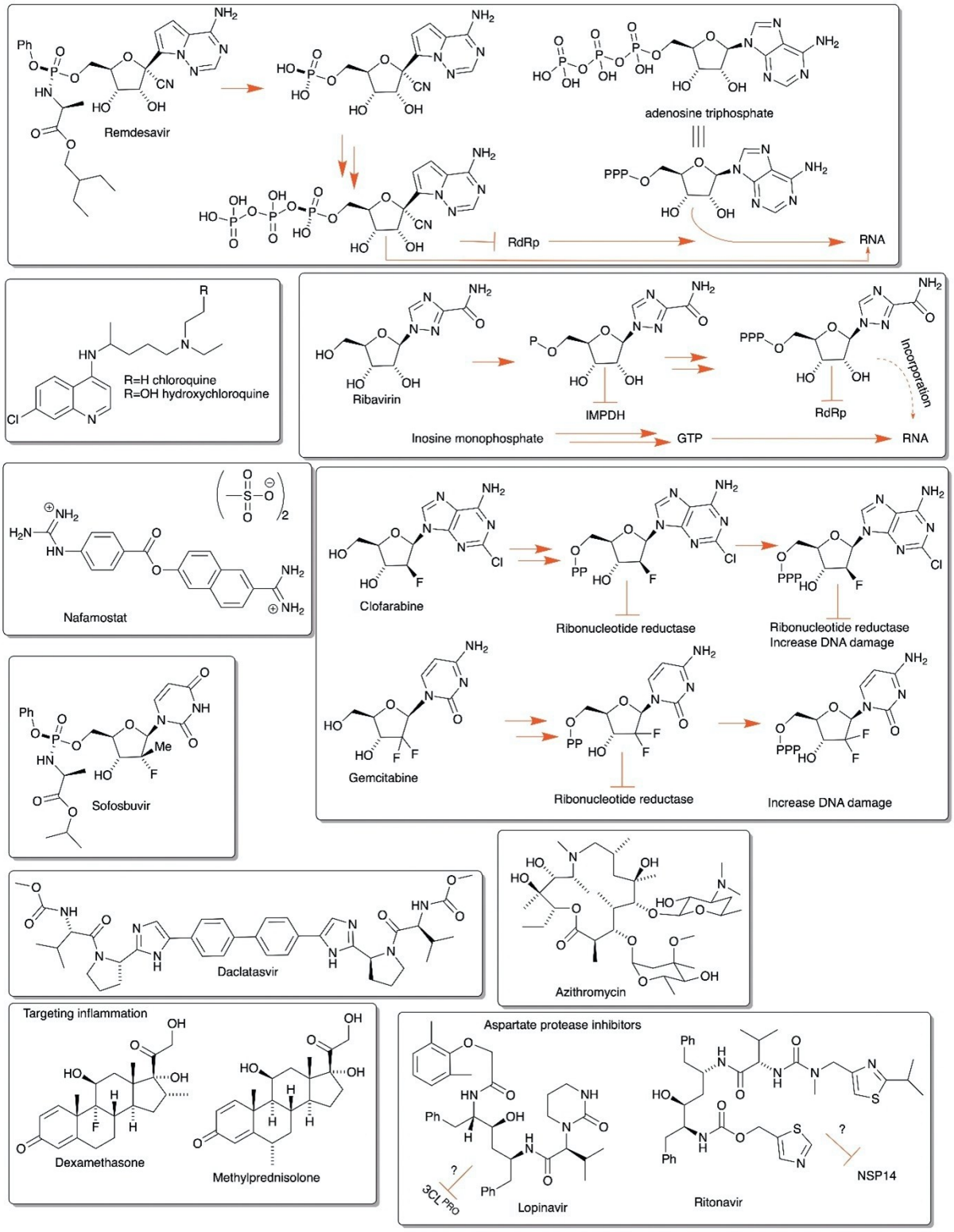

Figure 4. Structures and functions of compounds discussed above, highlighting bioactivities and potential behaviors.

currently considered to be effective at dropping recovery times by around one-third, although survival was not affected.[233] That being said, a study by the World Health Organization has published results to the contrary, with a final conclusion that there was no improvement on mortality, initiation of ventilation and hospital-stay duration.[234] The reason for these two trials (featuring similar dosing regimens) giving disparate results is unclear.

Notably, remdesivir is a nucleoside analog, like many widely-used approved drugs (e.g., the anticancer drugs chlofarabine and gemcitabine).[235] These molecules require activation to the di/triphosphate in order to be active and in many instances, monophosphorylation of the nucleoside can be rate limiting. To mitigate these concerns, remdesivir is essentially a protected monophosphate allowing bypassing of monophosphorylation, in a bid to normalize patient response. How prodrug activation differs across patients is less well known. Similar to its dNTP-mimicking cousins such as clofarabine and gemcitabine, remdesivir is also incorporated into the viral genome, leading to genomic-replication stall, and viral genomic stress.[236] The viral protein, NSP14, is protective against such effects for remdesivir and numerous nucleoside analogs sharing a similar mechanism.[65] It will be interesting to map NSP14 mutations as remdesivir is more widely used. More importantly, the observation that NSP14 is required to protect from remdesivir implies that NSP14 is a good drug target, although no NSP14 inhibitors are approved.[237] Some molecules like ritonavir (below, although these studies are very preliminary)[238] are possible candidates and could be considered for combination therapies. No drug-drug interactions have been reported for remdesivir.[239]

Inhibitors of other viral RdRps, e.g., sofosbuvir (another nucleoside-monophosphate prodrug),[240] approved for use against hepatitis-C virus, although only in conjunction with other drugs, have also entered trials.[241] Recent reports have indicated that sofosbuvir/daclatasvir may help reduce the number of patients with fatigue 1-month post CoVID-19 infection, although it did not significantly relieve virus-induced early symptoms.[242]

(Hydroxy)chloroquine

Aside from identification from the aforementioned screen, (hydroxy)chloroquine was also evaluated as a potential anti-CoVID-19 drug based off a CoVID-19/human-proteome-interaction screen. This screen showed that the Sigma-2 receptor (part of a family of proteins implicated in viral infection)[243] interacts with the CoVID-19 ORF9c. Knockout of Sigma-2 receptor reduces SARS-CoV-2 replication,[244] indicating that modulation of this protein may help treat CoVID-19 patients. In retrospect, two issues stand in the way of this logic. Firstly, ORF9c has been reported to contain premature stop codons in a subset of viral isolates, arguing that ORF9c may not be a particularly important protein for SARS-CoV-2 propagation in humans. Secondly, the mode of action of (hydroxy)chloroquine has been linked to effecting receptor activity, although this evidence is weak, as far as we know, relying upon drug combinations and comparisons with other drugs of presumed similar mechanism.[245]

Early reports[246] (often in combination with the antibiotic azithromycin)[247] on clinical use of hydroxychloroquine, that were admittedly later questioned,[248] were promising. Hydroxychloroquine was given limited emergency use authorization by the FDA in combination with azithromycin, which was subsequently revoked.[249] More recently, (hydroxy)chloroquine has been declared ineffective in numerous CoVID-19 trials.[250] Analysis across numerous publications indicates little beneficial effect of hydroxychloroquine on CoVID-19. The use of hydroxychloroquine with azithromycin may actually increase mortality[251] and negative symptoms associated with both drugs.[252] Some interest remains in (hydroxy)chloroquine serving as a prophylactic treatment against CoVID-19,[253] although recent reports are not encouraging.[254] Nevertheless, this is one of the most-trialed drugs to treat CoVID-19. As of writing, no other potential CoVID-19 drug is more emblematic of the disagreement among experts (and politicians) as to what the appropriate therapies of CoVID-19 should be than (hydroxy) chloroquine.[255] There is evidence that gravitation towards certain compounds may have been detrimental to the global response.[255]

Targeting inflammation: glucocorticoids

The logic for the use of dexamethasone and other glucocorticoids (Figure 4), that are now recommended for use in extreme cases of CoVID-19, is the goal of reducing extreme inflammation and ensuing elevated immune response that can be a key cause of CoVID-19 morbidity.[256] Although there have been debates about the general utility of corticoid steroids as therapies for CoVID-19,[257] dexamethasone at the time of writing, the only treatment approved to lower mortality of CoVID-19.[258] These results were backed up by several other studies.[259]

Several issues remain from clinical studies. From a practical standpoint, these include unclear exclusion criteria and the scant information in terms of levels of oxygen support given to patients during these trials. Admittedly, as noted above, these issues have not been unusual in CoVID-19 trails.[260] Furthermore, several detractors have voiced their disagreement with dexamethasone deployment and improvements to standard protocols have been suggested.[261] It has also been pointed out that glucocorticoids can lead to a pro-coagulatory environment, which could exacerbate the thrombotic aspects of CoVID-19.[252] SARS-CoV Viral loads post survival may be more persistent in patients treated with dexamethasone,[262] meaning that clinicians have a difficult choice to make about implicating dexamethasone as part of the treatment regimen.

Other glucocorticoid steroids have been used to treat CoVID-19. The most common alternative is methylprednisolone, which improved clinical outcome in several studies,[263] although not all.[264] The mode of action of methylprednisolone appears to be, at least in part, through reduction of inflammatory response.[265] Recently dexamethasone and methylprednisolone were compared head to head. In a relatively small study (100 people in total, split 33% in terms of dexamethasone and 66% to methylprendnisolone) there were no differences observed between the twain.[266] It should be noted that no control group was included in this study, meaning that it is difficult to assess how effective these drugs were.

Targeting infection and harnessing fortuitous antiviral effects: antibiotics

As was mentioned above, several antibiotics have been shown to have antiviral behaviors and have been trialed either alone, or in combination to treat CoVID-19. It should be stressed that although antibiotics are designed to target bacterial infections, and are often cautioned against being used in people with viral infections, this is very much a rule of thumb and it can be ignored upon advice from a suitably-qualified medical professional, for instance in cases where the antibiotic in question has antiviral activity, or where an adventitious bacterial infection has occurred. Aside from azithromycin, the glycopeptide antibiotic teicoplanin, used to treat staphylococcal infections, has been used as a treatment for CoVID-19,[267] and was previously used to treat MERS-CoV.[268] The mode of action is believed to occur through inhibition of S-protein cleavage by cathepsin L in late endosomes,[269] although this is not believed to be the only route by which S-protein cleavage can occur (Figure 2).[108] Intriguingly, it has been reported that blood stream infections can be elevated in CoVID-19 patients.[270] It has been suggested that the use of teicoplanin may assist lowering viral loads and preventing adventitious gram-positive bacterial infections.[271] Clearly more work is needed in this area, but in a disease where bacterial infections are a common side effects, dual acting therapeutics that ideally synergize with point-of-care antivirals is a neat solution that warrants investigation.

Targeting papain-like and 3 C-like proteases: lopinavir and natural products

The viral life cycle necessitates cleavage of the gene products of ORF1a and ORF1ab into active component proteins to allow replication. As discussed above (Figure 2), CoVs have two proteases that perform this function, PL^{PRO}, and $3CL^{PRO}$ (or M^{PRO}). In many viruses, these proteases have unusual canonical cleavage sequences (many are used as bioorthogonal proteases in chemical biology)[272] and hence are good drug targets. Nevertheless, these are both cysteine proteases (Figure 5). Unlike serine[273] /threonine proteases[274] and aspartate proteases,[275] cysteine proteases have proven particularly difficult to drug selectively and successfully,[276] despite being a deceptively simple class of proteases to target through blanket inhibition strategies.[277]

Lopinavir, an inhibitor of Type-I HIV aspartate protease, typically combined with the inhibitor of cytochrome p450, ritonavir, to increase lopinavir's half-life, is active against SARS-CoV (Figure 4).[278] The mode of action of these molecules against CoVs is unclear. We will use this as example of some of the *potential* errors of logic that can crop up during drug repurposing. Lopinavir appears to be active against MERS-CoV,[279] and indeed inhibits purified SARS-CoV $3CL^{PRO}$, albeit at high concentrations.[280] Such data do not prove that $3CL^{PRO}$ is the anti-CoVID-19 target of lopinavir, but they are at least indicative that an interaction with lopinavir that can lead to suppression of $3CL^{PRO}$ activity. Lopinavir's poor inhibitor of $3CL^{PRO}$ *in vitro* is unsurprising. Aspartate proteases and cysteine proteases are mechanistically dissimilar: the former use aspartates to promote water to directly hydrolyze the scissile peptide bond of the target; the latter use a nucleophilic cysteine to form an enzyme-substrate covalent intermediate which is hydrolyzed by water (Figure 5). Inhibitor scaffolds targeting these two protease families are typically different. Indeed, lopinavir contains a hydroxymethine group that is a stable analog of the peptide hydrolysis transition state facilitating reversible inhibition of aspartate proteases. Such a motif is not ideal for targeting cysteine proteases;[281] reactive Michael acceptors, ketones (which form a hemithioacetal as part of the mechanism), or other electrophiles that can harness the nucleophilicity of the reactive cysteine to create a covalent bond to the target are often used. Indeed, a screen for SARS-CoV M^{PRO} inhibitors identified mostly electrophilic compounds as hits from a screening set of 50,000 compounds.[282] However, molecular dynamics simulations appear to support that lopinavir can bind in the active site of SARS CoV-2 M^{PRO}. Clearly an off-active site binding mode is also possible. Although some have found some promise in the reported clinical trial data,[283] lopinavir/ritonavir was concluded to have no significant efficacy in hospitalized adults with CoVID-19 by two trials.[284] Further studies may change these conclusions, and should that be the case, it is important that the real target(s) of lopinavir/ritonavir be identified, as such insights could inform on new drug screens in the future.

With the publication of the crystal structure of SARS-CoV-2 PL^{PRO} and $3CL^{PRO}$,[285] more work has been done to identify potential inhibitors of these proteases.[286] It is worth noting that in the wake of SARS-CoV, numerous other inhibitors of PL^{PRO} or $3CL^{PRO}$ were released. Indeed, natural products inhibiting PL^{PRO} have been reported from a host of species, including *P. corylifolia*,[287] *P. tomentosa*,[288] *T. terrestris*,[289] and others. Despite being interesting, and although several trials using traditional Chinese medicines to treat CoVID-19 were initiated, little has come from these outputs so far.[290]

Other hypotheses

The pathology of CoVID-19 has indicated that acute hyper inflammation and cytokine storm is a critical contributing component in severe CoVID-19 cases; this is queried by some authors as cytokine levels are lower than in patients with sepsis and acute respiratory distress.[291] Nevertheless, IL-6 inhibitors are being trialed; several of these also may have inherent antiviral activity.[292] Several other treatments have been proposed to suppress the principal symptoms of the disease, such as aspirin (shown to have little clinical effect in a study of 183 patients in China,[293] although pre-existing aspirin prescription was found to decrease mortality),[294] tocizumab,[295] an immunosuppressive, and colchicine, an anti-inflammatory molecule used to treat gout[256] (initial patient data indicate a positive response in mild to severe CoVID-19 cases).[296] Oxidative stress

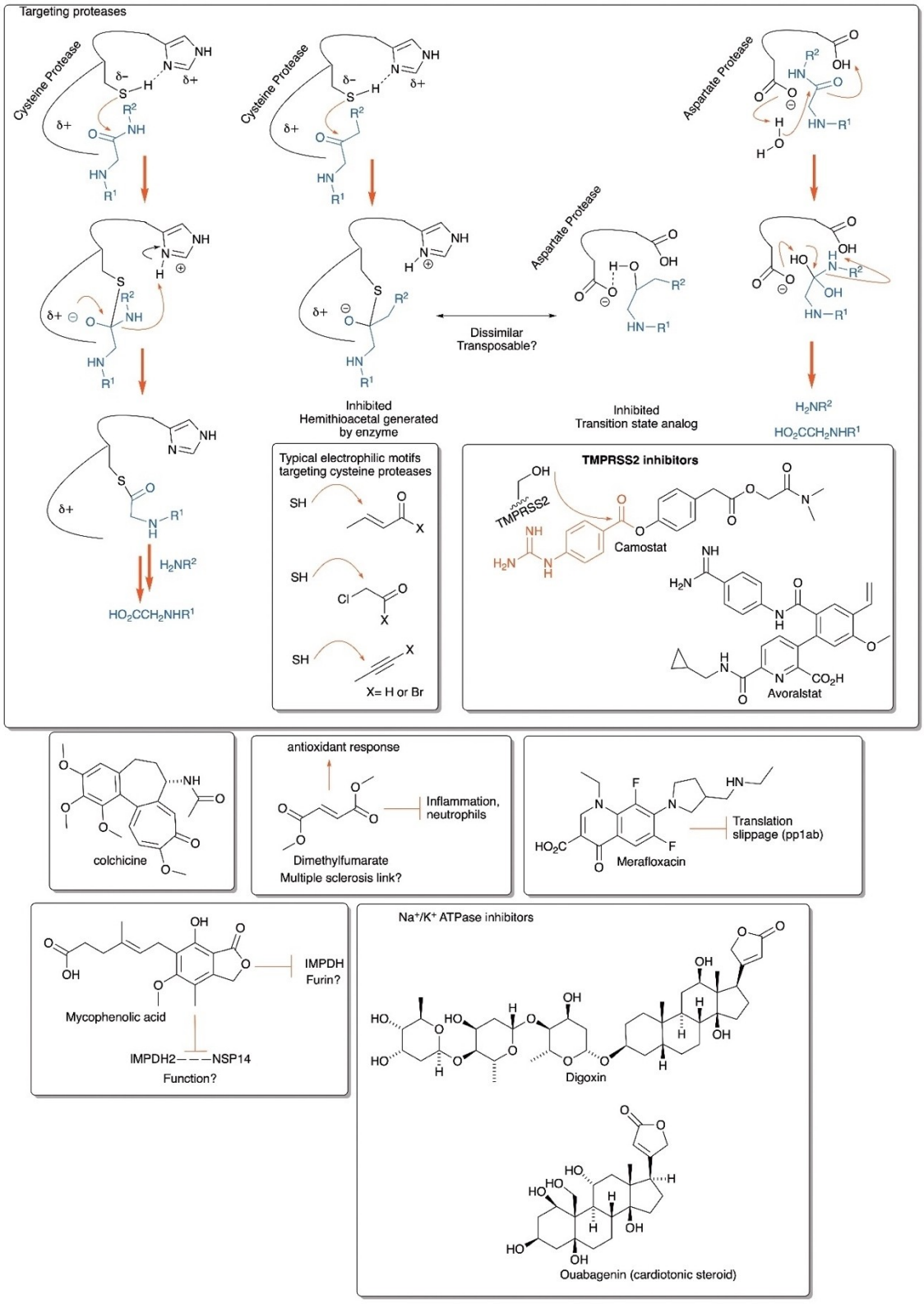

Figure 5. Top panel discusses similarities between aspartate and cysteine proteases. Below, other compounds discussed and their possible functions. Note in camostat, the red moiety becomes bound to the target protease (see red mechanistic arrow), and this moiety is identical to that in nafamostat (above).

is an important contributing factor to serious CoVID-19 cases and there are reports that CoVID-19 infection may suppress cellular antioxidant response.[297] In these respects, there has been proposed to be a link between multiple sclerosis (MS) and

severe CoVID-19 pathologies.[32] One interesting hypothesis to arise from this, albeit slightly tenuous, link is that dimethylfumarate (DMF; Tecfidera), a drug approved to treat relapsing MS, may be active against CoVID (Figure 5). This is because DMF is a known immunosuppressive drug that also stimulates cellular antioxidant response (likely not as part of its primary mechanism).[298] DMF is known to lower infiltrating neutrophil levels[299] and impede their function,[300] which could also help to suppress hyper inflammation.[301]

Oxygen/ozone therapy (another treatment known to promote antioxidant response) has also been proposed to help protect against ischemia-reperfusion injury and other pathological manifestations of severe CoVID-19.[302] Some reports on small cohorts of patients have reported numerical, but not statistically-significant effects of ozone on CoVID-19;[302] others, with similarly small numbers of people have reported positive effects.[303]

A recent study showed numerous pathways rewired upon CoVID-19 infection, including processing mRNA and several metabolic elements, including nucleic acid metabolism pathways. Inhibition of proteins identified in such pathways (albeit often by compounds not in clinical use) appeared to inhibit viral proliferation, although the effects on host cells were not thoroughly investigated. One very interesting observation is that approved inhibitors targeting inosine monophosphate dehydrogenase (IMPDH), the rate-limiting enzyme in guanine metabolism and a key immune-suppressive target, could suppress SARS-CoV-2 proliferation in cell culture models.[304] This observation is clearly worthy of further investigation, and ribavirin, a pleiotropic IMPDH-focused inhibitor with known antiviral properties, has entered clinical trials against CoVID-19.[305] Early reports were not encouraging.[306] Most recent reports indicate that ribavirin may affect CoVID-19 through lowering of ACE2 expression,[307] i.e., through an off-target effect or collateral damage. Nonetheless, several other IMPDH inhibitors exist,[308] and they are at different levels of development (see also below).

An analog of nafamostat,[309] camostat, an approved covalent inhibitor of TMPRSS2,[108] which cleaves the S-protein on cell entry, has also been proposed as an anti-CoVID-19 therapeutic. In early trials, admittedly with few participants, camostat decreased CoVID-19 severity; hydroxychloroquine was shown not to have similar effects in the same paper.[310] Further trials are ongoing.[311] Recently, avoralstat, an orphan drug against hereditary angioedema, was proposed to inhibit TMPRSS2. The quoted IC_{50}'s of avoralstat and camostat for purified TMPRSS2 (presumably derived by fitting to a tight-binding equation) were similar (single-digit nanomolar). Efficacy of the two drugs appears to be similar in mouse models,[312] although these may not be ideal for screening, given that the Axl-mediated import pathway is inactive.

Finally, early in the pandemic, it was proposed that some seemingly-unrelated viruses may share some similarity to CoVID-19 (e.g., 29% homology between the Macro domain of rubella and CoVID-19). Based on this, albeit relatively weak homology, and anticorrelation between mumps IgG titers and CoVID-19-related symptoms, the MMR vaccine was proposed to potentially help protect against CoVID-19.[313]

Choice of compounds to be evaluated in rapid screening clinical trials

Most studies above have focused on approved drugs, although some included molecules in "preclinical" evaluation. Given the situation, preclinical molecules were unlikely to lead to a timely solution, but, we believe that focusing solely on approved drugs was likely too narrow.[250] To explain this logic, we breakdown the trials process. Phase-0 (not a mandatory step, but becoming increasingly common in cancer research) is designed to validate that the intended target can be hit or that a drug can enter the blood stream in humans at low dose.[314] Phase-I usually focuses on gross tolerance/side effects and pharmacokinetics/pharmacodynamics. These two stages have little interest on drug efficacy, although if present, efficacy is recorded. Although side effects and toxicity etc., continue to be monitored, Phases-II and -III start to home in on the clinical benefits of the drug-candidate, in increasingly large cohorts. These trials are often first conducted vis-à-vis a control group of untreated or placebo patients (Phase-II), and later against approved therapies (Phase-III). Thus, in many cases, passing Phase-I clinical trials tells us a drug-candidate is in principal, safe, at least for acute exposure. Failure beyond this point indicates, in many instances, more about the application of the drug in a specific context, or contexts. In this way, looking at candidates that have entered Phase-II trials (incidentally, where the majority of drugs fail) and above (and even those withdrawn if not due to adverse side effects, or with manageable contraindications)[315] can help to broaden the scope of screening programs. Such experiments can be performed with knowledge of toxicity and having ideas about, e.g., tolerated doses, pharmacokinetics, in humans.[316] Such data and resources are highly exploitable.

Drug polypharmacology of effective compounds from clinical trials

It is intriguing that many of the molecules discussed above function through pleiotropic mechanisms. This property is certainly not uncommon in drug discovery. Even supposedly targeted drugs, like gleevec and Dasatinib, display multiple targets.[317] Nevertheless, the use of, for instance, repurposed IL-6 inhibitors, antibiotics or immunosuppressive drugs that *also* kill viruses is an appealing idea to use as treatment for a viral disease that is prone to causing pneumonia and immune catastrophes. Perhaps this is a hidden benefit of drug repurposing that deserves further investigation[318] and *could* stem from the necessary application of suboptimal drugs or just be serendipitous. Nevertheless, this concept could also be potentially incorporated into new drug design.[318]

The Pipeline

With an average cost of >1 billion USD and an average time of 12 years from preclinical testing to approval,[319] and a vaccine in the works, there seems to be little advantage in setting about a CoVID-19 drug *de novo*. However, many questions remain about vaccine efficacy, duration, and the effect that vaccination may have on CoVID-19 mutability, especially if the global vaccination response be uneven. Furthermore, there is the worrying trend of (retro)zoonotic events that have become more widespread and more deadly recently. Furthermore, given the similarity between zoonotic CoVs in general, it is possible that a drug targeting CoVID-19 may be active against future viruses (note: drugs active against much less homologous viruses and bacteria were deployed above). Thus, funding bodies, drug companies, and philanthropic organizations/communities seem to be set to provide sustained support to basic science research into CoVID-19 drugs post the pandemic. To sustain this interest, it is important that such drug studies focus on compounds targeting proteins in SARS-CoV-2 that are also general β-CoV drug targets with relatively low mutagenicity, i.e., targets that are likely to be retained amongst CoVs, rather than being quirks of SARS-CoV-2. Obviously one way to achieve this is to target human proteins necessary for the virus lifecycle,[320] although as we have seen the same human proteins are not always hijacked by different CoVs and some CoVs may be able to hijack several proteins redundantly. Either way, seeking broad-spectrum anti-CoV-drugs will give a better chance of developing drugs that are useful for the future. We accordingly suggest that future drug screening programs should be broad, focusing on screening several zoonotic CoVs, minimally MERS-CoV, SARS-CoV, and SARS-CoV2, for instance. This work must also gravitate to find medicinally relevant/realistic molecules that can provide results that allow hits to be moved forward quickly into trials. We cast a critical eye over the early fruits of such efforts. Obviously, some of the discussion in the section below is speculatory, and is intended for discussion among researchers versed in the art, and to stimulate their ideas only.

Obviously, it is critical that important targets be identified and screened for inhibitors. Drugging targets shown to be actively inhibited by effective repurposed compounds is one route towards new approved drugs. One alternative approach is to choose proteins or other functions that are not currently drugged but are necessary to the viral lifecycle. NSP14 is a likely candidate, especially, as noted above, its inhibition could synergize with other CoVID-19 drugs.[321] It should be noted that there are differences between NSP14 catalytic behaviors in terms of single- and double-stranded RNA cleavage between even very closely related CoV strains, which could affect inhibitor generality, although that is unknown.[322] Screens for inhibitors are already underway.[323]

One other common, and indeed unusual feature of several different viral translation programs is the −1-translation frameshift that occurs to create the ORF1ab gene product. Inhibitors of this process are also under development, fueled by a cell-based assay for translation slippage. One interesting lead from this screen is merafloxacin, a fluoroquinolone antibiotic. This molecule also shows inhibition of viral proliferation at low micromolar concentrations, albeit only in one cell culture model, which admittedly weakens the impact. Nevertheless, this is a particularly innovative and interesting approach[324] which should be expanded to more industry-level screens.

Branching the gap between naïve cell-culture models (poor mimics of CoV-mediated diseases) and human trails, especially as the population's immunity increases and case numbers drop will be important. Organoid models could fulfill this role. One study has shown proof of concept of organoid models for CoVID-19 (other SARS-like viruses were not examined) and performed preliminary screening. These models express the (standard) CoVID-19-susceptibility markers.[325] One (of several) interesting compounds emerging from an ensuing drug screen was mycophenolic acid (MPA), a non-nucleoside IMPDH inhibitor. In this instance, MPA was proposed to inhibit Furin expression (contrary to data from another IMPDH inhibitor, ribavirin, above). Such varied proposed mechanisms from two different IMPDH-inhibiting drugs is worrying. However, little work has been done to probe even if IMPDH activity is being hit by these compounds, e.g., by examining how exogenous guanosine can suppress viral inhibition. Nevertheless, MPA and ribavirin affect the interaction between NSP14 and IMPDH2 (one of the two isoforms of human IMPDH),[326] offering a potential IMPDH-related common mode of action for both drugs. However, it is unclear to us if such an interaction would even be beneficial for the virus; similar interactions between deoxynucleotide synthesis machinery and proofreading and damage-response enzymes have been proposed for the human replisome,[327] but functional evidence is weak. Of course, NSP14 could affect non-canonical modes of IMPDH or have an unexpected mechanism, which is also worthy of interest.[328] Finally, MPA selectively targets lymphocytes,[329] which could be an issue as lymphopenia is a marker for severe CoVID-19 and could contribute to cytokine storm.[330]

Nanobodies

Nanobodies, small, antibody-like molecules that are soluble and stable and can be readily engineered and mass produced, are a growing area of research. Several research efforts have been directed at discovering CoVID-19 neutralizing nanobodies. As the interaction between the nanobody and the virus is likely to be in blood, these studies have focused on blocking the first step of viral infection, through interaction with the S-protein, or blocking viral escape. Several of llama-derived nanobodies (binding to different epitopes) were reported to bind with below 500 nM affinity to the S-protein. A few of these nanobodies bound with picomolar affinity to an inactive (down) conformation of the S-protein at the receptor-binding domain, a region of high conservation believed to be a good target for prophylactics.[331] These nanobodies were shown to be effective in a cell-culture infection assay, although disappointingly no animal model data, or other advanced testing results, were shown. Such experiments are important as the immunogenic-

ity/tolerability of the nanobodies is unknown and cell-based assays have not been great predicters of CoVID-19 treatment efficacies. The report points out that identifying multiple epitopes as targets for nanobodies may help overcome resistance, which is an important consideration. Similar nanobodies were discovered from a yeast display screen.[332]

Natural products

Natural-product screening has also been undertaken. Natural products are no less easy to get approved as a drug than a man-made one, and oftentimes, efficacies of plant extracts used in traditional medicines are not necessarily ascribable to a single molecule alone.[333] Nevertheless, despite a recent downturn,[334] this group of molecules, and those that nature has inspired, makes up around 30% of all approved drugs.[333] One study reported that several cardiac glycosides (e.g. digoxin) exhibited nanomolar inhibition of CoVID-19 infection in a cell-culture model.[335] These are inhibitors of Na^+/K^+-ATPase, which is a target of many drugs and natural products, including cardiotonic steroids, some of the most widely used molecules in medicine.[336] These molecules also have anti-inflammatory properties along with several other complex behaviors that render them worth bearing in consideration in screening programs.[337]

Other screening efforts have included the use of DNA-encoded libraries;[338] cyclic peptides;[339] peptide aldehyde inhibitors of M^{PRO} or PL^{PRO};[340] and large-scale fragment screening by combined MS and crystallography. One such screen identified the *N*-chloroacetyl-*N*′-sulfonamidopiperazine or *N*-chlorocetylanilene motifs as frequent hits.[341] It also unveiled a 3-bromopropargyl pharmacophore as an M^{PRO} inhibiting motif. This unit is reminiscent of the propargyl reactive pharmacophore in some deubiquitinating enzyme inhibitors[342] although it is likely more electrophilic and generally more reactive. Nevertheless, based on this observation (and the fact that SARS-CoV-2 PL^{PRO} can bind to ubiquitin propargylamide),[343] propargyl-functionalized peptides that bind with high affinity to the M^{PRO} active site, could be worth investigating as low-reactivity irreversible M^{PRO} inhibitors. Despite opening some leads, this study unfortunately overall provided little in the way of toxicity studies, off-target effects, and focused on warheads that have not traditionally been viewed positively due to their high reactivity and proclivity to create permanently modified states semi-indiscriminately.[344]

Using patients to predict therapies

The flip side of the CoVID-19 drug-discovery pipeline examines genetic or expression-level-based causes of pathologies to predict novel drug usage. Such an approach is an extension, or perhaps inversion, of the concept of personalized medicine.[345] Of course, these data cannot aid in design of drugs *de novo*, but can aid repurposing, or guide drug-discovery efforts in the future. In some respects, such studies give more contextual data than what could be found from traditional drug-screening data, which are usually conducted in naïve models. We already discussed above how mutations in 3p21.31 leads to sensitization to CoVID-19. Other studies have uncovered other genetic mutations that predispose patients to CoVID-19, such as mutations impinging on Type-1 interferon signaling.[346]

Recent GWAS studies have elucidated new regions of patient susceptibility linked to severe CoVID-19. These studies were in part enabled by the large number of CoVID-19 cases, and the homogeneity observed amongst the most severe CoVID-19 cases.[347] One recent study analyzed data from 1676 individuals (of European descent) from across the UK suffering from severe CoVID-19 and sought to identify genetic signatures leading to susceptibility using GWAS. These individuals were matched to a control cohort of ancestry-matched individuals from the UK Biobank (five controls were examined per test subject, with controls known to have had a positive CoVID-19 test excluded).[348] These data identified 15 independent regions with significance at the $p < 5 \times 10^{-8}$ level. Several of the genes in these regions have been implicated in either early or severe CoVID-19. Intriguingly, high expression of interferon receptor subunit IFNAR2 conferred protection against severe CoVID-19. However, exogenous treatment with interferon did not reduce mortality in clinical trials.[349] This failure could reflect incorrect timing of dose, but nonetheless highlights that GWAS, despite being derived from data collected in a medical context, lack the ability to inform on the stage of the disease at which mutations confer predisposition/protection to the disease. This analysis was also backed up by analysis of transcription-wide associations (TWAS), which identified 5 transcripts, including several located around 3p21.31, which was also identified in the GWAS analysis, consistent with previous studies.[105] Such studies should of course incorporate/be incorporated into GWAS from SARS-CoV/MERS-CoV patients to broaden the scope of this research.

A commitment to introspective science reporting and collaborative discussion

When we look back on science coming out of 2020/2021, and likely subsequent years, it will be dominated by CoVID-19-related research. This is not unsurprising nor without precedent: there was indeed a spike in PL^{PRO} inhibitor design and other aspects of SARS-CoV after the first SARS infection; similar research initiatives have happened in the wake of new drug approvals, as occurred post the approval of paclitaxel.[350] What was different during this epidemic, in part because of the confluence of confinement measures, the general fear about CoVID-19 contraction, and the necessary blending of politicians and scientists to combat the disease, was that research actively played out almost entirely in public in real time. Such events are not without precedent,[351] but the scale and temporal contraction was on the whole at a new level.[352] Indeed, swathes of scientific data were released through open-access journals and even group websites that rapidly became news

headlines. Of course, such trying times are, in fact, when peer reviewing, correct use of trial design/statistics/planning[353] and our faith in the scientific process and the drug approval pipeline should be highest. These lessons should be learned by scientists, and indeed also politicians and journalists alike.[354] Better education of non-scientists in the scientific method and logic may help to limit these issues.

Obviously, with current practices and standards (many of which promote release of research material prior to peer review, possibly to allow scientists to rapidly elaborate on data),[355] it is difficult perhaps even impossible to prevent release of unreviewed work globally. However, the onus is on all people involved in scientific research (including doctors, field scientists, laboratory researchers etc.), to solicit the opinion of our peers prior to releasing information. Such checkpoints are critical because in situations such as a pandemic, the traditional scientific validation process may also lag behind the public's desire to act on published data. Certainly, scientists must be (re) trained to be more self-critical, and as reviewers and mentors we must encourage open criticism amongst our mentees *and* papers we review. In such a way, non-experts reading preprints etc. can have more context. One additional means to promote more introspective practices could be by establishing tangible ties (e.g. *scheduled* regular joint seminars, prereview meetings prior to major publications, and sharing common databases) between different departments, across different regions and countries in core response units (e.g. infectious diseases; bioweapons; emergency medicine). These links could in turn be used to orchestrate and standardize point of care responses, treatments, and trials in response to global or more widespread situations, more effectively than ad hoc initiatives, while being more flexible than larger governmental schemes. Such networks could be triggered early in emergency situations to ensure coordination of research etc. We see that such multilateral collaborations are emerging, and further think that the ties so formed must be maintained and broadened.[356] However, it is noteworthy that construction of so-called Fangcang hospitals in China, required a collaboration between a huge number of disciplines. Our considerations of what scientific collaboration means thus needs to be reconsidered.[45]

CoVID-19 targeting protection strategies?

In terms of mortality, CoVID-19 is a disease that targets the elderly highly selectively (89% of deaths in the over 65 age group). This trend holds up more or less independent of R value, geography,[357] and other factors.[358] In other words, for the vast majority of global working age people, little danger was posed from CoVID-19. Although established early in our understanding of the virus, this observation appears to have curiously been leveraged little in terms of guiding government or state responses. Although a strategy targeted towards shielding the elderly was advocated by a series of academics in the UK,[359] it was described as age-based apartheid by one National Health Service official.[360] It is true that the elderly are significantly prone to mental and physical issues associated with extreme isolation,[361] a situation referred to as the CoVID-19 Connectivity Paradox.[362]

Age-related mortality is very common amongst respiratory diseases, often with large swathes of the populous seemingly untouched by the disease. Hence such planning likely needs to be seriously considered in the future. We appreciate that the following discussion is weighted to a more Western perspective. However, the considerations could readily apply, in some respects, to all countries. High mortality in the elderly is common in many respiratory diseases. This means that we need to consider foundations for future confinement protocols (which are likely to remain the bulk of response to epidemics and pandemics) by providing resources for the elderly. These could include promoting education into the use of the internet, including government incentives to promote elderly people to go online (and use internet resources safely), as well as promoting engagement in remote access to clubs, religious/social meetings, and the like for the elderly. Contrary to CoVID-19, many respiratory diseases show substantial child mortality, with young to middle aged adults being spared.[363] Thus, provision certainly needs to be made for the protection of children from such pandemics as well; this could include ensuring that all children continue to have mandatory access to remote learning post the pandemic, and implementing remote learning as a necessary part of the curriculum.

On the other hand, The Spanish Flu of 1918 exhibited a trefoil or so-called w-shaped mortality. The three 3 principal peaks of mortality centered on the young, the very old *and those around 28 years of age.* The precise reasons for the susceptibility of young adults are not absolutely clear, but it is critical to appreciate that should such a profile have been displayed by CoVID-19, it would have likely pushed the impact of coronavirus on medical and other response teams way beyond breaking point.[364] This would have been particularly acute in more developing countries where the population is younger than in the Western world. One growing hypothesis for the unusual susceptibility of young adults to the Spanish Flu is original antigenic sin. In some respects this hypothesis is like vaccination, only its effect is a misguided immune response, leading to a weakening to exposure to a pathogen: once young people who had been affected by Russian Flu (another global virus that infected many people around 28 years prior to Spanish Flu) at a particular stage early in their lives, were exposed to the Spanish Flu they created a large number of T-cells targeted to Russian Flu and whose efficacy against Spanish Flu was low. This patterned response allowed the Spanish Flu to overwhelm these conditioned subjects, promoting their death. This is not an unusual behavior to different virus strains.[365] Given the severity and huge scale of the current pandemic, these considerations should be born in mind in planning: the CoVID-19 pandemic should not become the "Russian Flu". It should be noted that children can show positive tests for CoVID-19[366] and appear to be able to mount a strong immune response to CoVID-19[367] and that an outbreak of a CoV-related disease has arisen 3 times in the past 20 years. We encourage the readers to consider how department and governmental

policies may have differed as a function of these different morbidity profiles, if at all.

Conclusion

CoVID-19 was and continues to be a huge challenge. The huge research effort across a huge number of disciplines, as witnessed by this review, and many others, shows the scientific community's great positive impact on this disease. Armed with this research, and lessons we can learn from the way the community responded, we should be better prepared for future issues.

Conflict of Interest

The authors declare no conflict of interest.

[1] "WHO | Update 49 – SARS case fatality ratio, incubation period," can be found under https://www.who.int/csr/sarsarchive/2003_05_07a/en/.
[2] S. L. Wu, A. N. Mertens, Y. S. Crider, A. Nguyen, N. N. Pokpongkiat, S. Djajadi, A. Seth, M. S. Hsiang, J. M. Colford, A. Reingold, B. F. Arnold, A. Hubbard, J. Benjamin-Chung, *Nat. Commun.* **2020**, *11*, 4507.
[3] "Plague," can be found under https://www.who.int/news-room/fact-sheets/detail/plague.
[4] P. C. Y. Woo, S. K. P. Lau, Y. Huang, K.-Y. Yuen, *Exp. Biol. Med. (Maywood NJ U. S.)* **2009**, *234*, 1117–1127.
[5] E. Afonso, P. Tournant, J.-C. Foltête, P. Giraudoux, P.-E. Baurand, S. Roué, V. Canella, D. Vey, R. Scheifler, *Global Ecol. Conserv.* **2016**, *8*, 123–137.
[6] K. KupferschmidtOct. 30, 2013, 2:15 Pm, "Bats May Be Carrying the Next SARS Pandemic," can be found under https://www.sciencemag.org/news/2013/10/bats-may-be-carrying-next-sars-pandemic, **2013**.
[7] X.-D. Lin, W. Wang, Z.-Y. Hao, Z.-X. Wang, W.-P. Guo, X.-Q. Guan, M.-R. Wang, H.-W. Wang, R.-H. Zhou, M.-H. Li, G.-P. Tang, J. Wu, E. C. Holmes, Y.-Z. Zhang, *Virology* **2017**, *507*, 1–10.
[8] M. T. Valitutto, O. Aung, K. Y. N. Tun, M. E. Vodzak, D. Zimmerman, J. H. Yu, Y. T. Win, M. T. Maw, W. Z. Thein, H. H. Win, J. Dhanota, V. Ontiveros, B. Smith, A. Tremeau-Brevard, T. Goldstein, C. K. Johnson, S. Murray, J. Mazet, *PLoS One* **2020**, *15*, e0230802.
[9] J. Nziza, T. Goldstein, M. Cranfield, P. Webala, O. Nsengimana, T. Nyatanyi, A. Mudakikwa, A. Tremeau-Bravard, D. Byarugaba, J. C. Tumushime, I. E. Mwikarago, I. Gafarasi, J. Mazet, K. Gilardi, *Ecohealth* **2020**, *17*, 152–159.
[10] J. Qiu, "How China's 'Bat Woman' Hunted Down Viruses from SARS to the New Coronavirus," DOI 10.1038/scientificamerican0620-24can be found under https://www.scientificamerican.com/article/how-chinas-bat-woman-hunted-down-viruses-from-sars-to-the-new-coronavirus1/.
[11] K. G. Andersen, A. Rambaut, W. I. Lipkin, E. C. Holmes, R. F. Garry, *Nat. Med.* **2020**, *26*, 450–452.
[12] W. Yang, S. Kandula, M. Huynh, S. K. Greene, G. V. Wye, W. Li, H. T. Chan, E. McGibbon, A. Yeung, D. Olson, A. Fine, J. Shaman, *The Lancet Infectious Diseases* **2020**, *0*, DOI 10.1016/S1473-3099(20)30769–6.
[13] N. P. A. S. Johnson, J. Mueller, *Bull. Hist. Med.* **2002**, *76*, 105–115.
[14] G. Kolata, *The New York Times* **2020**.
[15] L. Di Domenico, G. Pullano, C. E. Sabbatini, P.-Y. Boëlle, V. Colizza, *BMC Med.* **2020**, *18*, 240.
[16] A. Barber, J. Griffin, M. Casey, Á. B. Collins, E. A. Lane, Q. T. Bosch, M. D. Jong, D. M. Evoy, A. W. Byrne, C. G. McAloon, F. Butler, K. Hunt, S. J. More, *medRxiv* **2020**, 2020.07.28.20163535.
[17] M. A. Billah, M. M. Miah, M. N. Khan, *PLoS One* **2020**, *15*, e0242128.
[18] J. Liu, W. Xie, Y. Wang, Y. Xiong, S. Chen, J. Han, Q. Wu, *Int. J. Surg. Pathol.* **2020**, *81*, 1–8.
[19] S. Choi, E. Jung, B. Y. Choi, Y. J. Hur, M. Ki, *J. Hosp. Infect.* **2018**, *99*, 162–168.
[20] Y. Liu, A. A. Gayle, A. Wilder-Smith, J. Rocklöv, *Journal of Travel Medicine* **2020**, *27*, DOI 10.1093/jtm/taaa021.
[21] E. Petersen, M. Koopmans, U. Go, D. H. Hamer, N. Petrosillo, F. Castelli, M. Storgaard, S. Al Khalili, L. Simonsen, *The Lancet Infectious Diseases* **2020**, *20*, e238–e244.
[22] B. Gates, *N. Engl. J. Med.* **2020**, *382*, 1677–1679.
[23] M. Cevik, M. Tate, O. Lloyd, A. E. Maraolo, J. Schafers, A. Ho, *The Lancet Microbe* **2021**, *2*, e13–e22.
[24] B. Nogrady, *Nature* **2020**, *587*, 534–535.
[25] M. Gandhi, D. S. Yokoe, D. V. Havlir, *N. Engl. J. Med.* **2020**, *328*, 2158–2160. DOI 10.1056/NEJMe2009758.
[26] A. M. Pollock, J. Lancaster, *BMJ Glob. Health* **2020**, *371*, m4851.
[27] N. Le Bert, A. T. Tan, K. Kunasegaran, C. Y. L. Tham, M. Hafezi, A. Chia, M. H. Y. Chng, M. Lin, N. Tan, M. Linster, W. N. Chia, M. I.-C. Chen, L.-F. Wang, E. E. Ooi, S. Kalimuddin, P. A. Tambyah, J. G.-H. Low, Y.-J. Tan, A. Bertoletti, *Nature* **2020**, *584*, 457–462.
[28] J. E. Millar, L. Neyton, S. Seth, J. Dunning, L. Merson, S. Murthy, C. D. Russell, S. Keating, M. Swets, C. H. Sudre, T. D. Spector, S. Ourselin, C. J. Steves, J. Wolf, I. Investigators, A. B. Docherty, E. M. Harrison, P. J. Openshaw, M. G. Semple, J. K. Baillie, *medRxiv* **2020**, 2020.08.14.20168088.
[29] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, S. Liu, P. Zhao, H. Liu, L. Zhu, Y. Tai, C. Bai, T. Gao, J. Song, P. Xia, J. Dong, J. Zhao, F.-S. Wang, *The Lancet Respiratory Medicine* **2020**, *8*, 420–422.
[30] Q. Ruan, K. Yang, W. Wang, L. Jiang, J. Song, *Intensive Care Med.* **2020**, *46*, 846–848.
[31] W. Jacobs, M. Lammens, A. Kerckhofs, E. Voets, E. V. San, S. V. Coillie, C. Peleman, M. Mergeay, S. Sirimsi, V. Matheeussen, H. Jansens, I. Baar, T. V. Berghe, P. G. Jorens, *ESC Heart Failure* **2020**, *7*, 3772–3781.
[32] C. A. Timpani, E. Rybalka, *Pharmaceuticals* **2021**, *14*, 15.
[33] L. Kuri-Cervantes, M. Betina Pampena, W. Meng, A. M. Rosenfeld, C. A. G. Ittner, A. R. Weisman, R. Agyekum, D. Mathew, A. E. Baxter, L. Vella, O. Kuthuru, S. Apostolidis, L. Bershaw, J. Dougherty, A. R. Greenplate, A. Pattekar, J. Kim, N. Han, S. Gouma, M. E. Weirick, C. P. Arevalo, M. J. Bolton, E. C. Goodwin, E. M. Anderson, S. E. Hensley, T. K. Jones, N. S. Mangalmurti, E. T. Luning Prak, E. J. Wherry, N. J. Meyer, M. R. Betts, bioRxiv https://www.biorxiv.org/content/10.1101/2020.05.18.101717v1.
[34] B. Ghebrehiwet, E. I. Peerschke, *J. Clin. Invest.* **2020**, *130*, 5674–5676.
[35] H. Wood, *Nature Reviews Neurology* **2020**, *16*, 403–403.
[36] M. A. Chary, D. L. Overbeek, A. Papadimoulis, A. Sheroff, M. M. Burns, *Clin. Toxicol.* **2020**, *0*, 1–6.
[37] "China Has Built Over 20 Mass Quarantine Centers For Coronavirus Patients In Wuhan," can be found under https://www.npr.org/2020/02/24/808995258/china-has-built-over-20-mass-quarantine-centers-for-coronavirus-patients-in-wuha.
[38] "'Liberation' as Wuhan's coronavirus lockdown ends after 76 days," can be found under http://www.theguardian.com/world/2020/apr/07/liberation-as-wuhans-coronavirus-lockdown-ends-after-76-days, **2020**.
[39] A. Sandford, "Coronavirus: Half of humanity on lockdown in 90 countries," can be found under https://www.euronews.com/2020/04/02/coronavirus-in-europe-spain-s-death-toll-hits-10-000-after-record-950-new-deaths-in-24-hou, **2020**.
[40] The Lancet, *The Lancet* **2020**, *395*, 1315.
[41] N. Haider, A. Y. Osman, A. Gadzekpo, G. O. Akipede, D. Asogun, R. Ansumana, R. J. Lessells, P. Khan, M. M. A. Hamid, D. Yeboah-Manu, L. Mboera, E. H. Shayo, B. T. Mmbaga, M. Urassa, D. Musoke, N. Kapata, R. A. Ferrand, P.-C. Kapata, F. Stigler, T. Czypionka, A. Zumla, R. Kock, D. McCoy, *BMJ Glob. Health* **2020**, *5*, e003319.
[42] P. C. Hallal, *The Lancet* **2021**, *397*, 373–374.
[43] K. Leung, M. H. Shum, G. M. Leung, T. T. Lam, J. T. Wu, *Eurosurveillance* **2021**, *26*, 2002106.
[44] J. W. Tang, O. T. R. Toovey, K. N. Harvey, D. D. S. Hui, *J. Infect.* **2021**, *82*, e8–e10. DOI 10.1016/j.jinf.2021.01.007.
[45] K.-W. Wang, J. Gao, X.-X. Song, J. Huang, H. Wang, X.-L. Wu, Q.-F. Yuan, X.-S. Li, F. Cheng, Y. Cheng, *One Health* **2020**, *10*, 100167.
[46] T. Burki, *The Lancet Infectious Diseases* **2020**, *20*, 1240–1241.
[47] Q. T. Angelerio, ctypa pestilentis status Algheriae Sardiniae. Ad Ill. D. D. Michaelem A. Moncada Regni Proregem etc. Calari: typ.Nic. Canelles per Franc.Guarnerium; **1588**.
[48] P. A. Mackowiak, P. S. Sehdev, *Clin. Infect. Dis.* **2002**, *35*, 1071–1072.
[49] N. Saeed, A.B ader, T. Y. Al-Naffouri, M. Alouini, Front. Comms. Net., **2020**, https://doi.org/10.3389/frcmn.2020.566853.
[50] O. B. Da'ar, M. Haji, H. Jradi, *The International Journal of Health Planning and Management* **2020**, *35*, 1240–1245.
[51] M. Tilli, P. Olliaro, F. Gobbi, Z. Bisoffi, A. Bartoloni, L. Zammarchi, *Journal of Travel Medicine* **2021**, *28*, DOI 10.1093/jtm/taaa179.

[52] O. M. Al-Quteimat, A. M. Amer, *Am. J. Clin. Oncol.* **2020**, *43*, 452–455.
[53] S. Amendola, V. Spensieri, M. P. Hengartner, R. Cerutti, *British Journal of Health Psychology* DOI https://doi.org/10.1111/bjhp.12502.
[54] X. Xie, K. G. Lokugamage, X. Zhang, M. N. Vu, A. E. Muruato, V. D. Menachery, P.-Y. Shi, *Nature Protocols* **2021**, 1–24.
[55] M. Chiara, A. M. D'Erchia, C. Gissi, C. Manzari, A. Parisi, N. Resta, F. Zambelli, E. Picardi, G. Pavesi, D. S. Horner, G. Pesole, *Briefings Bioinf.* **2020**, DOI 10.1093/bib/bbaa297.
[56] A. Tárnok, *Cytometry Part A* **2020**, *97*, 215–216.
[57] M. M. Lai, C. L. Liao, Y. J. Lin, X. Zhang, *Infect. Agents Dis.* **1994**, *3*, 98–105.
[58] J. A. Jaimes, N. M. André, J. S. Chappie, J. K. Millet, G. R. Whittaker, *J. Mol. Biol.* **2020**, *432*, 3309–3325.
[59] R. Lu, X. Zhao, J. Li, P. Niu, B. Yang, H. Wu, W. Wang, H. Song, B. Huang, N. Zhu, Y. Bi, X. Ma, F. Zhan, L. Wang, T. Hu, H. Zhou, Z. Hu, W. Zhou, L. Zhao, J. Chen, Y. Meng, J. Wang, Y. Lin, J. Yuan, Z. Xie, J. Ma, W. J. Liu, D. Wang, W. Xu, E. C. Holmes, G. F. Gao, G. Wu, W. Chen, W. Shi, W. Tan, *The Lancet* **2020**, *395*, 565–574.
[60] P. Zhou, X.-L. Yang, X.-G. Wang, B. Hu, L. Zhang, W. Zhang, H.-R. Si, Y. Zhu, B. Li, C.-L. Huang, H.-D. Chen, J. Chen, Y. Luo, H. Guo, R.-D. Jiang, M.-Q. Liu, Y. Chen, X.-R. Shen, X. Wang, X.-S. Zheng, K. Zhao, Q.-J. Chen, F. Deng, L.-L. Liu, B. Yan, F.-X. Zhan, Y.-Y. Wang, G.-F. Xiao, Z.-L. Shi, *Nature* **2020**, *579*, 270–273.
[61] Y. Wang, J.-M. Mao, G.-D. Wang, Z.-P. Luo, L. Yang, Q. Yao, K.-P. Chen, *Sci. Rep.* **2020**, *10*, 12331.
[62] S. Ricagno, M.-P. Egloff, R. Ulferts, B. Coutard, D. Nurizzo, V. Campanacci, C. Cambillau, J. Ziebuhr, B. Canard, *PNAS* **2006**, *103*, 11892–11897.
[63] E. Minskaia, T. Hertzig, A. E. Gorbalenya, V. Campanacci, C. Cambillau, B. Canard, J. Ziebuhr, *PNAS* **2006**, *103*, 5108–5113.
[64] Y. Chen, H. Cai, J. Pan, N. Xiang, P. Tien, T. Ahola, D. Guo, *PNAS* **2009**, *106*, 3484–3489.
[65] F. Ferron, L. Subissi, A. T. S. D. Morais, N. T. T. Le, M. Sevajol, L. Gluais, E. Decroly, C. Vonrhein, G. Bricogne, B. Canard, I. Imbert, *PNAS* **2018**, *115*, E162–E171.
[66] M. Bouvet, C. Debarnot, I. Imbert, B. Selisko, E. J. Snijder, B. Canard, E. Decroly, *PLoS Pathog.* **2010**, *6*, e1000863.
[67] E. J. Snijder, P. J. Bredenbeek, J. C. Dobbe, V. Thiel, J. Ziebuhr, L. L. M. Poon, Y. Guan, M. Rozanov, W. J. M. Spaan, A. E. Gorbalenya, *J. Mol. Biol.* **2003**, *331*, 991–1004.
[68] S. Angeletti, D. Benvenuto, M. Bianchi, M. Giovanetti, S. Pascarella, M. Ciccozzi, *J. Med. Virol.* **2020**, *92*, 584–588.
[69] E. C. Smith, H. Blanc, M. Vignuzzi, M. R. Denison, *PLoS Pathog.* **2013**, *9*, e1003565.
[70] S. Angeletti, D. Benvenuto, M. Bianchi, M. Giovanetti, S. Pascarella, M. Ciccozzi, *J. Med. Virol.* **2020**, *92*, 584–588.
[71] "Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations – SARS-CoV-2 coronavirus / nCoV-2019 Genomic Epidemiology," can be found under https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563, **2020**.
[72] T. N. Starr, A. J. Greaney, S. K. Hilton, D. Ellis, K. H. D. Crawford, A. S. Dingens, M. J. Navarro, J. E. Bowen, M. A. Tortorici, A. C. Walls, N. P. King, D. Veesler, J. D. Bloom, *Cell* **2020**, *182*, 1295–1310.e20.
[73] E. C. Freundt, L. Yu, C. S. Goldsmith, S. Welsh, A. Cheng, B. Yount, W. Liu, M. B. Frieman, U. J. Buchholz, G. R. Screaton, J. Lippincott-Schwartz, S. R. Zaki, X.-N. Xu, R. S. Baric, K. Subbarao, M. J. Lenardo, *J. Virol.* **2010**, *84*, 1097–1109.
[74] A. E. Firth, *J. Gen. Virol.* **2020**, *101*, 1085–1089.
[75] L. Miorin, T. Kehrer, M. T. Sanchez-Aparicio, K. Zhang, P. Cohen, R. S. Patel, A. Cupic, T. Makio, M. Mei, E. Moreno, O. Danziger, K. M. White, R. Rathnasinghe, M. Uccellini, S. Gao, T. Aydillo, I. Mena, X. Yin, L. Martin-Sancho, N. J. Krogan, S. K. Chanda, M. Schotsaert, R. W. Wozniak, Y. Ren, B. R. Rosenberg, B. M. A. Fontoura, A. García-Sastre, *PNAS* **2020**, *117*, 28344–28354.
[76] X. Lei, X. Dong, R. Ma, W. Wang, X. Xiao, Z. Tian, C. Wang, Y. Wang, L. Li, L. Ren, F. Guo, Z. Zhao, Z. Zhou, Z. Xiang, J. Wang, *Nat. Commun.* **2020**, *11*, 3810.
[77] R. Cagliani, D. Forni, M. Clerici, M. Sironi, *Infect. Genet. Evol.* **2020**, *83*, 104353.
[78] Z. A. Nizamudeen, E.-R. Xu, V. Karthik, M. Halawa, K. P. Arkill, A. M. Jackson, D. O. Bates, J. Emsley, *Biosci. Rep.* **2021**, *41*, DOI 10.1042/BSR20203837.
[79] H. Xia, Z. Cao, X. Xie, X. Zhang, J. Y.-C. Chen, H. Wang, V. D. Menachery, R. Rajsbaum, P.-Y. Shi, *Cell Rep.* **2020**, *33*, 108234.
[80] S. R. Schaecher, J. M. Mackenzie, A. Pekosz, *J. Virol.* **2007**, *81*, 718–731.
[81] B. E. Young, S.-W. Fong, Y.-H. Chan, T.-M. Mak, L. W. Ang, D. E. Anderson, C. Y.-P. Lee, S. N. Amrun, B. Lee, Y. S. Goh, Y. C. F. Su, W. E. Wei, S. Kalimuddin, L. Y. A. Chai, S. Pada, S. Y. Tan, L. Sun, P. Parthasarathy, Y. Y. C. Chen, T. Barkham, R. T. P. Lin, S. Maurer-Stroh, Y.-S. Leo, L.-F. Wang, L. Renia, V. J. Lee, G. J. D. Smith, D. C. Lye, L. F. P. Ng, *The Lancet* **2020**, *396*, 603–611.
[82] F. Pereira, *Infect. Genet. Evol.* **2020**, *85*, 104525.
[83] Y. C. F. Su, D. E. Anderson, B. E. Young, M. Linster, F. Zhu, J. Jayakumar, Y. Zhuang, S. Kalimuddin, J. G. H. Low, C. W. Tan, W. N. Chia, T. M. Mak, S. Octavia, J.-M. Chavatte, R. T. C. Lee, S. Pada, S. Y. Tan, L. Sun, G. Z. Yan, S. Maurer-Stroh, I. H. Mendenhall, Y.-S. Leo, D. C. Lye, L.-F. Wang, G. J. D. Smith, *mBio* **2020**, *11*, DOI 10.1128/mBio.01610-20.
[84] C. Meier, A. R. Aricescu, R. Assenberg, R. T. Aplin, R. J. C. Gilbert, J. M. Grimes, D. I. Stuart, *Structure* **2006**, *14*, 1157–1165.
[85] C.-S. Shi, H.-Y. Qi, C. Boularan, N.-N. Huang, M. Abu-Asab, J. H. Shelhamer, J. H. Kehrl, *The Journal of Immunology* **2014**, *193*, 3080–3089.
[86] A. D. Andres, Y. Feng, A. R. Campos, J. Yin, C.-C. Yang, B. James, R. Murad, H. Kim, A. J. Deshpande, D. E. Gordon, N. Krogan, R. Pippa, Z. A. Ronai, *bioRxiv* **2020**, 2020.08.18.256776.
[87] J.-Y. Lam, C.-K. Yuen, J. D. Ip, W.-M. Wong, K. K.-W. To, K.-Y. Yuen, K.-H. Kok, *Emerging Microbes & Infections* **2020**, *9*, 2685–2696.
[88] K. Pancer, A. Milewska, K. Owczarek, A. Dabrowska, M. Kowalski, P. P. Łabaj, W. Branicki, M. Sanak, K. Pyrc, *PLoS Pathog.* **2020**, *16*, e1008959.
[89] C.-S. Shi, N. R. Nabar, N.-N. Huang, J. H. Kehrl, *Cell Death Dis.* **2019**, *5*, 1–12.
[90] K.-L. Siu, K.-S. Yuen, C. Castano-Rodriguez, Z.-W. Ye, M.-L. Yeung, S.-Y. Fung, S. Yuan, C.-P. Chan, K.-Y. Yuen, L. Enjuanes, D.-Y. Jin, *The FASEB Journal* **2019**, *33*, 8865–8877.
[91] C. Castaño-Rodriguez, J. M. Honrubia, J. Gutiérrez-Álvarez, M. L. DeDiego, J. L. Nieto-Torres, J. M. Jimenez-Guardeño, J. A. Regla-Nava, R. Fernandez-Delgado, C. Verdia-Báguena, M. Queralt-Martín, G. Kochan, S. Perlman, V. M. Aguilella, I. Sola, L. Enjuanes, *mBio* **2018**, *9*, DOI 10.1128/mBio.02325–17.
[92] C. J. Michel, C. Mayer, O. Poch, J. D. Thompson, *Virol. J.* **2020**, *17*, 131.
[93] Y. Konno, I. Kimura, K. Uriu, M. Fukushi, T. Irie, Y. Koyanagi, D. Sauter, R. J. Gifford, S. Nakagawa, K. Sato, *Cell Rep.* **2020**, *32*, 1018185.
[94] C. W. Nelson, Z. Ardern, T. L. Goldberg, C. Meng, C.-H. Kuo, C. Ludwig, S.-O. Kolokotronis, X. Wei, *eLife* **2020**, *9*, e59633.
[95] S. H. Rosenthal, R. M. Kagan, A. Gerasimova, B. Anderson, D. Grover, M. Hua, Y. Liu, R. Owen, F. Lacbawan, *bioRxiv* **2020**, 2020.12.10.418855.
[96] J. K. Taylor, C. M. Coleman, S. Postel, J. M. Sisk, J. G. Bernbaum, T. Venkataraman, E. J. Sundberg, M. B. Frieman, *J. Virol.* **2015**, *89*, 11820–11833.
[97] T. G. Flower, C. Z. Buffalo, R. M. Hooy, M. Allaire, X. Ren, J. H. Hurley, *PNAS* **2021**, *118*, e2021785118. DOI 10.1073/pnas.2021785118.
[98] J.-Y. Li, C.-H. Liao, Q. Wang, Y.-J. Tan, R. Luo, Y. Qiu, X.-Y. Ge, *Virus Res.* **2020**, *286*, 198074.
[99] Y. Zhang, J. Zhang, Y. Chen, B. Luo, Y. Yuan, F. Huang, T. Yang, F. Yu, J. Liu, B. Liu, Z. Song, J. Chen, T. Pan, X. Zhang, Y. Li, R. Li, W. Huang, F. Xiao, H. Zhang, *bioRxiv* **2020**, 2020.05.24.111823.
[100] H. Jiang, H. Zhang, Q. Meng, J. Xie, Y. Li, H. Chen, Y. Zheng, X. Wang, H. Qi, J. Zhang, P.-H. Wang, Z.-G. Han, S. Tao, *Cell. Mol. Immunol.* **2020**, *17*, 998–1000.
[101] H. Jiang, Y. Li, H. Zhang, W. Wang, X. Yang, H. Qi, H. Li, D. Men, J. Zhou, S. Tao, *Nat. Commun.* **2020**, *11*, 3581.
[102] P. V'kovski, A. Kratzel, S. Steiner, H. Stalder, V. Thiel, *Nat. Rev. Microbiol.* **2020**, 1–16.
[103] J. Zahradník, S. Marciano, M. Shemesh, E. Zoler, J. Chiaravalli, B. Meyer, Y. Rudich, O. Dym, N. Elad, G. Schreiber, *bioRxiv* **2021**, 2021.01.06.425392.
[104] *N. Engl. J. Med.* **2020**, *383*, 1522–1534.
[105] The COVID-19 Host Genetics Initiative, *Eur. J. Hum. Genet.* **2020**, *28*, 715–718.
[106] S. Wang, Z. Qiu, Y. Hou, X. Deng, W. Xu, T. Zheng, P. Wu, S. Xie, W. Bian, C. Zhang, Z. Sun, K. Liu, C. Shan, A. Lin, S. Jiang, Y. Xie, Q. Zhou, L. Lu, J. Huang, X. Li, *Cell Research* **2021**, 1–15.
[107] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T. S. Schiergens, G. Herrler, N.-H. Wu, A. Nitsche, M. A. Müller, C. Drosten, S. Pöhlmann, *Cell* **2020**, *181*, 271–280.
[108] V. D. Menachery, K. H. Dinnon, B. L. Yount, E. T. McAnarney, L. E. Gralinski, A. Hale, R. L. Graham, T. Scobey, S. J. Anthony, L. Wang, B.

Graham, S. H. Randell, W. I. Lipkin, R. S. Baric, *J. Virol.* **2020**, *94*, DOI 10.1128/JVI.01774–19.
[109] A. C. Walls, Y.-J. Park, M. A. Tortorici, A. Wall, A. T. McGuire, D. Veesler, *Cell* **2020**, *181*, 281–292.
[110] T. Meng, H. Cao, H. Zhang, Z. Kang, D. Xu, H. Gong, J. Wang, Z. Li, X. Cui, H. Xu, H. Wei, X. Pan, R. Zhu, J. Xiao, W. Zhou, L. Cheng, J. Liu, *bioRxiv* **2020**, 2020.02.08.926006.
[111] X. Jin, K. Xu, P. Jiang, J. Lian, S. Hao, H. Yao, H. Jia, Y. Zhang, L. Zheng, N. Zheng, D. Chen, J. Yao, J. Hu, J. Gao, L. Wen, J. Shen, Y. Ren, G. Yu, X. Wang, Y. Lu, X. Yu, L. Yu, D. Xiang, N. Wu, X. Lu, L. Cheng, F. Liu, H. Wu, C. Jin, X. Yang, P. Qian, Y. Qiu, J. Sheng, T. Liang, L. Li, Y. Yang, *Emerging Microbes & Infections* **2020**, *9*, 1474–1488.
[112] L. Farrera-Soler, J.-P. Daguer, S. Barluenga, O. Vadas, P. Cohen, S. Pagano, S. Yerly, L. Kaiser, N. Vuilleumier, N. Winssinger, *PLoS One* **2020**, *15*, e0238089.
[113] Y. Finkel, O. Mizrahi, A. Nachshon, S. Weingarten-Gabbay, D. Morgenstern, Y. Yahalom-Ronen, H. Tamir, H. Achdout, D. Stein, O. Israeli, A. Beth-Din, S. Melamed, S. Weiss, T. Israely, N. Paran, M. Schwartz, N. Stern-Ginossar, *Nature* **2021**, *589*, 125–130.
[114] C. P. Grou, M. P. Pinto, A. V. Mendes, P. Domingues, J. E. Azevedo, *Sci. Rep.* **2015**, *5*, 12836.
[115] P. V'kovski, A. Kratzel, S. Steiner, H. Stalder, V. Thiel, *Nat. Rev. Microbiol.* **2020**, 1–16.
[116] M. Moustaqil, E. Ollivier, H.-P. Chiu, S. V. Tol, P. Rudolffi-Soto, C. Stevens, A. Bhumkar, D. J. B. Hunter, A. Freiberg, D. Jacques, B. Lee, E. Sierecki, Y. Gambin, *bioRxiv* **2020**, 2020.06.05.135699.
[117] S. G. Sawicki, in *Viral Genome Replication* (Eds.: K. D. Raney, M. Gotte, C. E. Cameron), Springer US, Boston, MA, **2009**, pp. 25–39.
[118] S. Ghosh, T. A. Dellibovi-Ragheb, A. Kerviel, E. Pak, Q. Qiu, M. Fisher, P. M. Takvorian, C. Bleck, V. W. Hsu, A. R. Fehr, S. Perlman, S. R. Achar, M. R. Straus, G. R. Whittaker, C. A. M. de Haan, J. Kehrl, G. Altan-Bonnet, N. Altan-Bonnet, *Cell* **2020**, *183*, 1520–1535.
[119] X. He, E. H. Y. Lau, P. Wu, X. Deng, J. Wang, X. Hao, Y. C. Lau, J. Y. Wong, Y. Guan, X. Tan, X. Mo, Y. Chen, B. Liao, W. Chen, F. Hu, Q. Zhang, M. Zhong, Y. Wu, L. Zhao, F. Zhang, B. J. Cowling, F. Li, G. M. Leung, *Nat. Med.* **2020**, *26*, 1491–1493.
[120] Y. Orooji, H. Sohrabi, N. Hemmat, F. Oroojalian, B. Baradaran, A. Mokhtarzadeh, M. Mohaghegh, H. Karimi-Maleh, *Nano-Micro Lett.* **2020**, *13*, 18.
[121] E. Han, M. M. J. Tan, E. Turk, D. Sridhar, G. M. Leung, K. Shibuya, N. Asgari, J. Oh, A. L. García-Basteiro, J. Hanefeld, A. R. Cook, L. Y. Hsu, Y. Y. Teo, D. Heymann, H. Clark, M. McKee, H. Legido-Quigley, *The Lancet* **2020**, *396*, 1525–1534.
[122] N. Güemes-Villahoz, B. Burgos-Blasco, A. Arribi-Vilela, P. Arriola-Villalobos, C. M. Rico-Luna, R. Cuiña-Sardiña, A. Delgado-Iribarren, J. García-Feijoó, *J. Med. Virol.* **2021**, *93*, 383–388.
[123] E. C. Leung, V. C. Chow, M. K. Lee, R. W. Lai, *J. Med. Virol.* **2021**, *93*, 533–536.
[124] B. W. Frazee, A. Rodríguez-Hoces de la Guardia, H. Alter, C. G. Chen, E. L. Fuentes, A. K. Holzer, M. Lolas, D. Mitra, J. Vohra, C. L. Dekker, *Annals of Emergency Medicine* **2018**, *71*, 509–517.e1.
[125] H. Jayamohan, C. J. Lambert, H. J. Sant, A. Jafek, D. Patel, H. Feng, M. Beeman, T. Mahmood, U. Nze, B. K. Gale, *Anal. Bioanal. Chem.* **2020**, 1–23.
[126] O. Vandenberg, D. Martiny, O. Rochas, A. van Belkum, Z. Kozlakidis, *Nat. Rev. Microbiol.* **2020**, 1–13.
[127] A. D. Paltiel, A. Zheng, R. P. Walensky, *JAMA Netw Open* **2020**, *3*, e2016818.
[128] T. Ogawa, T. Fukumori, Y. Nishihara, T. Sekine, N. Okuda, T. Nishimura, H. Fujikura, N. Hirai, N. Imakita, K. Kasahara, *J. Clin. Virol.* **2020**, *131*, 104612.
[129] K. Ramdas, A. Darzi, S. Jain, *Nat. Med.* **2020**, *26*, 810–811.
[130] H.-F. Tu, P. Yang, Z.-H. Lin, C. Zheng, S.-L. You, *Nat. Chem.* **2020**, *12*, 838–844.
[131] P. Subsoontorn, M. Lohitnavy, C. Kongkaew, *Sci. Rep.* **2020**, *10*, 22349.
[132] M. Shen, Y. Zhou, J. Ye, A. A. Abdullah AL-maskri, Y. Kang, S. Zeng, S. Cai, *Journal of Pharmaceutical Analysis* **2020**, *10*, 97–101.
[133] A. Anantharajah, R. Helaers, J. Defour, N. Olive, F. Kabera, L. Croonen, F. Deldime, J. Vaerman, C. Barbée, M. Bodéus, A. Scohy, A. Verroken, H. Rodriguez-Villalobos, B. Kabamba-Mukadi *Research Square* **2020**, DOI 10.21203/rs.3.rs-36512/v1.
[134] Y. Jung, G. Park, J. H. Moon, K. K., S. Beak, C. Lee, S. Kim, E. C. Park, D. Park, J. Lee, C. W. Byeon, J. J. Lee, J. Maeng, S. Kim, S. I. Kim, B. Kim, M. J. Lee, H. G. Kim *ACS Infect. Dis.* **2020**, *6*, 2513–2523.
[135] K. H. Hong, S. W. Lee, T. S. Kim, H. J. Huh, J. Lee, S. Y. Kim, J.-S. Park, G. J. Kim, H. Sung, K. H. Roh, J.-S. Kim, H. S. Kim, S.-T. Lee, M.-W. Seong, N. Ryoo, H. Lee, K. C. Kwon, C. K. Yoo, *Annals of Laboratory Medicine* **2020**, *40*, 351–360.
[136] P. H. Braz-Silva, A. C. Mamana, C. M. Romano, A. C. Felix, A. V. de Paula, N. E. Fereira, L. F. Buss, T. R. Tozetto-Mendoza, R. A. V. Caixeta, F. E. Leal, R. M. Z. Grespan, J. C. S. Bizário, A. B. C. Ferraz, D. Sapkota, S. Giannecchini, K. K. To, A. Doglio, M. C. Mendes-Correa, *Journal of Oral Microbiology* **2021**, *13*, 1858002.
[137] G. Guglielmi, *Nature* **2020**, *585*, 496–498.
[138] T. Suo, X. Liu, J. Feng, M. Guo, W. Hu, D. Guo, H. Ullah, Y. Yang, Q. Zhang, X. Wang, M. Sajid, Z. Huang, L. Deng, T. Chen, F. Liu, K. Xu, Y. Liu, Q. Zhang, Y. Liu, Y. Xiong, G. Chen, K. Lan, Y. Chen, *Emerging Microbes & Infections* **2020**, *9*, 1259–1268.
[139] L. Dong, J. Zhou, C. Niu, Q. Wang, Y. Pan, S. Sheng, X. Wang, Y. Zhang, J. Yang, M. Liu, Y. Zhao, X. Zhang, T. Zhu, T. Peng, J. Xie, Y. Gao, D. Wang, X. Dai, X. Fang, *Talanta* **2021**, *224*, 121726.
[140] C. M. Verdun, T. Fuchs, P. Harar, D. Elbrächter, D. S. Fischer, J. Berner, P. Grohs, F. J. Theis, F. Krahmer, *medRxiv* **2020**, 2020.04.30.20085290.
[141] G. W. Procop, M. Tuohy, C. Ramsey, D. D. Rhoads, B. P. Rubin, R. Figler, *Am. J. Clin. Pathol.* **2021**, DOI 10.1093/ajcp/aqaa273.
[142] A. Tahamtan, A. Ardebili, *Expert Rev. Mol. Diagn.* **2020**, *20*, 453–454.
[143] J. Kuang, X. Yan, A. J. Genders, C. Granata, D. J. Bishop, *PLoS One* **2018**, *13*, e0196438.
[144] S. A. Bustin, T. Nolan, *J. Biomol. Tech.* **2004**, *15*, 155–166.
[145] B. A. Oliveira, L. C. de Oliveira, E. C. Sabino, T. S. Okay, B. A. Oliveira, L. C. de Oliveira, E. C. Sabino, T. S. Okay, *Rev. Inst. Med. Trop. Sao Paulo* **2020**, *62*, DOI 10.1590/s1678-9946202062044.
[146] S. A. El-Kafrawy, M. M. El-Daly, A. M. Hassan, R. M. Kaki, A. M. Abuzenadah, M. A. Kamal, E. I. Azhar, *Healthcare* **2021**, *9*, 37.
[147] M. J. Mina, R. Parker, D. B. Larremore, *N. Engl. J. Med.* **2020**, *383*, e120.
[148] E. Callaway, *Nature* **2020**, *585*, 174–177.
[149] T. Phan, *Infect. Genet. Evol.* **2020**, *81*, 104260.
[150] D. Thompson, Y. Lei, *Sensors and Actuators Reports* **2020**, *2*, 100017.
[151] K. Shirato, T. Yano, S. Senba, S. Akachi, T. Kobayashi, T. Nishinaka, T. Notomi, S. Matsuyama, *Virol. J.* **2014**, *11*, 139.
[152] A. A. Nassir, M. J. Baptiste, I. Mwikarago, M. R. Habimana, J. Ndinkabandi, A. Murangwa, T. Nyatanyi, C. M. Muvunyi, S. Nsanzimana, M. Leon, C. Musanabaganwa, *medRxiv* **2020**, 2020.09.17.20196402.
[153] T. Chaibun, J. Puenpa, T. Ngamdee, N. Boonapatcharoen, P. Athamanolap, A. P. O'Mullane, S. Vongpunsawad, Y. Poovorawan, S. Y. Lee, B. Lertanantawong, *Nat. Commun.* **2021**, *12*, 802.
[154] Q. Wu, C. Suo, T. Brown, T. Wang, S. A. Teichmann, A. R. Bassett, *bioRxiv* **2020**, 2020.06.01.127019.
[155] M. Patchsung, K. Jantarug, A. Pattama, K. Aphicho, S. Suraritdechachai, P. Meesawat, K. Sappakhaw, N. Leelahakorn, T. Ruenkam, T. Wongsatit, N. Athipanyasilp, B. Eiamthong, B. Lakkanasirorat, T. Phoodokmai, N. Niljianskul, D. Pakotiprapha, S. Chanarat, A. Homchan, R. Tinikul, P. Kamutira, K. Phiwkaow, S. Soithongcharoen, C. Kantiwiriyawanitch, V. Pongsupasa, D. Trisrivirat, J. Jaroensuk, T. Wongnate, S. Maenpuen, P. Chaiyen, S. Kamnerdnakta, J. Swangsri, S. Chuthapisith, Y. Sirivatanauksorn, C. Chaimayo, R. Sutthent, W. Kantakamalakul, J. Joung, A. Ladha, X. Jin, J. S. Gootenberg, O. O. Abudayyeh, F. Zhang, N. Horthongkham, C. Uttamapinant, *Nature Biomedical Engineering* **2020**, *4*, 1140–1149.
[156] J. Joung, A. Ladha, M. Saito, N.-G. Kim, A. E. Woolley, M. Segel, R. P. J. Barretto, A. Ranu, R. K. Macrae, G. Faure, E. I. Ioannidi, R. N. Krajeski, R. Bruneau, M.-L. W. Huang, X. G. Yu, J. Z. Li, B. D. Walker, D. T. Hung, A. L. Greninger, K. R. Jerome, J. S. Gootenberg, O. O. Abudayyeh, F. Zhang, *N. Engl. J. Med.* **2020**, *383*, 1492–1491. DOI 10.1056/NEJMc2026172.
[157] D. Wang, *bioRxiv* **2020**, 2020.04.21.052530.
[158] T. Notomi, H. Okayama, H. Masubuchi, T. Yonekawa, K. Watanabe, N. Amino, T. Hase, *Nucleic Acids Res.* **2000**, *28*, e63–e63.
[159] I. P. Oscorbin, E. A. Belousova, A. I. Zakabunin, U. A. Boyarskikh, M. L. Filipenko, *BioTechniques* **2016**, *61*, 20–25.
[160] W. E. Huang, B. Lim, C.-C. Hsu, D. Xiong, W. Wu, Y. Yu, H. Jia, Y. Wang, Y. Zeng, M. Ji, H. Chang, X. Zhang, H. Wang, Z. Cui, *Microbial Biotechnology* **2020**, *13*, 950–961.
[161] L. E. Lamb, S. N. Bartolone, E. Ward, M. B. Chancellor, *medRxiv* **2020**, 2020.02.19.20025155.
[162] V. L. D. Thi, K. Herbst, K. Boerner, M. Meurer, L. P. Kremer, D. Kirrmaier, A. Freistaedter, D. Papagiannidis, C. Galmozzi, M. L. Stanifer, S. Boulant, S. Klein, P. Chlanda, D. Khalid, I. B. Miranda, P. Schnitzler, H.-G. Kräusslich, M. Knop, S. Anders, *Sci. Transl. Med.* **2020**, *12*, eabc7075, DOI 10.1126/scitranslmed.abc7075.

[163] J. L. Schmid-Burgk, R. M. Schmithausen, D. Li, R. Hollstein, A. Ben-Shmuel, O. Israeli, S. Weiss, N. Paran, G. Wilbring, J. Liebing, D. Feldman, M. Słabicki, B. Lippke, E. Sib, J. Borrajo, J. Strecker, J. Reinhardt, P. Hoffmann, B. Cleary, M. Hölzel, M. M. Nöthen, M. Exner, K. U. Ludwig, A. Regev, F. Zhang, *bioRxiv* **2020**, 2020.04.06.025635.
[164] M. A. Crone, M. Priestman, M. Ciechonska, K. Jensen, D. J. Sharp, A. Anand, P. Randell, M. Storch, P. S. Freemont, *Nat. Commun.* **2020**, *11*, 4464.
[165] C. Ma, F. Wang, X. Wang, L. Han, H. Jing, H. Zhang, C. Shi, *Chem. Commun.* **2017**, *53*, 10696–10699.
[166] J. S. Gootenberg, O. O. Abudayyeh, J. W. Lee, P. Essletzbichler, A. J. Dy, J. Joung, V. Verdine, N. Donghia, N. M. Daringer, C. A. Freije, C. Myhrvold, R. P. Bhattacharyya, J. Livny, A. Regev, E. V. Koonin, D. T. Hung, P. C. Sabeti, J. J. Collins, F. Zhang, *Science* **2017**, *356*, 438–442.
[167] J. S. Gootenberg, O. O. Abudayyeh, M. J. Kellner, J. Joung, J. J. Collins, F. Zhang, *Science* **2018**, *360*, 439–444.
[168] J. Arizti-Sanz, C. A. Freije, A. C. Stanton, B. A. Petros, C. K. Boehm, S. Siddiqui, B. M. Shaw, G. Adams, T.-S. F. Kosoko-Thoroddsen, M. E. Kemball, J. N. Uwanibe, F. V. Ajogbasile, P. E. Eromon, R. Gross, L. Wronka, K. Caviness, L. E. Hensley, N. H. Bergman, B. L. MacInnis, C. T. Happi, J. E. Lemieux, P. C. Sabeti, C. Myhrvold, *Nat. Commun.* **2020**, *11*, 5921.
[169] T. Hou, W. Zeng, M. Yang, W. Chen, L. Ren, J. Ai, J. Wu, Y. Liao, X. Gou, Y. Li, X. Wang, H. Su, B. Gu, J. Wang, T. Xu, *PLoS Pathog.* **2020**, *16*, e1008705.
[170] F. Zhang, O. O. Abudayyeh, J. S. Gootenberg, https://www.broadinstitute.org/files/publications/special/COVID-19%20detection%20(updated).pdf.
[171] C. M. Ackerman, C. Myhrvold, S. G. Thakku, C. A. Freije, H. C. Metsky, D. K. Yang, S. H. Ye, C. K. Boehm, T.-S. F. Kosoko-Thoroddsen, J. Kehe, T. G. Nguyen, A. Carter, A. Kulesa, J. R. Barnes, V. G. Dugan, D. T. Hung, P. C. Blainey, P. C. Sabeti, *Nature* **2020**, *582*, 277–282.
[172] J. P. Broughton, X. Deng, G. Yu, C. L. Fasching, V. Servellita, J. Singh, X. Miao, J. A. Streithorst, A. Granados, A. Sotomayor-Gonzalez, K. Zorn, A. Gopez, E. Hsu, W. Gu, S. Miller, C.-Y. Pan, H. Guevara, D. A. Wadford, J. S. Chen, C. Y. Chiu, *Nat. Biotechnol.* **2020**, *38*, 870–874.
[173] C. Lucia, P.-B. Federico, G. C. Alejandra, *bioRxiv* **2020**, 2020.02.29.971127.
[174] J. Joung, A. Ladha, M. Saito, M. Segel, R. Bruneau, M. W. Huang, N.-G. Kim, X. Yu, J. Li, B. D. Walker, A. L. Greninger, K. R. Jerome, J. S. Gootenberg, O. O. Abudayyeh, F. Zhang, *medRxiv* **2020**, 2020.05.04.20091231.
[175] D. Huang, Z. Shi, J. Qian, K. Bi, M. Fang, Z. Xu, *Biotechnol. Bioeng.* **2020**, *118*, 1568–1577.
[176] L. B. Harrington, D. Burstein, J. S. Chen, D. Paez-Espino, E. Ma, I. P. Witte, J. C. Cofsky, N. C. Kyrpides, J. F. Banfield, J. A. Doudna, *Science* **2018**, *362*, 839–842.
[177] O. of the Commissioner, "Coronavirus (COVID-19) Update: FDA Authorizes Antigen Test as First Over-the-Counter Fully At-Home Diagnostic Test for COVID-19," can be found under https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-antigen-test-first-over-counter-fully-home-diagnostic, **2020**.
[178] W. Stokes, B. M. Berenger, D. Portnoy, B. Scott, J. Szelewicki, T. Singh, A. A. Venner, L. Turnbull, K. Pabbaraju, S. Shokoples, A. A. Wong, K. Gill, T. Guttridge, D. Proctor, J. Hu, G. Tipples, *medRxiv* **2021**, 2021.01.02.21249138.
[179] M. Nagura-Ikeda, K. Imai, S. Tabata, K. Miyoshi, N. Murahara, T. Mizuno, M. Horiuchi, K. Kato, Y. Imoto, M. Iwata, S. Mimura, T. Ito, K. Tamura, Y. Kato, *J. Clin. Microbiol.* **2020**, *58*, DOI 10.1128/JCM.01438–20.
[180] Q.-X. Long, X.-J. Tang, Q.-L. Shi, Q. Li, H.-J. Deng, J. Yuan, J.-L. Hu, W. Xu, Y. Zhang, F.-J. Lv, K. Su, F. Zhang, J. Gong, B. Wu, X.-M. Liu, J.-J. Li, J.-F. Qiu, J. Chen, A.-L. Huang, *Nat. Med.* **2020**, *26*, 1200–1204.
[181] N. M. A. Okba, M. A. Müller, W. Li, C. Wang, C. H. Geurtsvan Kessel, V. M. Corman, M. M. Lamers, R. S. Sikkema, E. de Bruin, F. D. Chandler, Y. Yazdanpanah, Q. L. Hingrat, D. Descamps, N. Houhou-Fidouh, C. B. E. M. Reusken, B.-J. Bosch, C. Drosten, M. P. G. Koopmans, B. L. Haagmans, *Emerging Infect. Dis.* **2020**, *26*, 1478–1488. DOI 10.3201/eid2607.200841.
[182] O. of the Commissioner, "Coronavirus (COVID-19) Update: FDA Authorizes First Test that Detects Neutralizing Antibodies from Recent or Prior SARS-CoV-2 Infection," can be found under https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-test-detects-neutralizing-antibodies-recent-or, **2020**.
[183] Z. Li, Y. Yi, X. Luo, N. Xiong, Y. Liu, S. Li, R. Sun, Y. Wang, B. Hu, W. Chen, Y. Zhang, J. Wang, B. Huang, Y. Lin, J. Yang, W. Cai, X. Wang, J. Cheng, Z. Chen, K. Sun, W. Pan, Z. Zhan, L. Chen, F. Ye, *J. Med. Virol.* **2020**, *92*, 1518–1524.
[184] T. Prazuck, M. Colin, S. Giachè, C. Gubavu, A. Seve, V. Rzepecki, M. Chevereau-Choquet, C. Kiani, V. Rodot, E. Lionnet, L. Courtellemont, J. Guinard, G. Pialoux, L. Hocqueloux, *PLoS One* **2020**, *15*, DOI 10.1371/journal.pone.0237694.
[185] P. G. Choe, K.-H. Kim, C. K. Kang, H. J. Suh, E. Kang, S. Y. Lee, N. J. Kim, J. Yi, W. B. Park, M.-D. Oh, *Emerging Infect. Dis.* **2020**, *27*, DOI 10.3201/eid2703.204543.
[186] A. Petherick, *The Lancet* **2020**, *395*, 1101–1102.
[187] L. Farrera-Soler, J.-P. Daguer, S. Barluenga, O. Vadas, P. Cohen, S. Pagano, S. Yerly, L. Kaiser, N. Vuilleumier, N. Winssinger, *PLoS One* **2020**, *15*, e0238089.
[188] S. Griffin, *BMJ Glob. Health* **2020**, *371*, m4961.
[189] E. Murillo-Zamora, O. Mendoza-Cano, I. Delgado-Enciso, C. M. Hernandez-Suarez, *medRxiv* **2020**, 2020.10.14.20212720.
[190] R. L. Tillett, J. R. Sevinsky, P. D. Hartley, H. Kerwin, N. Crawford, A. Gorzalski, C. Laverdure, S. C. Verma, C. C. Rossetto, D. Jackson, M. J. Farrell, S. V. Hooser, M. Pandori, *The Lancet Infectious Diseases* **2021**, *21*, 52–58.
[191] J. Zhao, Q. Yuan, H. Wang, W. Liu, X. Liao, Y. Su, X. Wang, J. Yuan, T. Li, J. Li, S. Qian, C. Hong, F. Wang, Y. Liu, Z. Wang, Q. He, Z. Li, B. He, T. Zhang, Y. Fu, S. Ge, L. Liu, J. Zhang, N. Xia, Z. Zhang, *Clin. Infect. Dis.* **2020**, *71*, 2027–2034.
[192] J. Wise, *BMJ Glob. Health* **2020**, *371*, m4257.
[193] A. C. Karlsson, M. Humbert, M. Buggert, *Science Immunology* **2020**, *5*, eabe8063 DOI 10.1126/sciimmunol.abe8063.
[194] A. Quijano-Rubio, H.-W. Yeh, J. Park, H. Lee, R. A. Langan, S. E. Boyken, M. J. Lajoie, L. Cao, C. M. Chow, M. C. Miranda, J. Wi, H. J. Hong, L. Stewart, B.-H. Oh, D. Baker, *Nature* **2021**, 1–6.
[195] D. Wang, S. He, X. Wang, Y. Yan, J. Liu, S. Wu, S. Liu, Y. Lei, M. Chen, L. Li, J. Zhang, L. Zhang, X. Hu, X. Zheng, J. Bai, Y. Zhang, Y. Zhang, M. Song, Y. Tang, *Nature Biomedical Engineering* **2020**, *4*, 1150–1158.
[196] C. H. Woo, S. Jang, G. Shin, G. Y. Jung, J. W. Lee, *Nature Biomedical Engineering* **2020**, *4*, 1168–1179.
[197] R. Whelan, *Wall St. J. [Three Star] East. Ed.* **2020**.
[198] P. Jendrny, C. Schulz, F. Twele, S. Meller, M. von Köckritz-Blickwede, A. D. M. E. Osterhaus, J. Ebbers, V. Pilchová, I. Pink, T. Welte, M. P. Manns, A. Fathi, C. Ernst, M. M. Addo, E. Schalke, H. A. Volk, *BMC Infect. Dis.* **2020**, *20*, 536.
[199] F. Narita, Z. Wang, H. Kurita, Z. Li, Y. Shi, Y. Jia, C. Soutis, *Adv. Mater.* **2021**, *33*, 2005448.
[200] D. Caruso, M. Zerunian, M. Polici, F. Pucciarelli, T. Polidori, C. Rucci, G. Guido, B. Bracci, C. De Dominicis, A. Laghi, *Radiology* **2020**, *296*, E79–E85.
[201] T. Ai, Z. Yang, H. Hou, C. Zhan, C. Chen, W. Lv, Q. Tao, Z. Sun, L. Xia, *Radiology* **2020**, *296*, E32–E40.
[202] Y. Fang, H. Zhang, J. Xie, M. Lin, L. Ying, P. Pang, W. Ji, *Radiology* **2020**, *296*, E115–E117.
[203] C. Jin, W. Chen, Y. Cao, Z. Xu, Z. Tan, X. Zhang, L. Deng, C. Zheng, J. Zhou, H. Shi, J. Feng, *Nat. Commun.* **2020**, *11*, 5088.
[204] J. H. Epstein, S. J. Anthony, A. Islam, A. M. Kilpatrick, S. A. Khan, M. D. Balkey, N. Ross, I. Smith, C. Zambrana-Torrelio, Y. Tao, A. Islam, P. L. Quan, K. J. Olival, M. S. U. Khan, E. S. Gurley, M. J. Hossein, H. E. Field, M. D. Fielder, T. Briese, M. Rahman, C. C. Broder, G. Crameri, L.-F. Wang, S. P. Luby, W. I. Lipkin, P. Daszak, *PNAS* **2020**, *117*, 29190–29201.
[205] J. Shi, Z. Wen, G. Zhong, H. Yang, C. Wang, B. Huang, R. Liu, X. He, L. Shuai, Z. Sun, Y. Zhao, P. Liu, L. Liang, P. Cui, J. Wang, X. Zhang, Y. Guan, W. Tan, G. Wu, H. Chen, Z. Bu, *Science* **2020**, *368*, 1016–1020.
[206] K. J. Olival, P. M. Cryan, B. R. Amman, R. S. Baric, D. S. Blehert, C. E. Brook, C. H. Calisher, K. T. Castle, J. T. H. Coleman, P. Daszak, J. H. Epstein, H. Field, W. F. Frick, A. T. Gilbert, D. T. S. Hayman, H. S. Ip, W. B. Karesh, C. K. Johnson, R. C. Kading, T. Kingston, J. M. Lorch, I. H. Mendenhall, A. J. Peel, K. L. Phelps, R. K. Plowright, D. M. Reeder, J. D. Reichard, J. M. Sleeman, D. G. Streicker, J. S. Towner, L.-F. Wang, *PLoS Pathog.* **2020**, *16*, e1008758.
[207] P. Ball, *Nature* **2020**, *589*, 16–18.
[208] "New Thai-made rapid Covid test to slash screening costs," can be found under http://nationthailand/news/30397474.
[209] "Inventor of made-in-Viêt Nam COVID-19 quick test kits honoured as top inspirer - Society - Vietnam News | Politics, Business, Economy, Society, Life, Sports - VietNam News," can be found under https://vietnamnews.vn/society/828649/inventor-of-made-in-viet-nam-covid-19-quick-test-kits-honoured-as-top-inspirer.html.

[210] "Bats are worth $3.7bn to US agriculture," can be found under http://www.theguardian.com/sustainable-business/2015/oct/14/bats-worth-37bn-to-us-agriculture-research-california-texas, **2015**.
[211] Sheherazade, H. K. Ober, S. M. Tsang, *Biotropica* **2019**, *51*, 913–922.
[212] S. Wacharapluesadee, C. Sintunawa, T. Kaewpom, K. Khongnomnan, K. J. Olival, J. H. Epstein, A. Rodpan, P. Sangsri, N. Intarut, A. Chindamporn, K. Suksawa, T. Hemachudha, *Emerging Infect. Dis.* **2013**, *19*, 1349–1352.
[213] "Bats not the enemy in the fight against COVID-19," can be found under https://india.mongabay.com/2020/04/bats-not-the-enemy-in-the-fight-against-covid-19/, **2020**.
[214] R. Rocha, S. A. Aziz, C. E. Brook, W. D. Carvalho, R. Cooper-Bohannon, W. F. Frick, J. C.-C. Huang, T. Kingston, A. López-Baucells, B. Maas, F. Mathews, R. A. Medellin, K. J. Olival, A. J. Peel, R. K. Plowright, O. Razgour, H. Rebelo, L. Rodrigues, S. J. Rossiter, D. Russo, T. M. Straka, E. C. Teeling, T. Treuer, C. C. Voigt, P. W. Webala, *Animal Conservation* DOI https://doi.org/10.1111/acv.12636.
[215] J. Mair-Jenkins, M. Saavedra-Campos, J. K. Baillie, P. Cleary, F.-M. Khaw, W. S. Lim, S. Makki, K. D. Rooney, Convalescent Plasma Study Group, J. S. Nguyen-Van-Tam, C. R. Beck, A. L. P. Mateus, S. Reuter, J. Shin, X. Xu, D. Pereyaslov, I. Papieva, A. Tegnell, H. Englund, Å. Elfving, R. Cox, K. G.-I. Mohn, Y. F. Jenkins, *The Journal of Infectious Diseases* **2015**, *211*, 80–90.
[216] A. S. MacNalty, *Br. Med. J.* **1954**, *1*, 668–670.
[217] E. B. Pathak, *BMJ Glob. Health* **2020**, *371*, m4072.
[218] S. T. H. Liu, H.-M. Lin, I. Baine, A. Wajnberg, J. P. Gumprecht, F. Rahman, D. Rodriguez, P. Tandon, A. Bassily-Marcus, J. Bander, C. Sanky, A. Dupper, A. Zheng, F. T. Nguyen, F. Amanat, D. Stadlbauer, D. R. Altman, B. K. Chen, F. Krammer, D. R. Mendu, A. Firpo-Betancourt, M. A. Levin, E. Bagiella, A. Casadevall, C. Cordon-Cardo, J. S. Jhang, S. A. Arinsburg, D. L. Reich, J. A. Aberg, N. M. Bouvier, *Nat. Med.* **2020**, *26*, 1708–1713.
[219] R. Libster, G. Pérez Marc, D. Wappner, S. Coviello, A. Bianchi, V. Braem, I. Esteban, M. T. Caballero, C. Wood, M. Berrueta, A. Rondan, G. Lescano, P. Cruz, Y. Ritou, V. Fernández Viña, D. Álvarez Paggi, S. Esperante, A. Ferreti, G. Ofman, Á. Ciganda, R. Rodriguez, J. Lantos, R. Valentini, N. Itcovici, A. Hintze, M. L. Oyarvide, C. Etchegaray, A. Neira, I. Name, J. Alfonso, R. López Castelo, G. Caruso, S. Rapelius, F. Alvez, F. Etchenique, F. Dimase, D. Alvarez, S. S. Aranda, C. Sánchez Yanotti, J. De Luca, S. Jares Baglivo, S. Laudanno, F. Nowogrodzki, R. Larrea, M. Silveyra, G. Leberzstein, A. Debonis, J. Molinos, M. González, E. Perez, N. Kreplak, S. Pastor Argüello, L. Gibbons, F. Althabe, E. Bergel, F. P. Polack, *N. Engl. J. Med.* **2021**, *384*, 610–618.
[220] P. Bansal, A. Goyal, A. C. IV, S. Lahan, H. S. Dhaliwal, P. Bhyan, P. B. Bhattad, F. Aslam, S. Ranka, T. Dalia, L. Chhabra, D. Sanghavi, B. Sonani, J. M. D. III, *Annals of Medicine* **2021**, *53*, 117–134.
[221] C. Hodge, F. Marra, C. Marzolini, A. Boyle, S. Gibbons, M. Siccardi, D. Burger, D. Back, S. Khoo, *J. Antimicrob. Chemother.* **2020**, *75*, 3417–3424.
[222] R. R. Shah, *J. Clin. Pharm. Ther.* **2021**, *46*, 17–27.
[223] A. S. Perlmutter, V.-T. Tran, A. Dechartres, P. Ravaud, *Ann. Oncol.* **2017**, *28*, 688–695.
[224] A. Zumla, J. F. W. Chan, E. I. Azhar, D. S. C. Hui, K.-Y. Yuen, *Nat. Rev. Drug Discovery* **2016**, *15*, 327–347.
[225] T. P. Sheahan, A. C. Sims, R. L. Graham, V. D. Menachery, L. E. Gralinski, J. B. Case, S. R. Leist, K. Pyrc, J. Y. Feng, I. Trantcheva, R. Bannister, Y. Park, D. Babusis, M. O. Clarke, R. L. Mackman, J. E. Spahn, C. A. Palmiotti, D. Siegel, A. S. Ray, T. Cihlar, R. Jordan, M. R. Denison, R. S. Baric, *Sci. Transl. Med.* **2017**, *9*, eaal3653, DOI 10.1126/scitranslmed.aal3653.
[226] A. Savarino, L. D. Trani, I. Donatelli, R. Cauda, A. Cassone, *The Lancet Infectious Diseases* **2006**, *6*, 67–69.
[227] M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, Z. Shi, Z. Hu, W. Zhong, G. Xiao, *Cell Res* **2020**, *30*, 269–271.
[228] R. T. Eastman, J. S. Roth, K. R. Brimacombe, A. Simeonov, M. Shen, S. Patnaik, M. D. Hall, *ACS Cent. Sci.* **2020**, *6*, 672–683.
[229] T. P. Sheahan, A. C. Sims, S. R. Leist, A. Schäfer, J. Won, A. J. Brown, S. A. Montgomery, A. Hogg, D. Babusis, M. O. Clarke, J. E. Spahn, L. Bauer, S. Sellers, D. Porter, J. Y. Feng, T. Cihlar, R. Jordan, M. R. Denison, R. S. Baric, *Nat. Commun.* **2020**, *11*, 222.
[230] Y. Cao, Q. Deng, S. Dai, *Travel Medicine and Infectious Disease* **2020**, *35*, 101647.
[231] Y. Wang, D. Zhang, G. Du, R. Du, J. Zhao, Y. Jin, S. Fu, L. Gao, Z. Cheng, Q. Lu, Y. Hu, G. Luo, K. Wang, Y. Lu, H. Li, S. Wang, S. Ruan, C. Yang, C. Mei, Y. Wang, D. Ding, F. Wu, X. Tang, X. Ye, Y. Ye, B. Liu, J. Yang, W. Yin, A. Wang, G. Fan, F. Zhou, Z. Liu, X. Gu, J. Xu, L. Shang, Y. Zhang, L. Cao, T. Guo, Y. Wan, H. Qin, Y. Jiang, T. Jaki, F. G. Hayden, P. W. Horby, B. Cao, C. Wang, *The Lancet* **2020**, *395*, 1569–1578.
[232] J. H. Beigel, K. M. Tomashek, L. E. Dodd, A. K. Mehta, B. S. Zingman, A. C. Kalil, E. Hohmann, H. Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R. W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T. F. Patterson, R. Paredes, D. A. Sweeney, W. R. Short, G. Touloumi, D. C. Lye, N. Ohmagari, M. Oh, G. M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M. G. Kortepeter, R. L. Atmar, C. B. Creech, J. Lundgren, A. G. Babiker, S. Pett, J. D. Neaton, T. H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, H. C. Lane, *N. Engl. J. Med.* **2020**, *383*, 1813–1826.
[233] K. KupferschmidtOct. 16, 2020, 3:45 Am, "Remdesivir and interferon fall flat in WHO's megastudy of COVID-19 treatments," can be found under https://www.sciencemag.org/news/2020/10/remdesivir-and-interferon-fall-flat-who-s-megastudy-covid-19-treatments, **2020**.
[234] M. J. C. Long, A. Van Hall-Beauvais, Y. Aye, *Curr. Opin. Chem. Biol.* **2020**, *54*, 10–18.
[235] C. J. Gordon, E. P. Tchesnokov, E. Woolner, J. K. Perry, J. Y. Feng, D. P. Porter, M. Götte, *J. Biol. Chem.* **2020**, *295*, 6785–6797.
[236] F. Robson, K. S. Khan, T. K. Le, C. Paris, S. Demirbag, P. Barfuss, P. Rocchi, W.-L. Ng, *Mol. Cell* **2020**, *79*, 710–727.
[237] N. Narayanan, D. T. Nair, *Int. J. Biol. Macromol.* **2021**, *168*, 272–278.
[238] A. Jafari, S. Dadkhahfar, S. Perseh, *Crit. Rev. Oncol. Hematol.* **2020**, *151*, 102982.
[239] B. Sayad, M. Sobhani, R. Khodarahmi, *Arch. Med. Res.* **2020**, *51*, 577–581.
[240] S. Jockusch, C. Tao, X. Li, M. Chien, S. Kumar, I. Morozova, S. Kalachikov, J. J. Russo, J. Ju, *Sci. Rep.* **2020**, *10*, 16577.
[241] F. Roozbeh, M. Saeedi, R. Alizadeh-Navaei, A. Hedayatizadeh-Omran, S. Merat, H. Wentzel, J. Levi, A. Hill, A. Shamshirian, *J. Antimicrob. Chemother.* **2020**, DOI 10.1093/jac/dkaa501.
[242] J. M. Vela, *Front. Pharmacol.* **2020**, *11*, DOI 10.3389/fphar.2020.582310.
[243] K. Hashimoto, *Eur Arch Psychiatry Clin Neurosci* **2021**, DOI 10.1007/s00406-020-01231-x.
[244] Y. Hirata, H. Yamamoto, M. S. M. Atta, S. Mahmoud, K. Oh-hashi, K. Kiuchi, *J. Neurochem.* **2011**, *119*, 839–847.
[245] J.-C. Lagier, M. Million, P. Gautret, P. Colson, S. Cortaredona, A. Giraud-Gatineau, S. Honoré, J.-Y. Gaubert, P.-E. Fournier, H. Tissot-Dupont, E. Chabrière, A. Stein, J.-C. Deharo, F. Fenollar, J.-M. Rolain, Y. Obadia, A. Jacquier, B. La Scola, P. Brouqui, M. Drancourt, P. Parola, D. Raoult, *Trav. Med. Infect. Dis.* **2020**, *36*, 101791.
[246] P. Gautret, J.-C. Lagier, P. Parola, V. T. Hoang, L. Meddeb, M. Mailhe, B. Doudier, J. Courjon, V. Giordanengo, V. E. Vieira, H. Tissot-Dupont, S. Honoré, P. Colson, E. Chabrière, B. La Scola, J.-M. Rolain, P. Brouqui, D. Raoult, *Int. J. Antimicrob. Agents* **2020**, *56*, 105949.
[247] K. El Bakkouri, *Int. J. Antimicrob. Agents* **2021**, *57*, 106170.
[248] O. of the Commissioner, "Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine," can be found under https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and, **2020**.
[249] https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and-hydroxychloroquine.
[250] G. Wang, C.-J. Lu, A. W. Trafford, X. Tian, H. M. Flores, P. Maj, K. Zhang, Y. Niu, L. Wang, Y. Du, X. Ji, Y. Xu, L. Wu, D. Li, N. Herring, D. Paterson, C. L.-H. Huang, H. Zhang, M. Lei, G. Hao, *bioRxiv* **2020**, 2020.05.21.108605.
[251] T. Fiolet, A. Guihur, M. E. Rebeaud, M. Mulot, N. Peiffer-Smadja, Y. Mahamat-Saleh, *Clin. Microbiol. Infect.* **2021**, *27*, 19–27.
[252] M. Monti, B. Vertogen, C. Masini, C. Donati, C. Lilli, C. Zingaretti, G. Musuraca, U. De Giorgi, C. Cerchione, A. Farolfi, P. Cortesi, P. Viale, G. Martinelli, O. Nanni, *Front. Pharmacol.* **2020**, *11*, DOI 10.3389/fphar.2020.605185.
[253] K. Lewis, D. Chaudhuri, F. Alshamsi, L. Carayannopoulos, K. Dearness, Z. Chagla, W. Alhazzani, for the G. Group, *PLoS One* **2021**, *16*, e0244778.
[254] M. L. Idda, D. Soru, M. Floris, *Front. Public Health* **2020**, *8*, DOI 10.3389/fpubh.2020.00497.
[255] A. Z. Reyes, K. A. Hu, J. Teperman, T. L. W. Muskardin, J.-C. Tardif, B. Shah, M. H. Pillinger, *Ann. Rheum. Dis.* **2020**, DOI 10.1136/annrheumdis-2020-219174.
[256] C. D. Russell, J. E. Millar, J. K. Baillie, *The Lancet* **2020**, *395*, 473–475.
[257] G. P. Mishra, J. Mulani, *The Lancet Respiratory Medicine* **2021**, *9*, E8, DOI: https://doi.org/10.1016/S2213-2600(20)30530-0.

[258] WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, J. A. C. Sterne, S. Murthy, J. V. Diaz, A. S. Slutsky, J. Villar, D. C. Angus, D. Annane, L. C. P. Azevedo, O. Berwanger, A. B. Cavalcanti, P.-F. Dequin, B. Du, J. Emberson, D. Fisher, B. Giraudeau, A. C. Gordon, A. Granholm, C. Green, R. Haynes, N. Heming, J. P. T. Higgins, P. Horby, P. Jüni, M. J. Landray, A. Le Gouge, M. Leclerc, W. S. Lim, F. R. Machado, C. McArthur, F. Meziani, M. H. Møller, A. Perner, M. W. Petersen, J. Savovic, B. Tomazini, V. C. Veiga, S. Webb, J. C. Marshall, *Jama* **2020**, *324*, 1330–1341.
[259] M. A. Matthay, B. T. Thompson, *The Lancet Respiratory Medicine* **2020**, *8*, 1170–1172.
[260] T. C. Theoharides, P. Conti, *J. Biol. Regul. Homeostatic Agents* **2020**, *34*, 1241–1243.
[261] N. Lee, K. C. Allen Chan, D. S. Hui, E. K. O. Ng, A. Wu, R. W. K. Chiu, V. W. S. Wong, P. K. S. Chan, K. T. Wong, E. Wong, C. S. Cockram, J. S. Tam, J. J. Y. Sung, Y. M. D. Lo, *J. Clin. Virol.* **2004**, *31*, 304–309.
[262] Y. Wang, W. Jiang, Q. He, C. Wang, B. Wang, P. Zhou, N. Dong, Q. Tong, *Signal Transduction and Targeted Therapy* **2020**, *5*, 1–3.
[263] H.-M. Zhu, Y. Li, B.-Y. Li, S. Yang, D. Peng, X. Yang, X.-L. Sun, M. Zhang, *World Journal of Clinical Cases* **2020**, *8*, 5952–5961.
[264] Administrator, "Efficacy of methylprednisolone pulse therapy in patients with COVID-19," can be found under http://cmac-journal.ru/en/publication/2020/2/cmac-2020-t22-n2-p088/, **2020**.
[265] S. A. Fatima, M. Asif, K. A. Khan, N. Siddique, A. Z. Khan, *Annals of Medicine and Surgery* **2020**, *60*, 413–416.
[266] S. A. Baron, C. Devaux, P. Colson, D. Raoult, J.-M. Rolain, *Int. J. Antimicrob. Agents* **2020**, *55*, 105944.
[267] T. Pan, N. Zhou, H. Zhang, Use of Teicoplanin Anti-Middle East Respiratory Syndrome Coronavirus, **2016**.
[268] N. Zhou, T. Pan, J. Zhang, Q. Li, X. Zhang, C. Bai, F. Huang, T. Peng, J. Zhang, C. Liu, L. Tao, H. Zhang, *J. Biol. Chem.* **2016**, *291*, 9218–9232.
[269] E. C. Somers, G. A. Eschenauer, J. P. Troost, J. L. Golob, T. N. Gandhi, L. Wang, N. Zhou, L. A. Petty, J. H. Baang, N. O. Dillman, D. Frame, K. S. Gregg, D. R. Kaul, J. Nagel, T. S. Patel, S. Zhou, A. S. Lauring, D. A. Hanauer, E. Martin, P. Sharma, C. M. Fung, J. M. Pogue, *Clin. Infect. Dis.* **2020**, DOI 10.1093/cid/ciaa954.
[270] G. Ceccarelli, F. Alessandri, A. Oliva, S. Dell'Isola, M. Rocco, F. Ruberto, F. Pugliese, G. d'Ettorre, M. Venditti, *Eur. J. Clin. Invest.* **2021**, *51*, e13418.
[271] M. J. C. Long, C. Rogg, Y. Aye, *Acc. Chem. Res.* **2020**, DOI 10.1021/acs.accounts.0c00537.
[272] G. Liang, J. P. Bowen, *Curr. Top. Med. Chem.* **2016**, *16*, 1506–1529.
[273] P. M. Cromm, C. M. Crews, *ACS Cent. Sci.* **2017**, *3*, 830–838.
[274] J. Eder, U. Hommel, F. Cumin, B. Martoglio, B. Gerhartz, *Curr. Pharm. Des.* **2007**, *13*, 271–285.
[275] M. J. C. Long, A. P. Lawson, R. Baggio, Y. Qian, L. Rozhansky, D. Fasci, F. El Oualid, E. Weerapana, L. Hedstrom, *Bioorg. Med. Chem. Lett.* **2019**, *29*, 204–211.
[276] L. K. Hedstrom, M. J. Long, A. P. Lawson, *Inhibitors of Deubiquitinating Proteases* **2016**, WO2016014522 A1.
[277] C. M. Chu, V. C. C. Cheng, I. F. N. Hung, M. M. L. Wong, K. H. Chan, K. S. Chan, R. Y. T. Kao, L. L. M. Poon, C. L. P. Wong, Y. Guan, J. S. M. Peiris, K. Y. Yuen, *Thorax* **2004**, *59*, 252–256.
[278] A. H. de Wilde, D. Jochmans, C. C. Posthuma, J. C. Zevenhoven-Dobbe, S. van Nieuwkoop, T. M. Bestebroer, B. G. van den Hoogen, J. Neyts, E. J. Snijder, *Antimicrob. Agents Chemother.* **2014**, *58*, 4875–4884.
[279] C.-Y. Wu, J.-T. Jan, S.-H. Ma, C.-J. Kuo, H.-F. Juan, Y.-S. E. Cheng, H.-H. Hsu, H.-C. Huang, D. Wu, A. Brik, F.-S. Liang, R.-S. Liu, J.-M. Fang, S.-T. Chen, P.-H. Liang, C.-H. Wong, *PNAS* **2004**, *101*, 10012–10017.
[280] M. Siklos, M. BenAissa, G. R. J. Thatcher, *Acta Pharm. Sin. B* **2015**, *5*, 506–519.
[281] J. E. Blanchard, N. H. Elowe, C. Huitema, P. D. Fortin, J. D. Cechetto, L. D. Eltis, E. D. Brown, *Chem. Biol.* **2004**, *11*, 1445–1453.
[282] A. B. Owa, O. T. Owa, *Journal of Microbiology, Immunology and Infection* **2020**, *53*, 674–675.
[283] S. Griffin, *BMJ Glob. Health* **2020**, *370*, m2650.
[284] L. Zhang, D. Lin, X. Sun, U. Curth, C. Drosten, L. Sauerhering, S. Becker, K. Rox, R. Hilgenfeld, *Science* **2020**, *368*, 409–412.
[285] V. L. Kouznetsova, A. Zhang, M. Tatineni, M. A. Miller, I. F. Tsigelny, *PeerJ* **2020**, *8*, e9965.
[286] D. W. Kim, K. H. Seo, M. J. Curtis-Long, K. Y. Oh, J.-W. Oh, J. K. Cho, K. H. Lee, K. H. Park, *J. Enzyme Inhib. Med. Chem.* **2014**, *29*, 59–63.
[287] J. K. Cho, M. J. Curtis-Long, K. H. Lee, D. W. Kim, H. W. Ryu, H. J. Yuk, K. H. Park, *Bioorg. Med. Chem.* **2013**, *21*, 3051–3057.
[288] Y. H. Song, D. W. Kim, M. J. Curtis-Long, H. J. Yuk, Y. Wang, N. Zhuang, K. H. Lee, K. S. Jeon, K. H. Park, *Biol. Pharm. Bull.* **2014**, *37*, 1021–1028.
[289] B. Pang, J. Zhang, M. S. Lee, W. Zheng, *Integr Med Res* **2020**, *9*, 100481.
[290] D. E. Leisman, L. Ronner, R. Pinotti, M. D. Taylor, P. Sinha, C. S. Calfee, A. V. Hirayama, F. Mastroiani, C. J. Turtle, M. O. Harhay, M. Legrand, C. S. Deutschman, *The Lancet Respiratory Medicine* **2020**, *8*, 1233–1244.
[291] K. Smetana, D. Rosel, J. Brábek, *In Vivo* **2020**, *34*, 3027–3028.
[292] S. Yuan, P. Chen, H. Li, C. Chen, F. Wang, D. W. Wang, *J. Cell. Mol. Med.* **2020**, DOI 10.1111/jcmm.16198.
[293] T. F. Osborne, Z. P. Veigulis, D. M. Arreola, S. Mahajan, E. Röösli, C. M. Curtin, *medRxiv* **2020**, 2020.12.13.20248147.
[294] Y. Gokhale, R. Mehta, N. Karnik, U. Kulkarni, S. Gokhale, *EClinicalMedicine* **2020**, *24*, 100467.
[295] M. I. Lopes, L. P. Bonjorno, M. C. Giannini, N. B. Amaral, M. N. Benatti, U. C. Rezek, L. L. E. Filho, B. A. Sousa, S. C. Almeida, R. Luppino-Assad, F. P. Veras, A. Schneider, T. S. Rodrigues, L. O. Leiria, L. D. Cunha, J. C. Alves-Filho, T. M. Cunha, E. Arruda, C. H. Miranda, A. Pazin-Filho, M. A. Martins, M. C. Borges, B. A. Fonseca, V. R. Bollela, C. M. Del-Ben, F. Q. Cunha, D. S. Zamboni, R. C. Santana, F. C. Vilar, P. Louzada-Junior, R. D. Oliveira, *medRxiv* **2020**, 2020.08.06.20169573.
[296] D. Olagnier, E. Farahani, J. Thyrsted, J. Blay-Cadanet, A. Herengt, M. Idorn, A. Hait, B. Hernaez, A. Knudsen, M. B. Iversen, M. Schilling, S. E. Jørgensen, M. Thomsen, L. S. Reinert, M. Lappe, H.-D. Hoang, V. H. Gilchrist, A. L. Hansen, R. Ottosen, C. G. Nielsen, C. Møller, D. van der Horst, S. Peri, S. Balachandran, J. Huang, M. Jakobsen, E. B. Svenningsen, T. B. Poulsen, L. Bartsch, A. L. Thielke, Y. Luo, T. Alain, J. Rehwinkel, A. Alcamí, J. Hiscott, T. H. Mogensen, S. R. Paludan, C. K. Holm, *Nat. Commun.* **2020**, *11*, 4938.
[297] U. Schulze-Topphoff, M. Varrin-Doyer, K. Pekarek, C. M. Spencer, A. Shetty, S. A. Sagan, B. A. C. Cree, R. A. Sobel, B. T. Wipke, L. Steinman, R. H. Scannevin, S. S. Zamvil, *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 4777–4782.
[298] H. Chen, J. C. Assmann, A. Krenz, M. Rahman, M. Grimm, C. M. Karsten, J. Köhl, S. Offermanns, N. Wettschureck, M. Schwaninger, *J. Clin. Invest.* **2014**, *124*, 2188–2192.
[299] S. Müller, M. Behnen, K. Bieber, S. Möller, L. Hellberg, M. Witte, M. Hänsel, D. Zillikens, W. Solbach, T. Laskay, R. J. Ludwig, *J. Invest. Dermatol.* **2016**, *136*, 117–126.
[300] J. Brück, R. Dringen, A. Amasuno, I. Pau-Charles, K. Ghoreschi, *Exp. Dermatol.* **2018**, *27*, 611–624.
[301] A. Gavazza, A. Marchegiani, G. Rossi, M. Franzini, A. Spaterna, S. Mangiaterra, M. Cerquetella, *Front. Public Health* **2020**, *8*, DOI 10.3389/fpubh.2020.00417.
[302] A. Hernández, M. Viñals, A. Pablos, F. Vilás, P. J. Papadakos, D. N. Wijeysundera, S. D. Bergese, M. Vives, *Int. Immunopharmacol.* **2021**, *90*, 107261.
[303] D. Bojkova, K. Klann, B. Koch, M. Widera, D. Krause, S. Ciesek, J. Cinatl, C. Münch, *Nature* **2020**, *583*, 469–472.
[304] Bausch Health Americas, Inc., An Open-Label Study to Evaluate the Safety and Efficacy of VIRAZOLE® (RIBAVIRIN FOR INHALATION SOLUTION, USP) in Hospitalized Adult Participants With Respiratory Distress Due to COVID-19, Clinicaltrials.Gov, **2020**.
[305] S. Tong, Y. Su, Y. Yu, C. Wu, J. Chen, S. Wang, J. Jiang, *Int. J. Antimicrob. Agents* **2020**, *56*, 106114.
[306] M. A. Unal, C. V. Bitirim, G. Y. Summak, S. Bereketoglu, I. C. Zeytin, O. Bul, C. Gurcan, D. Aydos, E. Goksoy, E. Kocakaya, Z. Eran, M. Murat, N. Demir, J. Somers, E. Demir, H. Nazir, S. A. Ozkan, A. Ozkul, A. Azap, A. Yilmazer, K. C. Akcali, *bioRxiv* **2020**, 2020.12.04.410092.
[307] N. Bukreyeva, E. K. Mantlo, R. A. Sattler, C. Huang, S. Paessler, J. Zeldis, *bioRxiv* **2020**, 2020.04.07.028589.
[308] M. Hoffmann, S. Schroeder, H. Kleine-Weber, M. A. Müller, C. Drosten, S. Pöhlmann, *Antimicrob. Agents Chemother.* **2020**, *64*, DOI 10.1128/AAC.00754-20.
[309] H. Hofmann-Winkler, O. Moerer, S. Alt-Epping, A. Bräuer, B. Büttner, M. Müller, T. Fricke, J. Grundmann, L.-O. Harnisch, D. Heise, A. Kernchen, M. Pressler, C. Stephani, B. Tampe, A. Kaul, S. Gärtner, S. Kramer, S. Pöhlmann, M. S. Winkler, *Crit. Care Explor.* **2020**, *2*, e0284.
[310] K. KupferschmidtApr. 2, 2020, 11:10 Am, "These drugs don't target the coronavirus – they target us," can be found under https://www.sciencemag.org/news/2020/04/these-drugs-don-t-target-coronavirus-they-target-us, **2020**.
[311] Y. J. Sun, G. Velez, D. Parsons, K. Li, M. Ortiz, S. Sharma, P. B. McCray, A. G. Bassuk, V. B. Mahajan, *bioRxiv* **2021**, 2021.01.04.425289.
[312] A. Young, B. Neumann, R. F. Mendez, A. Reyahi, A. Joannides, Y. Modis, R. J. Franklin, *medRxiv* **2020**, 2020.04.10.20053207.

[313] M. J. Fromer, *Oncology Times* **2006**, *28*, 18–19.
[314] G. Bjorn, *Nat. Med.* **2008**, *14*, 226–226.
[315] G. A. Petsko, *BMC Biol.* **2010**, *8*, 61.
[316] M. J. Long, X. Liu, Y. Aye, *Curr. Opin. Chem. Biol.* **2019**, *51*, 48–56.
[317] A. S. Reddy, S. Zhang, *Expert Rev Clin Pharmacol* **2013**, *6*, 41–47.
[318] G. A. Van Norman, *JACC: Basic to Translational Science* **2016**, *1*, 170–179.
[319] V. C. Chitalia, A. H. Munawar, *Journal of Translational Medicine* **2020**, *18*, 390.
[320] N. S. Ogando, J. C. Zevenhoven-Dobbe, Y. van der Meer, P. J. Bredenbeek, C. C. Posthuma, E. J. Snijder, *J. Virol.* **2020**, *94*, DOI 10.1128/JVI.01246-20.
[321] H. T. Baddock, S. Brolih, Y. Yosaatmadja, M. Ratnaweera, M. Bielinski, L. P. Swift, A. Cruz-Migoni, G. M. Morris, C. J. Schofield, O. Gileadi, P. J. McHugh, *bioRxiv* **2020**, 2020.08.13.248211.
[322] C. Selvaraj, D. C. Dinesh, U. Panwar, R. Abhirami, E. Boura, S. K. Singh, *Journal of Biomolecular Structure and Dynamics* **2020**, *0*, 1–12.
[323] Y. Sun, L. Abriola, Y. V. Surovtseva, B. D. Lindenbach, J. U. Guo, *bioRxiv* **2020**, 2020.10.21.349225.
[324] Y. Han, X. Duan, L. Yang, B. E. Nilsson-Payant, P. Wang, F. Duan, X. Tang, T. M. Yaron, T. Zhang, S. Uhl, Y. Bram, C. Richardson, J. Zhu, Z. Zhao, D. Redmond, S. Houghton, D.-H. T. Nguyen, D. Xu, X. Wang, J. Jessurun, A. Borczuk, Y. Huang, J. L. Johnson, Y. Liu, J. Xiang, H. Wang, L. C. Cantley, B. R. tenOever, D. D. Ho, F. C. Pan, T. Evans, H. J. Chen, R. E. Schwartz, S. Chen, *Nature* **2021**, *589*, 270–275.
[325] D. E. Gordon, G. M. Jang, M. Bouhaddou, J. Xu, K. Obernier, K. M. White, M. J. O'Meara, V. V. Rezelj, J. Z. Guo, D. L. Swaney, T. A. Tummino, R. Hüttenhain, R. M. Kaake, A. L. Richards, B. Tutuncuoglu, H. Foussard, J. Batra, K. Haas, M. Modak, M. Kim, P. Haas, B. J. Polacco, H. Braberg, J. M. Fabius, M. Eckhardt, M. Soucheray, M. J. Bennett, M. Cakir, M. J. McGregor, Q. Li, B. Meyer, F. Roesch, T. Vallet, A. Mac Kain, L. Miorin, E. Moreno, Z. Z. C. Naing, Y. Zhou, S. Peng, Y. Shi, Z. Zhang, W. Shen, I. T. Kirby, J. E. Melnyk, J. S. Chorba, K. Lou, S. A. Dai, I. Barrio-Hernandez, D. Memon, C. Hernandez-Armenta, J. Lyu, C. J. P. Mathy, T. Perica, K. B. Pilla, S. J. Ganesan, D. J. Saltzberg, R. Rakesh, X. Liu, S. B. Rosenthal, L. Calviello, S. Venkataramanan, J. Liboy-Lugo, Y. Lin, X.-P. Huang, Y. Liu, S. A. Wankowicz, M. Bohn, M. Safari, F. S. Ugur, C. Koh, N. S. Savar, Q. D. Tran, D. Shengjuler, S. J. Fletcher, M. C. O'Neal, Y. Cai, J. C. J. Chang, D. J. Broadhurst, S. Klippsten, P. P. Sharp, N. A. Wenzell, D. Kuzuoglu-Ozturk, H.-Y. Wang, R. Trenker, J. M. Young, D. A. Cavero, J. Hiatt, T. L. Roth, U. Rathore, A. Subramanian, J. Noack, M. Hubert, R. M. Stroud, A. D. Frankel, O. S. Rosenberg, K. A. Verba, D. A. Agard, M. Ott, M. Emerman, N. Jura, M. von Zastrow, E. Verdin, A. Ashworth, O. Schwartz, C. d'Enfert, S. Mukherjee, M. Jacobson, H. S. Malik, D. G. Fujimori, T. Ideker, C. S. Craik, S. N. Floor, J. S. Fraser, J. D. Gross, A. Sali, B. L. Roth, D. Ruggero, J. Taunton, T. Kortemme, P. Beltrao, M. Vignuzzi, A. García-Sastre, K. M. Shokat, B. K. Shoichet, N. J. Krogan, *Nature* **2020**, *583*, 459–468.
[326] Y. Aye, M. Li, M. J. C. Long, R. S. Weiss, *Oncogene* **2015**, *34*, 2011–2021.
[327] S. E. Mortimer, D. Xu, D. McGrew, N. Hamaguchi, H. C. Lim, S. J. Bowne, S. P. Daiger, L. Hedstrom, *J. Biol. Chem.* **2008**, *283*, 36354–36360.
[328] B. Chaigne-Delalande, G. Guidicelli, L. Couzi, P. Merville, W. Mahfouf, S. Bouchet, M. Molimard, B. Pinson, J.-F. Moreau, P. Legembre, *J. Immunol.* **2008**, *181*, 7630–7638.
[329] L. Tang, Z. Yin, Y. Hu, H. Mei, *Front. Immunol.* **2020**, *11*, DOI 10.3389/fimmu.2020.570993.
[330] Y. Xiang, S. Nambulli, Z. Xiao, H. Liu, Z. Sang, W. P. Duprex, D. Schneidman-Duhovny, C. Zhang, Y. Shi, *Science* **2020**, *370*, 1479–1484.
[331] M. Schoof, B. Faust, R. A. Saunders, S. Sangwan, V. Rezelj, N. Hoppe, M. Boone, C. B. Billesbølle, C. Puchades, C. M. Azumaya, H. T. Kratochvil, M. Zimanyi, I. Deshpande, J. Liang, S. Dickinson, H. C. Nguyen, C. M. Chio, G. E. Merz, M. C. Thompson, D. Diwanji, K. Schaefer, A. A. Anand, N. Dobzinski, B. S. Zha, C. R. Simoneau, K. Leon, K. M. White, U. S. Chio, M. Gupta, M. Jin, F. Li, Y. Liu, K. Zhang, D. Bulkley, M. Sun, A. M. Smith, A. N. Rizo, F. Moss, A. F. Brilot, S. Pourmal, R. Trenker, T. Pospiech, S. Gupta, B. Barsi-Rhyne, V. Belyy, A. W. Barile-Hill, S. Nock, Y. Liu, N. J. Krogan, C. Y. Ralston, D. L. Swaney, A. García-Sastre, M. Ott, M. Vignuzzi, Q. S. B. Consortium, P. Walter, A. Manglik, *Science* **2020**, *370*, 1473–1479.
[332] N. E. Thomford, D. A. Senthebane, A. Rowe, D. Munro, P. Seele, A. Maroyi, K. Dzobo, *Int. J. Mol. Sci.* **2018**, *19*, 1578.
[333] A. A. Siddiqui, F. Iram, S. Siddiqui, K. Sahu, *International Journal of Drug Development and Research* **2014**, *6*.
[334] Z.-R. Zhang, Y.-N. Zhang, X.-D. Li, H.-Q. Zhang, S.-Q. Xiao, F. Deng, Z.-M. Yuan, H.-Q. Ye, B. Zhang, *Signal Transduction and Targeted Therapy* **2020**, *5*, 1–3.
[335] H. R. Khatri, B. Bhattarai, W. Kaplan, Z. Li, M. J. Curtis Long, Y. Aye, P. Nagorny, *J. Am. Chem. Soc.* **2019**, *141*, 4849–4860.
[336] A. M. Orellana, P. F. Kinoshita, J. A. Leite, E. M. Kawamoto, C. Scavone, *Front. Endocrinol.* **2016**, *7*, DOI 10.3389/fendo.2016.00010.
[337] S. Dawadi, N. Simmons, G. Miklossy, K. M. Bohren, J. C. Faver, M. N. Ucisik, P. Nyshadham, Z. Yu, M. M. Matzuk, *PNAS* **2020**, *117*, 16782–16789.
[338] A. Norman, C. Franck, M. Christie, P. M. E. Hawkins, K. Patel, A. S. Ashhurst, A. Aggarwal, J. K. K. Low, R. Siddiquee, C. L. Ashley, M. Steain, J. A. Triccas, S. Turville, J. P. Mackay, T. Passioura, R. J. Payne, *bioRxiv* **2020**, 2020.12.22.424069.
[339] W. Dai, B. Zhang, X.-M. Jiang, H. Su, J. Li, Y. Zhao, X. Xie, Z. Jin, J. Peng, F. Liu, C. Li, Y. Li, F. Bai, H. Wang, X. Cheng, X. Cen, S. Hu, X. Yang, J. Wang, X. Liu, G. Xiao, H. Jiang, Z. Rao, L.-K. Zhang, Y. Xu, H. Yang, H. Liu, *Science* **2020**, *368*, 1331–1335.
[340] A. Douangamath, D. Fearon, P. Gehrtz, T. Krojer, P. Lukacik, C. D. Owen, E. Resnick, C. Strain-Damerell, A. Aimon, P. Ábrányi-Balogh, J. Brandão-Neto, A. Carbery, G. Davison, A. Dias, T. D. Downes, L. Dunnett, M. Fairhead, J. D. Firth, S. P. Jones, A. Keeley, G. M. Keserü, H. F. Klein, M. P. Martin, M. E. M. Noble, P. O'Brien, A. Powell, R. N. Reddi, R. Skyner, M. Snee, M. J. Waring, C. Wild, N. London, F. von Delft, M. A. Walsh, *Nat. Commun.* **2020**, *11*, 5047.
[341] X. Tan, J. Bai, S. Ding, Y. Ren, D. Hong, Z. Mei, Y.-M. Li, *Chin. Chem. Lett.* **2019**, *30*, 743–746.
[342] T. Klemm, G. Ebert, D. J. Calleja, C. C. Allison, L. W. Richardson, J. P. Bernardini, B. G. Lu, N. W. Kuchel, C. Grohmann, Y. Shibata, Z. Y. Gan, J. P. Cooney, M. Doerflinger, A. E. Au, T. R. Blackmore, G. J. van der Heden van Noort, P. P. Geurink, H. Ovaa, J. Newman, A. Riboldi-Tunnicliffe, P. E. Czabotar, J. P. Mitchell, R. Feltham, B. C. Lechtenberg, K. N. Lowes, G. Dewson, M. Pellegrini, G. Lessene, D. Komander, *The EMBO Journal* **2020**, *39*, e106275.
[343] M. J. C. Long, Y. Aye, *Cell Chem. Biol.* **2017**, *24*, 787–800.
[344] F. R. Vogenberg, C. Isaacson Barash, M. Pursel, *P T* **2010**, *35*, 560–576.
[345] Q. Zhang, P. Bastard, Z. Liu, J. L. Pen, M. Moncada-Velez, J. Chen, M. Ogishi, I. K. D. Sabli, S. Hodeib, C. Korol, J. Rosain, K. Bilguvar, J. Ye, A. Bolze, B. Bigio, R. Yang, A. A. Arias, Q. Zhou, Y. Zhang, F. Onodi, S. Korniotis, L. Karpf, Q. Philippot, M. Chbihi, L. Bonnet-Madin, K. Dorgham, N. Smith, W. M. Schneider, B. S. Razooky, H.-H. Hoffmann, E. Michailidis, L. Moens, J. E. Han, L. Lorenzo, L. Bizien, P. Meade, A.-L. Neehus, A. C. Ugurbil, A. Corneau, G. Kerner, P. Zhang, F. Rapaport, Y. Seeleuthner, J. Manry, C. Masson, Y. Schmitt, A. Schlüter, T. L. Voyer, T. Khan, J. Li, J. Fellay, L. Roussel, M. Shahrooei, M. F. Alosaimi, D. Mansouri, H. Al-Saud, F. Al-Mulla, F. Almourfi, S. Z. Al-Muhsen, F. Alsohime, S. A. Turki, R. Hasanato, D. van de Beek, A. Biondi, L. R. Bettini, M. D'Angio', P. Bonfanti, L. Imberti, A. Sottini, S. Paghera, E. Quiros-Roldan, C. Rossi, A. J. Oler, M. F. Tompkins, C. Alba, I. Vandernoot, J.-C. Goffard, G. Smits, I. Migeotte, F. Haerynck, P. Soler-Palacin, A. Martin-Nalda, R. Colobran, P.-E. Morange, S. Keles, F. Çölkesen, T. Ozcelik, K. K. Yasar, S. Senoglu, Ş. N. Karabela, C. Rodríguez-Gallego, G. Novelli, S. Hraiech, Y. Tandjaoui-Lambiotte, X. Duval, C. Laouénan, C.-S. Clinicians†, C. Clinicians†, I. C. Group†, F. C. C. S. Group†, C.-C. Cohort†, A. U. C.–19 Biobank†, C. H. G. Effort†, N.-U. C. I. Group†, A. L. Snow, C. L. Dalgard, J. D. Milner, D. C. Vinh, T. H. Mogensen, N. Marr, A. N. Spaan, B. Boisson, S. Boisson-Dupuis, J. Bustamante, A. Puel, M. J. Ciancanelli, I. Meyts, T. Maniatis, V. Soumelis, A. Amara, M. Nussenzweig, A. García-Sastre, F. Krammer, A. Pujol, D. Duffy, R. P. Lifton, S.-Y. Zhang, G. Gorochov, V. Béziat, E. Jouanguy, V. Sancho-Shimizu, C. M. Rice, L. Abel, L. D. Notarangelo, A. Cobat, H. C. Su, J.-L. Casanova, *Science* **2020**, *370*, DOI 10.1126/science.abd4570.
[346] A. B. Docherty, E. M. Harrison, C. A. Green, H. E. Hardwick, R. Pius, L. Norman, K. A. Holden, J. M. Read, F. Dondelinger, G. Carson, L. Merson, J. Lee, D. Plotkin, L. Sigfrid, S. Halpin, C. Jackson, C. Gamble, P. W. Horby, J. S. Nguyen-Van-Tam, A. Ho, C. D. Russell, J. Dunning, P. J. Openshaw, J. K. Baillie, M. G. Semple, *BMJ Glob. Health* **2020**, *369*, m1985.
[347] E. Pairo-Castineira, S. Clohisey, L. Klaric, A. Bretherick, K. Rawlik, N. Parkinson, D. Pasko, S. Walker, A. Richmond, M. H. Fourman, A. Law, J. Furniss, E. Gountouna, N. Wrobel, C. D. Russell, L. Moutsianas, B. Wang, A. Meynert, Z. Yang, R. Zhai, C. Zheng, F. Griffith, W. Oosthuyzen, B. Shih, S. Keating, M. Zechner, C. Haley, D. J. Porteous, C. Hayward, J. Knight, C. Summers, M. Shankar-Hari, L. Turtle, A. Ho, C. Hinds, P. Horby, A. Nichol, D. Maslove, L. Ling, P. Klenerman, D. McAuley, H.

Montgomery, T. Walsh, T. G. Investigators, T. I. Investigators, T. C., H. G. Initiative, X. Shen, K. Rowan, A. Fawkes, L. Murphy, C. P. Ponting, A. Tenesa, M. Caulfield, R. Scott, P. J. Openshaw, M. G. Semple, V. Vitart, J. F. Wilson, J. K. Baillie, *medRxiv* **2020**, 2020.09.24.20200048.
[348] W. S. T. Consortium, *N. Engl. J. Med.* **2020**, DOI 10.1056/NEJMoa2023184.
[349] D. G. I. Kingston, *Chem. Commun.* **2001**, 867–880.
[350] M. Honigsbaum, Living with Enza: The Forgotten Story of Britain and the Great Flu Pandemic of 1918, Palgrave Macmillan US, **2009**.
[351] S. E. Sattui, J. W. Liew, E. R. Graef, A. Coler-Reilly, F. Berenbaum, A. Duarte-García, C. Harrison, M. F. Konig, P. Korsten, M. S. Putman, P. C. Robinson, E. Sirotich, M. F. Ugarte-Gil, K. Webb, K. J. Young, A. H. J. Kim, J. A. Sparks, *Expert Rev. Clin. Immunol.* **2020**, *16*, 659–666.
[352] D. Shyr, Y. Shyr, *Expert Opin. Invest. Drugs* **2020**, *0*, 1–7.
[353] S. Anderson, J. Windscheffel, K. Gunning, *Innov. Pharm.* **2021**, *12*, 1–1.
[354] D. A. Erlanson, *Nat. Commun.* **2020**, *11*, 5048.
[355] Anonymous, "EU and South Korean research organisations sign an agreement to work together on the development of a COVID-19 treatment using Raloxifene," can be found under https://ec.europa.eu/digital-single-market/en/news/eu-and-south-korean-research-organisations-sign-agreement-work-together-development-covid-19, **2020**.
[356] J. R. Goldstein, R. D. Lee, *PNAS* **2020**, *117*, 22035–22041.
[357] R. Omori, R. Matsuyama, Y. Nakata, *Sci. Rep.* **2020**, *10*, 16642.
[358] J. Wise, *BMJ Glob. Health* **2020**, *370*, m3702.
[359] G. Iacobucci, *BMJ Glob. Health* **2020**, *370*, m3788.
[360] R. Armitage, L. B. Nellums, *The Lancet Public Health* **2020**, *5*, e256.
[361] M. L. Smith, L. E. Steinman, E. A. Casey, *Front. Public Health* **2020**, *8*, DOI 10.3389/fpubh.2020.00403.
[362] N. Pearce, G. Moirano, M. Maule, M. Kogevinas, X. Rodo, D. A. Lawlor, J. Vandenbroucke, C. Vandenbroucke-Grauls, F. P. Polack, A. Custovic, *medRxiv* **2020**, 2020.06.01.20116608.
[363] G. D. Shanks, *Journal of Travel Medicine* **2020**, *27*, DOI 10.1093/jtm/taaa086.
[364] P. Klenerman, R. M. Zinkernagel, *Nature* **1998**, *394*, 482–485.
[365] D. F. Gudbjartsson, A. Helgason, H. Jonsson, O. T. Magnusson, P. Melsted, G. L. Norddahl, J. Saemundsdottir, A. Sigurdsson, P. Sulem, A. B. Agustsdottir, B. Eiriksdottir, R. Fridriksdottir, E. E. Gardarsdottir, G. Georgsson, O. S. Gretarsdottir, K. R. Gudmundsson, T. R. Gunnarsdottir, A. Gylfason, H. Holm, B. O. Jensson, A. Jonasdottir, F. Jonsson, K. S. Josefsdottir, T. Kristjansson, D. N. Magnusdottir, L. le Roux, G. Sigmundsdottir, G. Sveinbjornsson, K. E. Sveinsdottir, M. Sveinsdottir, E. A. Thorarensen, B. Thorbjornsson, A. Löve, G. Masson, I. Jonsdottir, A. D. Möller, T. Gudnason, K. G. Kristinsson, U. Thorsteinsdottir, K. Stefansson, *N. Engl. J. Med.* **2020**, *382*, 2302–2315.
[366] S. Tosif, M. R. Neeland, P. Sutton, P. V. Licciardi, S. Sarkar, K. J. Selva, L. A. H. Do, C. Donato, Z. Quan Toh, R. Higgins, C. Van de Sandt, M. M. Lemke, C. Y. Lee, S. K. Shoffner, K. L. Flanagan, K. B. Arnold, F. L. Mordant, K. Mulholland, J. Bines, K. Dohle, D. G. Pellicci, N. Curtis, S. McNab, A. Steer, R. Saffery, K. Subbarao, A. W. Chung, K. Kedzierska, D. P. Burgner, N. W. Crawford, *Nat. Commun.* **2020**, *11*, 5703.
[367] M. C. Grant, L. Geoghegan, M. Arbyn, Z. Mohammed, L. McGuinness, E. L. Clarke, R. G. Wade, *PLoS One* **2020**, *15*, DOI 10.1371/journal.pone.0234765.
[368] Y. Lu, K. Sun, S. Guo, J. Wang, A. Li, X. Rong, T. Wang, Y. Shang, W. Chang, S. Wang, *Front. Med.* **2020**, *7*, DOI 10.3389/fmed.2020.00432.
[369] M. H. Aly, S. S. Rahman, W. A. Ahmed, M. H. Alghamedi, A. A. A. Shehri, A. M. Alkalkami, M. H. Hassan, *IDR* **2020**, *13*, 1995–2000.
[370] Y. A. Helmy, M. Fawzy, A. Elaswad, A. Sobieh, S. P. Kenney, A. A. Shehata, *Journal of Clinical Medicine* **2020**, *9*, 1225.
[371] S. G. Fang, H. Shen, J. Wang, F. P. L. Tay, D. X. Liu, *Virology* **2008**, *379*, 175–180.
[372] J. L. Daly, B. Simonetti, K. Klein, K.-E. Chen, M. K. Williamson, C. Antón-Plágaro, D. K. Shoemark, L. Simón-Gracia, M. Bauer, R. Hollandi, U. F. Greber, P. Horvath, R. B. Sessions, A. Helenius, J. A. Hiscox, T. Teesalu, D. A. Matthews, A. D. Davidson, B. M. Collins, P. J. Cullen, Y. Yamauchi, *Science* **2020**, *370*, 861–865.

Manuscript received: January 30, 2021
Revised manuscript received: March 14, 2021
Accepted manuscript online: April 2, 2021
Version of record online: June 22, 2021