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COVID-19 breakthroughs: separating fact from fiction

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Abbreviations

ACE - Angiotensin-converting enzyme; ACE2 - Angiotensin-converting enzyme 2; BAME - Black, Asian and minority ethnic; COPD - Chronic obstructive pulmonary disease; COVID-19 - Coronavirus disease; COX – Cyclooxygenases; FDA - Food and Drug Administration; HIV - Human immunodeficiency virus; MERS – Middle East respiratory syndrome; NICE - National Institute for Health and Care Excellence; nAChR - Nicotinic acetylcholine receptor; NSAID - Non-steroidal anti-inflammatory drug; PMIS - Paediatric multisystem inflammatory syndrome; RAS - Renin–angiotensin system; SARS - Severe acute respiratory syndrome; SARS-CoV – Severe acute respiratory syndrome coronavirus; SARS-CoV-2 - Severe acute

respiratory syndrome coronavirus 2; TMPRSS2 - Transmembrane Serine Protease 2; TNF - Tumour necrosis factor; WHO – World Health Organization; WIV - Wuhan Institute of Virology

Abstract

The newly recognised coronavirus SARS-CoV-2, causative agent of COVID-19, has caused a pandemic with huge ramifications for human interactions around the globe. As expected, research efforts to understand the virus and curtail the disease are moving at a frantic pace alongside the spread of rumours, speculations and falsehoods. In this article, we aim to clarify the current scientific view behind several claims or controversies related to COVID-19. Starting with the origin of the virus, we then discuss the effect of ibuprofen and nicotine on the severity of the disease. We highlight the knowledge on fomites and SARS-CoV-2 and discuss the evidence and explications for a disproportionately stronger impact of COVID-19 on ethnic minorities, including a potential protective role for vitamin D. We further review what is known about the effects of SARS-CoV-2 infection in children, including their role in transmission of the disease, and conclude with the science on different mortality rates between different countries and whether this hints at the existence of more pathogenic cohorts of SARS-CoV-2.

Introduction

Just about every corner of the world has been affected by the ongoing COVID-19 pandemic. The infection, caused by a coronavirus named SARS-CoV-2, was first recognised in Wuhan, China in December 2019 and has since spread like wildfire, killing more than 300,000 people worldwide as of May 2020 [1]. Many countries are now in the midst of – or just emerging from – the log phase of viral transmission and are taking measures to 'flatten the curve' by implementing nation-wide lockdowns. In the era of social media and advanced online technologies, physical distancing between individuals hasn't necessarily translated to 'social distancing' as most of us are still able to communicate with our family members and friends, do our jobs, be entertained and keep up to date with news. The many communication channels that individuals have at their fingertips also facilitates the sharing of science, and particularly advances in understanding, preventing transmission of the virus and treating COVID-19.

The downside is that much of the science being generated is in its infancy and is frequently circulated prior to peer review, via preprint servers and social media. Although this expedites the sharing of data that could assist in the research efforts to tackle the virus, it can also result in the potentially harmful

public dissemination of information that has not been properly validated. Even those who work in science have reached the point of information overload, with it becoming increasingly difficult to wade through the tidal wave of new COVID-19-related research articles, preprints and news items being generated on a daily basis. Here, we have addressed seven key sources of controversy in the SARS-CoV-2 story so far, which have been widely discussed via news channels and social media. For each of these themes, we highlight the different outlooks presented in the media and summarise the available research at this time, with emphasis on the debunking of pervasive COVID-19-related myths by science. This is by no means an exhaustive update on research relating to the novel coronavirus, and we refer readers to other sources for a summary of anti-viral drug candidates and advances in vaccine development, the two fastest-moving research areas in the global fight against this pandemic [2-8].

Origin of the novel coronavirus

As is apt, we will start with the origin of SARS-CoV-2, which has proven to be a contentious issue since the earliest reports of the novel disease. The official version of events according to authorities in China, as relayed to the World Health Organisation (WHO), is that the outbreak originated in the Huanan Seafood Market in Wuhan [9]. Given that many of the earliest cases of pneumonia caused by the novel coronavirus were linked to this market, and that other coronaviruses (such as SARS-CoV, the coronavirus that causes severe acute respiratory syndrome, or SARS) arose via zoonotic transfer [10], it seems reasonable to infer that the virus passed from an animal to a human in this setting. Accordingly, the local health authority shut the market down on January 1st 2020. Nonetheless, a clinical study on a cluster of cases in Wuhan reported that of 41 patients confirmed through laboratory diagnosis to be infected with SARS-CoV-2 (at that point known as novel coronavirus 2019), 14 bore no direct link to the seafood market [11]. Another incongruity brought to light by the *Lancet* article relates to the timing of the outbreak. An epidemiological alert was raised by the local health authority on December 31st 2019; however, symptom onset for one case included in the clinical study occurred much earlier, on December 1st. Crucially, this patient was reported to have no direct exposure to the seafood market. Similarly, a study involving a higher number of laboratory-confirmed cases, published in the *New England Journal of Medicine*, indicated that 45 percent of those whose symptoms started in December 2019 had no connections to the market [12], making the role of this setting in the outbreak unclear.

The US government has been openly sceptical about the Chinese authorities' official statement on the origin of the outbreak. In late April, the President Donald Trump claimed to have seen 'strong evidence' that COVID-19 originated in a laboratory in Wuhan [13]. This view is held also by the US secretary of state Mike Pompeo, though neither he nor Trump have provided details about the supportive evidence they

allude to in news interviews [14]. A high-profile research laboratory, Wuhan Institute of Virology (WIV), together with a second research facility located near to the seafood market (the Wuhan Center for Disease Control and Prevention), has come under intense scrutiny following these claims. Both are biosafety research facilities in which bat coronaviruses are studied, and it has been speculated that the virus escaped from one of these settings, either by intent (for use as a bioweapon) or because of a lapse in safety procedures. Another public figure who has endorsed the idea that the virus is man-made is Luc Montagnier, a French virologist who was awarded a Nobel Prize in 2008 for his involvement in the discovery of the HIV family. Montagnier claimed that SARS-CoV-2 contains sequences from HIV-1 [15], and in support of this referenced a study conducted by researchers in New Delhi and posted on bioRxiv. His claim was widely dismissed as a conspiracy theory and the supporting preprint was quickly withdrawn in response to critique from the research community [16]. Furthermore, a peer-reviewed report has highlighted the lack of evidence that SARS-CoV-2 is an engineered hybrid virus containing HIV-1 sequences [17].

Kristian Andersen and co-authors categorically refute the idea that the virus has been engineered, based on the comparative analysis of coronavirus genomic data [18]. Instead, they propose that the virus is likely to have arisen through natural selection, either in an animal host before zoonotic transfer or in humans after the zoonotic event. The authors also suggest that it's unlikely that the particular pattern of receptor-binding domain mutations that optimise binding of the virus spike protein to human angiotensin-converting enzyme 2 (ACE2; thought to be the functional receptor for SARS-CoV-2 entry [19]) could have been acquired through serial passage in cell lines or animal models, arguing against the idea that the virus inadvertently leaked from a lab. Other epidemiologists have also publicly discredited theories that the virus emerged from a laboratory environment, although it cannot be ruled out entirely, highlighted by the active discussion triggered on PubPeer [20] and elsewhere by the *Nature Medicine* study.

Whether the now-infamous seafood market is the site that 'patient zero' or the index case became infected remains inconclusively known, but the scientific consensus on the origin is SARS-CoV-2 is that, like other coronaviruses, it evolved naturally and was transferred to humans via an animal. In their landmark *Nature* article reporting the initial isolation and characterisation of the coronavirus [21], Zheng-Li Shi and colleagues at the WIV noted the close similarity of its genome sequence to that of SARS-CoV, which is thought to originate in bats [22]. Moreover, Shi and authors reported 96% identity at the whole-genome level between the novel coronavirus and a bat coronavirus, suggesting that the newly characterised member of the coronavirus family is also derived from bats. This hypothesis is now supported by a number of other peer-reviewed studies [23-26].

The involvement of an intermediate host that facilitated transfer from bats to humans is strongly suspected. The identification of several novel beta-coronaviruses with similarity to SARS-CoV-2 in Malayan pangolins, which are illegally imported into southern China, suggests that these may be the host from which the virus was transmitted to humans [27-29], although this remains unclear [30]. Snakes [31] and turtles [32] have also been implicated as the mystery intermediate host for zoonotic transfer of SARS-CoV-2 to humans, but many virologists have suggested that a mammalian host is more likely [33]. There is evidence that a diverse range of animals can potentially act as reservoirs of coronaviruses, highlighting the need for broader wildlife sampling to determine the intermediate host for SARS-CoV-2 transmission and to predict future viral outbreaks. In addition, increased analysis of data from the early stages of the outbreak, including hospital archives in China, is needed to fully trace the evolutionary path of this virus and the seeding of infections elsewhere, especially in light of recent reports that the virus was circulating in Europe [34] and USA [35] earlier than officially documented.

Ibuprofen: friend or foe to COVID-19 patients?

In mid-March, the French health minister Olivier Veran issued advice to avoid the use of ibuprofen to manage the symptoms of COVID-19. A news item in the *British Medical Journal* [36] stated that this advice came after an infectious diseases specialist in south-west France reported that a handful of patients' symptoms worsened after taking ibuprofen or other non-steroidal anti-inflammatory drug (NSAID). Although other public health experts - including Charlotte Warren-Gash, a professor of epidemiology at the London School of Hygiene and Tropical Medicine - were subsequently quoted as giving credence to this, no supporting evidence for a link between NSAID usage and severe COVID-19 was provided [36]. Furthermore, a letter in *The Lancet respiratory medicine* hypothesizing that SARS-CoV-2 infectivity could be enhanced because of a drug-induced increase in the expression of ACE2, the receptor for viral entry, is of a purely theoretical nature and fails to cite any studies showing that ibuprofen has this up-regulatory effect on ACE2 [37]. In addition, a rapid systematic review of studies in which NSAIDs were used for the treatment of acute respiratory infections was carried out by the WHO in late March, and this concluded that there is currently no evidence for adverse effects of ibuprofen treatment in COVID-19 [38]. This conclusion was corroborated by a similar literature-based review performed by the National Institute for Health and Care Excellence (NICE), who stated that it "could not find any evidence to suggest whether acute use of NSAIDs is related to increased risk of developing COVID-19 or increased risk of a more severe illness [39]. In light of the limited evidence, the WHO has retracted its earlier warning against the use of ibuprofen to manage COVID-19 symptoms and the U.S. Food and Drug Administration (FDA) has issued a

statement to say that they are investigating the potential link and will provide more information publicly when available [40].

A key limitation of the literature-based reviews exploring this putative link is that there is a paucity of clinical data from patients with COVID-19, or even SARS or another coronavirus infection, Middle Eastern Respiratory Syndrome (MERS). A pre-COVID-19 review published in the *Journal of Clinical Medicine* suggested that there *is* sufficient empirical evidence to indicate that NSAIDs use is linked to a greater incidence of complications in patients with lower respiratory tract infections [41]. This has led the authors of a newer review to conclude that although not mandatory, preferential use of acetaminophen/paracetamol is sensible to treat fever and pain in COVID-19 patients [42]. The same authors largely dismiss the hypothesis that ACE2 expression is upregulated by ibuprofen [42], yet it remains plausible that the negative effects of NSAIDs can be explained by its inhibitory effect on cyclooxygenases (COX), which delays the resolution of inflammation [41, 43].

An important aspect in the assessment of ibuprofen use to treat acute infections is the confounding effect of disease severity, also known as channeling bias – a stronger anti-inflammatory drug tends to be administered for more severe symptoms, and the presence of the drug in these cases could be misidentified as the culprit for the severity of the infection [44]. Thus, a worse prognosis in ibuprofen-treated infections might not represent causality in all studies that explore this possibility. One can also speculate that as anti-inflammatory drugs, NSAIDs could alleviate the overactive cytokine response or 'cytokine storm' that is seen as a hallmark of severe COVID-19 [45, 46]. Indeed, a protective role for NSAIDs in COVID-19 cannot be ruled out on the basis of current data [47].

Overall, there currently is no strong supporting evidence for a causal relationship between ibuprofen usage and severe COVID-19. Nonetheless, it seems sensible to take a precautionary approach in taking the drug as a first-line treatment to manage symptoms, particularly considering the potential of NSAIDs to mask symptoms. Further studies are needed to better define the impact of NSAIDs and other COX inhibitors, as well as drugs that increase expression of ACE2, in COVID-19 and related pathologies.

Nicotine: a counterintuitively protective role in COVID-19?

In early May, the WHO released a statement that urged scientists and the media to be cautious about publishing unproven claims that tobacco or nicotine could reduce the risks of infection with SARS-CoV-2 [38]. This statement was prompted by the release of a controversial preprint article from researchers in France who hypothesised that nicotine could have a protective effect against SARS-CoV-2 infection, based on unpublished observations that relatively few smokers were found among hospitalised COVID-19

patients in Paris [48]. As a result, the media ran stories with salacious headlines, leading the public to believe that smoking can reduce the risk of contracting COVID-19.

But is there a link between smoking and COVID-19? Firstly, a distinction must be made between 'smoking' and 'nicotine'. In the article that attracted a lot of media attention, the researchers did not propose a protective role for smoking per se; rather, they hypothesised that the plant alkaloid stimulant in cigarettes, *nicotine*, plays a part in counteracting infection. The so-called nicotinic hypothesis proposes that nicotine antagonises an interaction between SARS-CoV-2 and the nicotinic acetylcholine receptor (nAChR), the known receptor for nicotine, thus blocking viral entry [48]. Despite being theoretically plausible, there is no concrete evidence in favour of this model and it has been widely discredited based on several perceived flaws and biases [49]. Nonetheless, other research teams also believe that nicotine might protect against COVID-19. An analysis of patient characteristics data from China revealed that unexpectedly low levels of smokers were hospitalised in early 2020 with COVID-19, considering the population-level prevalence of smoking in this country [50]. This is consistent with another report that active smoking might not be linked to severe COVID-19 [51]. On the basis of these findings, Konstantinos Farsalinos, a cardiologist and research fellow at the University of Patras, postulated that nicotine may correlate with relatively mild COVID-19 and could be used therapeutically [52]. The central hypothesis behind this correlation is that nicotine reduces inflammation through its interaction with the nAChR, a component of the cholinergic system. Contrary to the potential role of the molecule nicotine, smoking itself certainly has no therapeutic role against COVID-19 and smokers should actively be encouraged to quit, as co-morbidities associated with smoking, such as cardiovascular diseases and chronic obstructive pulmonary disease (COPD), are significant risk factors for a negative outcome in COVID-19 [53] as in other respiratory diseases.

Whilst there is no indication that nicotine prevents the entry of SARS-CoV-2 into host cells, the idea that nicotine could have defensive anti-inflammatory effects is a tantalising one. Nicotine is an inhibitor of pro-inflammatory cytokines, which have been shown to be elevated in COVID-19 patients [45] [54]. Treatment with inhibitors of pro-inflammatory cytokines such as anti-tumour necrosis factor (TNF) medications are already being explored as treatment options [55]. The key proponents of this model propose that nicotine can effectively inhibit several cytokines through modulation of the cholinergic anti-inflammatory system, which could provide a means to sustain a stable immune response against SARS-CoV-2 [52]. If an anti-inflammatory role for nicotine is confirmed, nAChR-agonists such as GTS-21 might be more suited for therapeutic use as they do not appear to have the unwanted side effects of nicotine such as addictive potential, toxicity and lack of specificity [56].

Another circulating theory is that nicotine inhibits expression of ACE2. Since having been identified as the most likely receptor for SARS-CoV-2, ACE2 has been a hot topic in the media and in research groups on the hunt for an effective COVID-19 therapy [57]. ACE2 is an important mediator of the renin–angiotensin system (RAS) [58] and is expressed in a variety of human tissues including the heart, lung, kidney, and gastrointestinal tract, suggesting that SARS-CoV-2 may infect a similar spectrum of sites as SARS-CoV [59] [60]. Earlier analyses suggest that nicotine modulates the homeostasis of RAS by up-regulating the angiotensin-converting enzyme (ACE)/angiotensin (ANG)-II/ANG II type 1 receptor axis, and down-regulating the compensatory ACE2/ANG-(1–7)/Mas receptor axis [61, 62], leading to the development of cardiovascular and pulmonary diseases [63]. By downregulating the docking sites for SARS-CoV-2, nicotine could lower the possibility of infection [64] [65].

There is conflicting evidence, however, on the potential modulation of ACE2 by nicotine. Recent research has identified that nicotine can induce ACE2 overexpression in the lower airways of current smokers and COPD patients [66], which is supported by other studies reporting significantly higher ACE2 gene expression in smokers [67, 68]. Higher levels of ACE2 induced by nicotine exposure would mean more doors of entry for the SARS-CoV-2 virus; thus, systematic exposure to nicotine via smoking or vaping could promote susceptibility to COVID-19. ACE2 overexpression may be mediated through the α7 nAChR, offering a potential cellular mechanism for this model [69]. Furthermore, it has been hypothesised that SARS-CoV-2 entry and proliferation can be promoted via cellular mechanisms of nicotinic receptor activity, which converge on ACE2 regulation and signalling [70]. Here, activation of nicotinic receptors could lead to enhanced protease activation, apoptosis and inflammatory signalling, priming individuals with prior exposure to nicotine for more severe COVID-19 infection. In-depth research is needed to explore the interactions between nicotine receptor and ACE2 signalling to test the validity of these ideas. But given the wealth of evidence indicating that nicotine potentiates cardiopulmonary diseases and viral infections [71, 72], notwithstanding the well-documented negative impact of tobacco smoke on respiratory and overall health, it is unlikely that smoking or vaping will offer therapeutic benefit in COVID-19.

Despite the lack of empirical evidence for their theory, the scientists who proposed the nicotinic hypothesis have launched a clinical trial to test any differences in susceptibility to COVID-19 between healthcare workers who have worn either a nicotine or placebo patch for a set period of time [73]. It must be strongly emphasised that the theories that propose a protective role for the compound currently have no scientific backing to them, and as such the true effects of nicotine in this infection remain unknown.

Does SARS-CoV-2 linger on surfaces?

During a virus-induced pandemic, in addition to the risk of interacting with infected humans, items and places may not be safe anymore. The virus might linger everywhere – on surfaces in public spaces, on clothes, or even your food or the floor you are walking on. This is somewhat an extension on the incertitude that comes with results on the dispersion capacities of the virus, where the recommended 1.5-2m distance between humans does not seem sufficient to avoid transmission entirely in numerous situations where movement and wind are added to the equation [74]. The capacity of coronaviruses to be detectable and infectious on surfaces has been studied previously [75]; the behaviour of SARS-CoV-2 is likely to be comparable. An important distinction is thereby: did the respective study detect viral RNA on surfaces, providing no information on the capacity of these traces to represent pathogenically active viral cohorts? Or was the sample taken on the surface infectious material that was capable of infecting cells in culture or may be infective to an individual?

How successful is SARS-CoV-2 in remaining a potential thread outside the human body? Van Doremalen and colleagues gave a useful estimation of SARS-CoV-2 stability on different surfaces, using the virus titre after addition to cells as a read-out. The stability of SARS-CoV-2 on fomites was comparable to SARS-CoV and increased from 3 hours on copper to 24 hours on cardboard to a stability of 2-3 days on steel and plastic. However, the decay of the viral titre was exponential on all surfaces, with a half-life of 6-8 hours even on the 'favourable' surfaces plastic and steel [76]. In another study, no infectious virus was found after just a few hours on paper and after one day on treated wood and cloth, whereas it took several days to lose infectious SARS-CoV-2 from glass and banknotes (4 days) and steel and plastic (7 days). Worryingly, the authors also noted that some infectious material was still found on surgical masks after a week and that the virus was stable at 4°C, but barely survived a couple of minutes at 70°C [77]. A prolonged survival of up to 7 days of the virus on plastic, steel, glass, wood, gloves and masks was found by Liu and colleagues, who also observed a slow decline in infectivity; cotton, cloth and paper again showed rapid infectivity decline (1 hour) and no infectious virus after 4-5 days [78]. Therefore, smooth surfaces do maintain a quantity of SARS-CoV-2 that might lead to an infection in humans, judged by an infectivity of the viral titre for cell lines. It is, however, important to note that all studies above deviated slightly in the volume of inoculation or the titre of the viral stock used – a simple statement on the number of days the virus survives on fomites and the probability of human transmission is therefore challenging to make.

Several studies also addressed the abundance of viral RNA – not concluding on the viability and infection capacity of these samples – on surfaces in hospital settings: in a Chinese hospital, viral RNA was found in eight of 22 samples – on pillows, duvet covers and sheets in a room where patients were quarantined [79]. In hospitals in Wuhan, 38 of 200 and 85 of 626 samples were positive for SARS-CoV-2 RNA and could

be found on commonly touched surfaces such as elevator buttons, the water fountain, doorknobs or computer keyboards [80, 81]. Similarly, the virus was found in laboratory settings in Madrid in four out of 22 cases [82]. Importantly, the authors noted that no virus had been transferred to personal items, underlining the importance of avoiding transmission through hygiene and social distancing measures. These findings also echo the results of testing potential exposure to SARS-CoV at Taiwan University Hospital in 2004, where the authors found viral RNA contamination on bookshelves and water fountain buttons [83], but also emphasized the need for environmental cleaning and handwashing. In addition to the aforementioned laboratory conditions and tests in hospital setting, recent work has also looked at viral RNA traces in urban areas: a study from Brazil detected SARS-CoV-2 in 17/101 sample cases from bus stations and park benches in the vicinity of hospitals [84]. Considering all of these findings, it is clear that the virus persists on smooth surfaces and is enriched in areas where SARS-CoV-2-positive individuals spent time, which should be taken into consideration when working in or visiting these areas, as the levels of infectious particles may be sufficient to transmit the virus. In line with guidelines across the world, frequent handwashing and disinfection of surfaces will strongly minimise the risk of such transmission, however.

Besides all efforts on contact-related transmission routes, there's increasing evidence for and attention towards airborne transmission of the virus: Liu and colleagues identified viral RNA in aerosols from potentially crowded, ventilated areas such as patients' toilets in a Wuhan hospital [85]; similar results came from a study conducted at the University of Nebraska Medical Center [86] and the measurements by van Doremalen and colleagues [76]. Given that residual virus-laden droplet nuclei could travel far in gas clouds emitted by sneezing, as reported for other viruses [87], social distancing and personal hygiene might not be sufficient to prevent spreading episodes after flattening of the curve in respective countries [88, 89]. There is a need to ensure sufficient ventilation, control the air flow and avoid recirculation of air in indoor environments and confined spaces, especially those where a higher density of people might be expected; for example, on public transport, in offices and restaurants [88, 90, 91].

In combination with wearing facemasks in public places [92], ventilation/air flow control might prove to become one of the key measures for the curtailment of new COVID-19 infections in countries going forward from the first phase of the 2020 lockdown.

COVID-19 in ethnic minorities

As the pandemic has progressed, an alarming trend has come to light in some of the worst affected countries: ethnic minorities seem to be disproportionally affected by severe COVID-19. The earliest clinical

studies of COVID-19 patients identified increasing age, male sex and comorbidities such as diabetes and cardiovascular disease as key risk factors for adverse outcomes and mortality [93]. However, these reports focused on the relatively ethnically homogeneous population of China. The growing number of cases in the more ethnically diverse populations of USA and UK allow the impact of ethnicity in COVID-19, labelled as 'an urgent public health priority' [94], to be more adequately assessed.

In the UK, around 14% of the population is comprised of ethnic minorities [95]. Strikingly, two-thirds of UK-based healthcare workers who had died because of the virus by 22nd April were from a Black, Asian and minority ethnic (BAME) group [96], despite individuals in this category making up only a fifth of the healthcare workforce [97]. A report generated by the Intensive Care National Audit and Research Centre indicates that BAME individuals constitute one-third of critically ill COVID-19 patients [98]. Because the UK has not been reporting ethnicity in its data on COVID-19-related mortalities, this trend has proven difficult to pinpoint. However, the Office for National Statistics used self-reported census data to provide a breakdown of coronavirus-related deaths across the UK population by ethnic group; this highlighted that, even outside of the healthcare sector, ethnic minorities have a statistically significant raised risk of death [99]. This is particularly marked in Black individuals, with males and females in this category being 4.2 or 4.3 times more likely to die because of the virus than White males or females, respectively.

Racial disparities have also been documented in US-derived COVID-19 data. In Chicago (Illinois), half of the reported COVID-positive patients and two-thirds of those who had died of the virus as of April 9th were African American [100]. This trend has been mirrored across other major US cities and is at odds with the proportion of the overall US population contributed by this ethnic group (around 14%) [101]. Although the nation-wide statistics are incomplete, ethnic minorities seem to be the hardest hit by the virus in the USA, as in the UK [102].

A number of reasons could explain why BAME individuals are at increased risk of being infected and experiencing more severe symptoms. Firstly, ethnic minorities have a higher incidence of comorbidities such as diabetes and cardiovascular disease [103, 104]. Socioeconomic and behavioural factors are also likely to play a part. In the UK, BAME are more likely to live in urban areas with overcrowded housing and in multi-generational households, making social distancing less achievable [105]. Ethnic minorities may also be overrepresented in high-risk essential employment roles, such as those in health and social care [106], thus increasing their exposure to the virus. Likewise, in the USA, ethnic minorities - particularly African Americans – tend to reside in poor areas with a high density of housing, be frontline workers, and may have limited access to healthcare [102]. Furthermore, language and educational barriers might have reduced penetration of the governmental messages advising social distancing [107]. Although

contentious, it is likely that underlying discrimination experienced by BAME in the workplace, including the healthcare sector, also contributes to enhancing this group's risk of contracting the virus [108]. There is no doubt that that this crisis has amplified the significant and pervasive social and economic disparities that lead to poorer health outcomes for ethnic minorities.

Even after adjusting for age, socio-demographic characteristics, and co-morbidities, people from BAME backgrounds are almost twice as likely to die because of COVID-19 than White people in the UK [109], a finding that is supported by an analysis of COVID-19-positive patients from UK biobank [110]. This suggests that biological factors could contribute to the increased risk.

One theory that has been put forward to explain why ethnic minorities with darker skin are more susceptible to COVID-19 is because these individuals are more likely to have low serum concentrations of 25-hydroxyvitamin D i.e. be deficient in vitamin D, particularly those living in the northern hemisphere during winter months [111-113]. Several observational studies have linked vitamin D deficiency to enhanced susceptibility to acute respiratory infections, and it has previously been suggested that supplementation could have a protective effect in influenza [114]. A number of recent preprint-posted studies suggest a link between low vitamin D status and COVID-19 [115, 116]. However, a study by researchers at the University of Glasgow looked at the vitamin D status of confirmed COVID-19 cases using UK biobank data, and found no link between the concentration of the vitamin and COVID-19 susceptibility, after adjusting for confounding factors [117]. Consistent with this, a prospective cohort study reports that there is no positive correlation between low serum vitamin D and COVID-19 infection, while also noting that individuals of Asian, Black and Mixed ethnicity in the sample set analysed were more likely to be deficient in vitamin D [118]. Many of the studies that have explored the link between vitamin D deficiency and susceptibility to SARS-CoV-2 are underpowered and have not yet been peer-reviewed. The cumulative findings reported to date were reviewed by a team of UK-based researchers who conclude that there isn't yet strong enough evidence for a causal relationship [119]. These authors nonetheless emphasise the importance of vitamin D for optimum health and recommend supplementation to those who are self-quarantining, while cautioning against overdose.

Further studies focused on ethnic group-specific prevalence of COVID-19 and outcomes are needed to better understand the multitude of factors that contribute to the disproportionate effect on ethnic minorities. It is also critical to track racial and ethnic information on positive cases and deaths and report these data transparently, to inform ongoing public health interventions across the globe.

COVID-19 in children

Since the emergence of COVID-19, it has become apparent that children are considerably less impacted by the disease than adults. Analysis of the early laboratory-confirmed cases in Wuhan reported no cases in under 15s at all [11, 12] and a low incidence in children (around 1-2% of cases) has been mirrored in subsequent epidemiological studies performed in other countries [120-123]. Children also seem to experience milder symptoms than adults or have no symptoms at all; severe and life-threatening cases are rare [124, 125]. There is a clear positive correlation between increasing age and worse outcomes in COVID-19 - in stark contrast to influenza, which tends to place the greatest burden on individuals at both ends of the age spectrum [126].

COVID-19 transmission to and from children

Are children less likely to acquire the infection or are positive cases not being detected? In many countries, testing has been skewed towards hospitalised patients, which could mean that cases in children are missed if they frequently experience mild or asymptomatic infections. Consistent with this, two studies of clinical data in China indicate that children are just a susceptible as adults, although less likely to show severe symptoms [124, 127]. However, countries that have engaged in population-level screening for SARS-CoV-2, including Iceland, Italy and South Korea, detected relatively few positive cases amongst children, particularly those under the age of 10 [120, 128, 129]. Likewise, an analysis of household transmission in China revealed a 'secondary attack rate' of only 4% to children compared with ~17% from adult-adult [130].

At this point it is unknown whether the lower incidence of SARS-CoV-2 infection in younger age groups is because of a biological characteristic or because of reduced exposure. Arguably, the widespread closure of schools in many countries could have minimised opportunities for transmission to children in recent months. This is supported by a community screening study conducted in Korea, where strict lockdown measures were implemented early on in the crisis; most confirmed cases were in 20-29 year olds [120], who potentially engaged in the most movement outside of their households during the timeframe of the analysis. However, a detailed study of transmission dynamics within 15 schools in New South Wales (Australia), which began in early March - prior to partial school closure in late March - demonstrated that only two individuals acquired the virus through transmission in a school environment, despite close contact between 18 initial confirmed cases across the schools and up to 863 others [131]. This - albeit preliminary - study supports the theory that children are not highly susceptible to SARS-CoV-2 infection and also that they aren't major drivers of its transmission to others. This theory is further bolstered by an observational study by researchers from the University of Queensland; the authors report that children were unlikely to have been the primary sources (index cases) of documented household clusters of the

infection in Iran, China, Japan, South Korea and Singapore between December 2019-March 2020 [132]. Moreover, a SARS-CoV-2-positive child identified in the French Alps did not transmit the virus to anybody else, despite being in contact with over 100 people [133]. By contrast, children act as 'super-spreaders' of other respiratory infections such as influenza [134]. These findings call into question the effectiveness of containment measures focused on children, notably large-scale school closures, to reduce the total number of COVID-19 cases in a given community [135, 136]. The role of children in transmitting the disease undoubtedly requires further investigation, particularly the transmissibility of subclinical or asymptomatic infections, which seem to be disproportionally accounted for by children [137]. A team led by Berlin-based virologist Christian Drosten recently analysed viral loads in different age categories and concluded that children might be just as infectious as adults, despite their relatively mild symptoms [138]. However, this high-profile but non-peer-reviewed study has come under heavy criticism for its potentially flawed statistical analyses, so the conclusion might be premature [139]. Reports of persistent fecal viral shedding in COVID-19-positive children also raise the possibility of fecal-oral transmission, which necessitates exploration [140, 141]. Ultimately, large-scale sero-surveillance is the only means to determine the full extent of paediatric transmission in communities.

ACE2: the key to reduced susceptibility of children to COVID-19?

Several hypotheses have been put forward to explain why, from the biological point of view, children might be relatively resistant to COVID-19. Firstly, differential levels of ACE2, the point of host entry for SARS-CoV-2, could underlie the lower susceptibility of children. Recently, Bunyavanich et al. examined *ACE2* expression in nasal epithelial samples collected from children and adults, and showed that expression of the gene was age-dependent, with children expressing lower levels than adults [142]. This is supported by the results of a single-cell RNA sequencing study assessing the expression of *ACE2* across multiple cell types in healthy donors; expression of the receptor gene and the gene for TMPRSS2, a serine protease that is also involved in viral entry, was enriched in the nasal region and upper airway of adults while being barely detectable in fetal tissues [143] (tissue taken from children was not examined in this study, however). Upregulation of ACE2 through the action of certain drugs including angiotensin II type-I receptor blockers (and ibuprofen, discussed earlier) has been implicated as a risk factor for severe COVID-19 [37], while an inherently lower level of the target receptor could limit virus entry and thus counteract infection in children. The reported upregulation of *ACE2* expression by other respiratory viruses and of *TMPRSS2* by IL-13 – a mediator of allergic inflammation - in a paediatric cohort gives insight into how co-infections and conditions such as asthma might modulate disease severity in children [144].

Counterintuitively, a higher level of ACE2 has been hypothesised to have a *beneficial* effect, based on earlier studies in mice showing that the protein protects against severe acute lung injury [145], including in the context of SARS-CoV infection [146]. Recent studies lend support to the theory that elevated ACE2 has a protective role in SARS-CoV-2 infection ([147-149]. But how can this hypothesis be reconciled with the apparently lower levels of ACE2 in the nasal epithelium of children, as reported by Bunyavanich et al.? Expression of the receptor could vary depending on tissue type; thus, a relative abundance of ACE2 in lung pneumocytes or circulating in the plasma of children could protect younger patients against severe outcomes during the later stages in viral infection [148, 150]. Given the conflicting findings to date, further investigative studies are required to define the precise role of ACE2 in different stages of SARS-CoV-2 infection and to determine whether ACE2 could be used as a biomarker for COVID-19 susceptibility. Beyond the disparity between children and adults, understanding the functional relevance and tissue distribution of ACE2 could be the key to dissecting the mechanisms driving the overactive inflammatory response characterising fatal cases of COVID-19 [46, 93], and the potential immunomodulatory effects of hormones and drugs such as ibuprofen and nicotine (discussed earlier). Other known viral entry factors should not be ignored, illustrated by a recent intriguing report that the expression of *TMPRSS2* increases in an age-dependent manner in mouse and human lung tissue, potentially contributing to the relative protection of children against severe COVID-19 [151].

The role of the immune system

It has also been speculated that the high incidence of respiratory infections in children, including other coronaviruses that are responsible for common colds, might bestow them with a degree of cross-immunity to the novel coronavirus. Frequent exposure to viruses as well as vaccines could prime the innate immune system of children to cope more effectively with new pathogens than adults [152]. The possibility that pre-existing immunity offers a degree of protection against SARS-CoV-2 is gaining traction [153, 154]. Immunosenescence, or ageing of the immune system, has also been peddled as an explanatory factor – the inevitable decline of the innate and adaptive immune systems with age could leave the elderly with a weaker defensive barrier than children [155]. Differences in abundance and type of immune cell, particularly T cells, between the young and old could account for varying degrees of susceptibility [156].

Critical illness and complications in children

It should be noted that although serious illness and death are rare in children, they do occur, and infants or those with co-morbidities may be particularly vulnerable [121, 124, 157, 158]. Moreover, a newly described paediatric multisystem inflammatory syndrome (PMIS) has recently been linked to COVID-19: the clinical features of this hyperinflammatory syndrome overlap with those of Kawasaki disease, a form of vasculitis of unknown aetiology (although an infectious agent of some kind is suspected) that most commonly affects children below the age of 5 [159]. On May 15th, the WHO released a scientific brief highlighting the urgent need to investigate the new syndrome, following reports from Europe and North America on clusters of children and adolescents with laboratory-confirmed COVID-19 displaying features reminiscent of Kawasaki disease [160]. In New York and Italy, which have been badly affected by the coronavirus outbreak, the putative link between the inflammatory syndrome and the novel virus was particularly compelling. A team of researchers in Bergamo, Italy, analysed the clinical features of a series of patients in the region who displayed symptoms of the Kawasaki-like syndrome following the local peak of the SARS-CoV-2 outbreak, and reported that many of those who had been diagnosed during this time period showed an immune response to the virus [161]. Interestingly, the children were on average older than those usually affected by Kawasaki disease and displayed a hyperinflammatory phenotype reminiscent of the cytokine storm documented in adults with severe COVID-19 [54], although there was a distinct lag in children between initial infection and overreaction of the immune system. Despite a 30-fold increase in incidence of the disease compared to previous years, the authors note that it remains a rare condition, affecting 1/1000 children exposed to SARS-CoV-2 [161]. Its rarity could explain why it is currently coming to light in COVID-19 hotspots. More than 150 cases are being investigated in New York State for a potential genetic link, using whole-genome sequencing of children and their families, as well as sequencing of the virus. Across the USA and in Canada, similar cases have arisen, while a significant cluster of cases has also emerged in London [162]. A clinical study of eight children afflicted with the syndrome in the UK reported that six of them were of Afro-Caribbean descent, five were male and all but one were above the 75th centile in weight [163]. Three children presenting with symptoms of the hyperinflammatory syndrome in Geneva, Switzerland, are male and of BAME origin and described as being clinically obese [164]. Other studies have corroborated the temporal link to infection with SARS-CoV-2 and also report that the majority of affected individuals are of African or Asian ancestry [165, 166]. These studies pinpoint potential risk factors for development of the post-infection complication, but given the small sample size analysed to date, the findings must be interpreted with caution.

Professor Russell Viner, President of the Royal College of Paediatrics and Child Health, stressed that severe illness in children with COVID-19 remains "extremely rare" [167]. Naturally, there is growing

concern about this syndrome, particularly amongst parents, but paediatric infectious disease specialists emphasise that the children do respond to treatment – fast recognition of the clinical hallmarks, irrelevant of SARS-CoV-2 test status, and referral to specialist care is imperative [162, 168]. This is particularly crucial given the potential for misdiagnosis as other conditions, such as appendicitis [166] or sepsis. An international registry of cases may be beneficial for the generation of data on PMIS as newer cases emerge.

In sum, the current evidence indicates that children are less likely than adults to acquire the infection after exposure, less likely to test positive for SARS-CoV-2 at the population-level, and potentially less likely to transmit the infection to others, although the latter conclusion is based on research performed during a period in which schools have generally been closed, so isn't necessarily reflective of the true infectivity of children. The disease in children seems to follow a milder course than in adults, with many cases being asymptomatic, but critical cases have been described and there are rare instances of a serious post-infection hyperinflammatory syndrome. There is relatively limited information about the clinical course, risk factors, infectivity and long-term outcomes of children with COVID-19, posing a challenge for governments as they weigh up the negative consequences of keeping children out of education for an extended period against the potential risks of reopening schools. Given the breadth of ongoing research on this subtopic, we refer interested readers to a comprehensive, regularly updated summary of all manuscripts published to date on COVID-19 and children, hosted by 'Don't Forget The Bubbles' [169].

Mortality rates and the possibility of a more dangerous SARS-CoV-2 cohort

One statistical read-out that has been scrutinized from the onset of the pandemic, to praise or criticise political leaders and their decision-making process, is the variation in mortality rate across Europe. Much like the overall number of infected people or the death toll in a country, however, the mortality rate is a number that should not be used as a stand-alone indicator that a country has successfully curtailed the spread of SARS-CoV-2 or succumbed to the virus. It is obvious that the mortality rate as a fraction value depends on the denominator - the total number of people tested; countries that engaged early on in a mass-testing approach such as Germany report a lower mortality rate [170], as the number of pre- or asymptomatic cases in any given population is high [171]. Conversely, countries that test those who are already admitted to hospitals with severe symptoms will inevitably report a higher mortality rate because of this pre-selection of individuals contributing to the denominator. For the UK, the death rate of COVID-

19-positive patients admitted to a hospital is 33% [172], which approaches the mortality rate of the Ebola virus during the West African 2014-2015 outbreak [173]. In addition, undocumented cases contribute to the spread of the virus, inevitably resulting in more fatalities [174]. Furthermore, some countries like Spain perform post-mortem tests for COVID-19, unlike the UK or Germany [175]. Therefore, the staggering differences between European mortality rates such as ~15% for France and ~4% for Portugal [176] are partially explained by the approach to testing each country undertakes. In addition, there are further major contributing factors, such as age distribution of the population, as COVID-19 has an age-dependent effect [177], [93] and overall government lockdown measures [178]. The tracking of excess deaths compared to previous years could give a more reliable read-out of the impact of COVID-19 than mortality rates and total numbers [179].

An alternative explanation for the differences in mortality has been put forward recently: that mutation events in the viral genome have generated more transmissible and therefore dangerous cohorts of SARS-CoV-2. While the prospect of a mutated virus having become "far deadlier in Europe" [180] provides a template for science-fiction movie enthusiasts and doomsday aficionados, there is accumulating evidence of independent mutation events creating genetic diversity of SARS-CoV-2 and different sub-groups, likely providing an adaptation of the virus to its human host [181-184]. Much like any living organism that depends on DNA- or RNA-polymerase-driven replication, SARS-CoV-2 (an RNA virus) will introduce mutations in its genome and diversify over time from the early cohorts identified in China. Therefore, there is potential for a virus with a high transmission rate and elevated mortality rates to become even more pathogenic if mutations in highly evolvable sites affect the host-viral interface [185-187]. However, SARS-CoV-2 has a mutation rate that is considerably lower than that of SARS-CoV and the seasonal flu [188-190]. The basis of the news stories on more dangerous versions of SARS-CoV-2 in Europe and the US were reports on mutated viral sub-groups with a higher pathogenicity and certain mutated forms of the virus being more prevalent in highly affected regions or countries of the world [191, 192]. The mutations in the viral genome in both studies focus on the spike (S) protein of the virus, which has been identified as an anchor point for viral transmission and the global vaccine strategy. However, both datasets are far from being conclusive: the tests on viral pathogenicity were run on monkey cells and a very small sample size and the standard in virus sampling in this study remains unclear. The dominant occurrence of mutated viral cohorts may be due to a favourable environment of transmission for the virus, not an inherent increased transmissibility: "The increase in the […] variant may well reflect a population bottleneck, in which it happens to be the one that gets into the (relatively inattentive) European population and then spreads like wildfire. That's what I think happened", commented Bill Hanage,

Associate Professor at the Center for Communicable Disease Dynamics, Department of Epidemiology at the Harvard T.H. Chan School of Public Health on social media [193]. In addition, there appear to be problems with the sequencing data of SARS-CoV-2 and its interpretation, which may lead to artefacts in the identification of viral mutations [194-196]. In a similar way, another study that had gained much media attention by claiming the existence of two different types of SARS-CoV-2, the S-lineage and a "more aggressive" L-lineage [195], has been called into question by the scientific community for over-interpretation of data and technical flaws [197]. These cases further highlight the importance of a thorough peer-review process for quality control of new findings during a pandemic.

Whereas it is of central importance to monitor and analyse the evolution of the genome of SARS-CoV-2, it is clearly too early to conclude that any shift has happened to generate more pathogenic strains that may even account for the increased mortality rate in certain countries. Instead, the mortality rate is a value that needs to be discussed in the context of the overall testing approach and statistical method of the respective country, and in comparison with other regions or nations.

Conclusions and Outlook

SARS-CoV-2 has swept through the world at a staggering pace since its murky beginnings in late 2019, and its exponential growth has been paralleled by the research efforts undertaken to understand the biology and transmission dynamics of the virus. There has never been a better time for the rapid dissemination of research, with the rise of preprint servers and social media. Publishers have also risen to the challenge, fast-tracking normal processes so that COVID-19 research can be published as quickly as possible and, in many cases, the content is made freely available. Speed is paramount during a novel disease outbreak as new information can immediately guide public health policies and treatment strategies. However, pandemics have historically been breeding grounds for conspiracy theories, and COVID-19 has proven no exception to this. Digital information channels - particularly social media - are rife with misinformation and fake news, fuelling confusion, fear, and potentially harmful actions such as self-treatment with supposed cures for the disease. The surge in preprints has made it particularly easy for anybody to access new studies relating to the virus – studies that have not been peer-reviewed and thus may be ill-founded.

Nonetheless, the extraordinary efforts of the research community have ensured that a picture of SARS-CoV-2 is emerging through the haze – its history and characteristics, risk factors for infection and details of the clinical course. We hope that by sifting through some of the ever-growing literature and providing a summary of current hypotheses on seven COVID-19-related topics that have prompted lively discussion, we have helped our readers get to grips with the science-based facts relevant to these research threads.

We also hoped to highlight key gaps in knowledge that prevent a consensus from being reached on certain questions, although must emphasise that some of the information presented here will almost certainly be out of date by the time that the article is published.

Ironically, despite the churning out of information, there is a lot that we still don't know about SARS-COV-2. The unexpected clinical characteristics of the disease, described by intensive care unit doctors as 'baffling' [198] may challenge attempts to take breakthroughs from the bench to bedside. As lockdowns are eased and we warily assess the impact on COVID-19 cases, particularly of 'superspreader' events that could trigger clusters of new infections [199], we also eagerly await new evidence on the impact of the virus at the level of the immune system, which is critical for effective prevention and treatment of the disease. Now is not the time for science to lose momentum. But as the literature grows, we urge you to read the original research, not the headlines.

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