

COVID-19 Research in Brief: December, 2019 to June, 2020

This week marks our last COVID-19 Research in Brief. COVID-19 research has been progressing at a staggering speed. But a lot still needs to be uncovered to effectively fight this pandemic. We look back at 6 months of biomedical research on COVID-19.

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Clinical testing

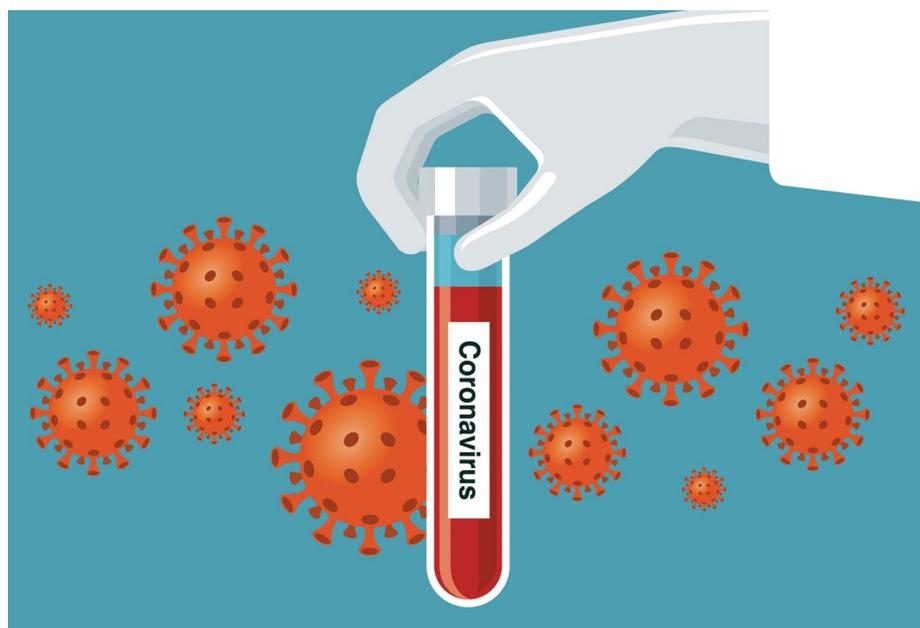
RT-PCR tests for viral detection were the first available clinical tests, though scaling up their production and availability has been a persistent challenge in many countries. Important testing advances have included the development of [saliva-based protocols](#) and [loop-mediated isothermal amplification protocols](#) for SARS-CoV-2 detection. Serological testing for SARS-CoV-2 received an early boost by the development and sharing of reagents by the [Krammer lab at Mount Sinai, New York](#).

Drug repurposing

The rapid spread of COVID-19, which by March had led to nationwide lockdowns in Italy and Spain, spurred attempts at drug repurposing. On 22 March, the [WHO launched SOLIDARITY](#), a global trial of four therapies: the RNA polymerase inhibitor remdesivir, chloroquine and hydroxychloroquine ([this arm has now been stopped](#)), the HIV protease inhibitor combination lopinavir and ritonavir (results so far are [not encouraging](#)), and lopinavir-ritonavir plus interferon- β (which has shown reduced viral shedding and alleviated symptoms in [one open-label trial](#)). At time of writing, two drugs have been shown to be effective in clinical trials, remdesivir and the corticosteroid dexamethasone. In randomized control trials, remdesivir [shortened the length of hospitalization](#), but did not have a significant impact on mortality; dexamethasone [significantly reduced mortality](#) in patients requiring supplemental oxygen.

Candidate vaccines

By April, human trials were underway for several vaccine candidates, including established approaches like [inactivated SARS-CoV-2](#) preparations as well as more recent strategies such as [RNA-](#) and [adenovirus-derived](#) products. Early results on safety and immunogenicity are already available for some of these, with Moderna



Credit: sorbetto / DigitalVision Vectors / Getty

announcing that its RNA SARS-CoV-2 vaccine induced a specific antibody [response in phase I trials](#), and CanSino also showing [specific antibody induction](#) by its adenovirus-based vaccine. Passive immunization is also being pursued by various means, including [convalescent plasma](#), [hyperimmune serum](#) preparations and the development of SARS-CoV-2-specific [monoclonal antibodies](#).

Pathogenesis

While the infectious agent was rapidly identified, understanding COVID-19 pathogenesis has proven much more difficult. Though respiratory failure remains the most frequent serious clinical feature of COVID-19, reports have linked SARS-CoV-2 infection to [coagulopathy and vascular disease](#), neurological defects (predominantly [loss of taste and smell](#)),

[kidney disease](#), [stroke in young people](#), [Kawasaki-like syndrome in children](#), and an array of other conditions. The risk of severe COVID-19 is clearly not evenly distributed, with age the single most important risk factor, and a clear [increased susceptibility in males](#). A [genome-wide association study](#) has also shown a link between ABO blood groups and severe COVID-19, with blood type A conferring increased susceptibility and blood type O conferring moderate protection. Hypertension and [diabetes](#) remain the most important comorbidities. Several studies have found that commonly used angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers have no negative effect on the outcomes of patients with COVID-19.

Our knowledge of tissue tropism of SARS-CoV-2 is [also rapidly expanding](#),

Global events

December 2019	January 2020	February 2020	March 2020	April 2020	May 2020	June 2020
<p>31 December Chinese authorities notify WHO of an outbreak of "pneumonia of unknown causes" in Wuhan City, Hubei</p>	<p>11 January First reported COVID-19 death in Wuhan</p> <p>23 January China decrees a lockdown of Wuhan, a city of 11 million people</p> <p>21 January First confirmed US case of COVID-19 in Washington state</p>	<p>2 February First COVID-19 death outside of mainland China, in the Philippines</p> <p>14 February Egypt reports first African COVID-19 case</p> <p>19 February Iran reports first two deaths from COVID-19</p> <p>20 February First case in Lombardy, Italy</p> <p>25 February Lockdown decreed in 11 towns in Lombardy</p> <p>26 February Brazil reports first COVID-19 case in Latin America</p>	<p>9 March Nationwide lockdown in Italy</p> <p>11 March WHO declares COVID-19 a pandemic</p>	<p>2 April Global COVID-19 cases pass 1 million, with 50,000 deaths</p> <p>8 April Wuhan lockdown ends</p> <p>10 April Global COVID-19 death toll exceeds one 100,000</p> <p>28 April 1 million confirmed COVID-19 cases in the USA</p>	<p>5 May UK records highest number of deaths in Europe, with 30,000</p> <p>21 May Global cases pass the 5 million mark</p> <p>23 May China reports no new infections for the first time since the beginning of its outbreak</p> <p>27 May US COVID-19 deaths exceed 100,000</p>	<p>22 June COVID-19 deaths in Brazil pass 50,000</p> <p>23 June Global COVID-19 cases pass 9.1 million, with over 470,000 deaths</p>

Medical and scientific events of importance

<p>9 January China announces preliminary identification of a new virus associated with the pneumonia outbreak, after two days of rumors</p> <p>10 January First draft of SARS-CoV-2 genome posted</p>	<p>3 February SARS-CoV-2 shown to be 96% identical to bat RaTG13</p> <p>21 February Asymptomatic carriers implicated in SARS-CoV-2 transmission</p> <p>25 February NIH announces phase 3 trial of remdesivir to treat COVID-19</p>	<p>16 March Moderna begins phase 1 trials of its RNA-based COVID-19 vaccine</p> <p>17 March Genomic analysis strongly supports a natural origin for SARS-CoV-2</p> <p>22 March WHO launches Solidarity trial of four COVID-19 therapies</p> <p>27 March Oxford adenovirus COVID-19 vaccine trial begins phase 1</p> <p>27 and 30 March Three groups report structures of SARS-CoV-2 spike protein RBD bound to human receptor ACE2</p> <p>30 March Study of patients with COVID-19 admitted to Seattle area ICUs finds 50% mortality</p>	<p>15 April Remdesivir shown to reduce SARS-CoV-2 titers in rhesus macaques</p> <p>15 April Early peak in SARS-CoV-2 viral load points to importance of transmission by presymptomatic carriers</p> <p>16 April Protease TMPRSS2 shown to prime SARS-CoV-2 spike protein for binding to human ACE2</p> <p>17 April Sinovac begins phase 1 trials of its inactivated SARS-CoV-2 vaccine</p> <p>29 April NIAID director Anthony Fauci announces remdesivir is a "new standard of care" for COVID-19; the drug shows no effect on mortality, but reduces hospitalization time</p>	<p>6 May Autopsy study suggests coagulopathy is important in the pathogenesis of lethal COVID-19</p> <p>13 and 14 May Italian and French centers report an abnormal incidence of a Kawasaki-like syndrome in children, associated with COVID-19</p> <p>14 May T cell reactivity to SARS-CoV-2 antigens is found in unexposed people</p> <p>22 May CanSino publishes results of phase 1 studies of its adenovirus-based COVID-19 vaccine showing positive safety and immunogenicity data</p>	<p>11 June Regeneron initiates phase 1 trials of its dual monoclonal antibody cocktail against SARS-CoV-2</p> <p>16 June Dexamethasone becomes the first drug shown to reduce COVID-19 mortality in a clinical trial</p> <p>20 June NIH halts hydroxychloroquine COVID-19 trial, citing no evidence of clinical benefit</p>
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WHO, World Health Organization; NIH, US National Institutes of Health; ICU, intensive care unit; RBD, receptor-binding domain; NIAID, National Institute of Allergy and Infectious Diseases.

Six months of COVID-19 research Credit: Nature Medicine

and it is clear that cell types outside the respiratory system can be infected, particularly in the gut epithelium. The role of SARS-CoV-2 infection in different tissues during COVID-19 pathogenesis is a key open question. Efforts to understand innate immune components of resistance to SARS-CoV-2 are also ongoing, including genetic surveys of the role of primary immunodeficiencies.

Immunity

Fundamental questions about immunity to SARS-CoV-2 remain. Perhaps chief among these are the immune correlates of protection, and the duration of immunity. The most consistent link to high serum anti-SARS-CoV-2 antibody levels has been with severity of disease, and a recent study has found a significant drop in specific antibody levels after three months. T cell

immunity to SARS-CoV-2 is also only beginning to be understood, and there is some indication that cross-reactive T cell immunity to other coronaviruses may be relatively frequent.

Transmission

The susceptibility of children to SARS-CoV-2 infection and their role in transmission remain the subject of debate, particularly in the context of discussion on efficacy of school-closure measures. A widely publicized study from Harvard's Chan School of Public Health predicted that "prolonged or intermittent social distancing may be necessary into 2022", and modeling suggests that seasonal climate variation effects on SARS-CoV-2 transmission will not be sufficient to halt the COVID-19 pandemic. Several studies are now attempting to unravel

the efficacy of lockdown, social isolation, mask usage, contact tracing, and other non-pharmacological interventions in containing COVID-19. The looming question in COVID-19 epidemiology is without doubt the existence, timing, and severity of a putative second wave. If and when this wave arrives, we will be facing it armed with an impressive amount of basic scientific knowledge, a set of tools and practices ranging from prone positioning of patients to cutting-edge pharmacological approaches, and the hope of responsible public health policies.

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