Some important issues about COVID-19

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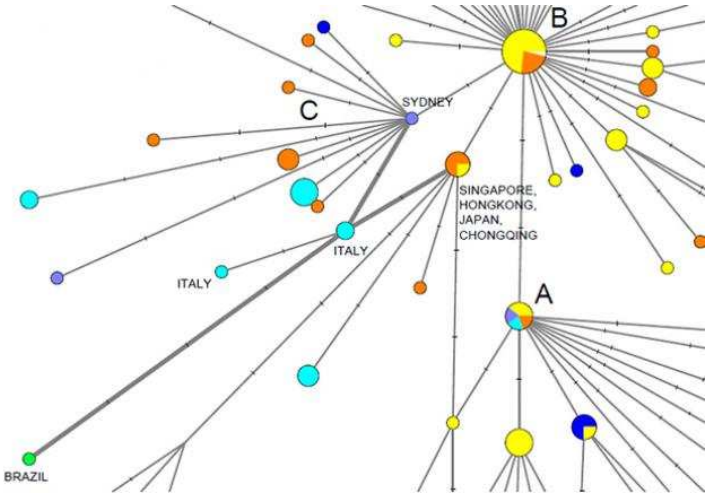
a. Where is the origin of COVID-19?

Study charts the "incipient supernova" of COVID-19 through genetic mutations as it spread from China and Asia to Australia, Europe and North America. Researchers say their methods could be used to help identify undocumented infection sources.

Researchers from Cambridge, UK, and Germany have reconstructed the early "evolutionary paths" of COVID-19 in humans – as infection spread from Wuhan out to Europe and North America – using genetic network techniques.
By analysing the first 160 complete virus genomes to be sequenced from human patients, the scientists have mapped some of the original spread of the new coronavirus through its mutations, which creates different viral lineages.

COVID-19: genetic network analysis provides 'snapshot' of pandemic origins



"These techniques are mostly known for mapping the movements of prehistoric human populations through DNA. We think this is one of the first times they have been used to trace the infection routes of a coronavirus like COVID-19."

The team used data from virus genomes sampled from across the world between 24 December 2019 and 4 March 2020. The research revealed three distinct "variants" of COVID-19, consisting of clusters of closely related lineages, which they label 'A', 'B' and 'C'.

Forster and colleagues found that the closest type of COVID-19 to the one discovered in bats – type 'A', the "original human virus genome" – was present in Wuhan, but surprisingly was not the city's predominant virus type.
Mutated versions of 'A' were seen in Americans reported to have lived in Wuhan, and a large number of A-type viruses were found in patients from the US and Australia.

Wuhan's major virus type, 'B', was prevalent in patients from across East Asia. However, the variant didn't travel much beyond the region without further mutations – implying a "founder event" in Wuhan, or "resistance" against this type of COVID-19 outside East Asia, say researchers.
The 'C' variant is the major European type, found in early patients from France, Italy, Sweden and England. It is absent from the study's Chinese mainland sample, but seen in Singapore, Hong Kong and South Korea.
The new analysis also suggests that one of the earliest introductions of the virus into Italy came via the first documented German infection on January 27, and that another early Italian infection route was related to a "Singapore cluster".

Importantly, the researchers say that their genetic networking techniques accurately traced established infection routes: the mutations and viral lineages joined the dots between known cases.

Variant 'A', most closely related to the virus found in both bats and pangolins, is described as "the root of the outbreak" by researchers. Type 'B' is derived from 'A', separated by two mutations, then 'C' is in turn a "daughter" of 'B'.

Researchers say the localization of the 'B' variant to East Asia could result from a "founder effect": a genetic bottleneck that occurs when, in the case of a virus, a new type is established from a small, isolated group of infections.

Forster argues that there is another explanation worth considering. "The Wuhan B-type virus could be immunologically or environmentally adapted to a large section of the East Asian population. It may need to mutate to overcome resistance outside East Asia. We seem to see a slower mutation rate in East Asia than elsewhere, in this initial phase."

https://www.cam.ac.uk/research/news/covid-19-genetic-network-analysis-provides-snapshot-of-pandemic-origins

b. Stop the coronavirus stigma now

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The pandemic is fueling deplorable racism and discrimination, especially against Asian people. Education and research will also pay the price.

When the World Health Organization (WHO) announced in February that the disease caused by the new coronavirus would be called COVID-19, the name was quickly adopted by organizations involved in communicating public-health information. As well as naming the illness, the WHO was implicitly sending a reminder to those who had erroneously been associating the virus with Wuhan and with China in their news coverage— including *Nature*. That we did so was an error on our part, for which we take responsibility and apologize.

For years, it was common for viral diseases to be associated with the landscapes, places or regions where the first outbreaks occurred — as in Middle East respiratory syndrome, or Zika virus, named after a forest in Uganda. But in 2015, the WHO introduced guidelines to stop this practice and thereby reduce stigma and negative impacts such as fear or anger directed towards those regions or their people. The guidelines underlined the point that viruses infect all humans: when an outbreak happens, everyone is at risk, regardless of who they are or where they are from.

And yet, as countries struggle to control the spread of the new coronavirus, a minority of politicians are sticking with the outdated script. US President Donald Trump has repeatedly associated the virus with China. Brazilian lawmaker Eduardo Bolsonaro — the son of President Jair Bolsonaro — has called it “China’s fault”. Politicians elsewhere, including in the United Kingdom, are also saying that China bears responsibility.
Continuing to associate a virus and the disease it causes with a specific place is irresponsible and needs to stop. As infectious-disease epidemiologist Adam **Kucharski** reminds us in his timely book The Rules of Contagion, published in February, history tells us that pandemics lead to communities being stigmatized, which is why we all need to exercise more care. If in doubt, seek advice, and always fall back on the consensus of the evidence.

c. How strong is this virus?

The “incubation period” means the time between catching the virus and beginning to have symptoms of the disease. Most estimates of the incubation period for COVID-19 according to

WHO range from 1-14 days, most commonly around five days. These estimates will be updated as more data become available[1].

The research paper on " Clinical characteristics of 2019 novel coronavirus infection in China" led by Zhong Nanshan was published on the preprint server medRxiv on 09 Feb. 2020. According to the paper, the median incubation period for new coronary pneumonia is 3.0 days, up to 24 days (only 1 out of 1,099 patients has incubation period of 24 days)[2].

The coronavirus that causes Covid-19 can produce more than three times the amount of pathogens than the strain that caused the severe acute respiratory syndrome (SARS) outbreak in 2003, although patients may display less inflammatory and immune responses, a study has found.

The finding from the research, led by prominent Hong Kong microbiologist Yuen Kwok-yung, is the first of its kind based on tests conducted on lung tissue removed from patients. The results underlined the virality of the disease, as well as difficulties for health authorities worldwide to detect it compared to SARS.

The virus is like a ninja, replicating inside the body with lower interferons and inflammatory response Jasper Chan, clinical assistant professor, University of Hong Kong medical school "In some cases, Sars-CoV-2 could replicate by about 100 times within 48 hours, while the Sars virus may have peaked at about 10 to 20 times of replications," Dr Chu Hin, research assistant professor from HKU's medical school, said.

Despite reproducing more efficiently, the new virus induced slower immune and inflammatory responses, according to the study. Unlike the SARS virus, the SARS-CoV-2 almost did not induce any signaling protein interferons within 48 hours, which is key in triggering the immune system to counteract against the virus.The replication capacity of the new coronavirus is about 3.2 times higher than that of the SARS virus. In addition, when the human body is infected with the virus, the body cells secrete interferon with antiviral function, but the study found that 48 hours after the lung tissue was infected with the new coronavirus It has only risen two or three times, which is lower than the ten-fold increase in SARS infection.

Thus, unlike SARS and Middle East respiratory syndrome which have viral loads peaking at day 7 to day 10 and therefore sufficient time for antivirals to act and reduce the peak viral loads, early initiation of antiviral therapy would be even more important to improve the clinical outcome of COVID-19[3] [4].

This report was Published: 10:29pm, 11 Apr, 2020

(Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: an *ex vivo* study with implications for the pathogenesis of COVID-19 on Clinical Infectious Diseases)[5].

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1 https://www.who.int/news-room/q-a-detail/q-a-coronaviruses

2 https://www.medrxiv.org/content/10.1101/2020.02.06.20020974v1

3 Peiris JS, Chu CM, Cheng VC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003; 361(9371): 1767-72.

4 Chan JF, Lau SK, To KK, Cheng VC, Woo PC, Yuen KY. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. Clin Microbiol Rev 2015; 28(2): 465-522.

5 https://www.scmp.com/news/hong-kong/health-environment/article/3079502/coronavirus-causes-covid-19-can-produce-more

d. How many people are infected now?

COVID-19 appears to be highly efficient in person-toperson transmission and frequently cause asymptomatic infections[6].

The clinical manifestations of COVID-19 can vary from asymptomatic virus shedding among household contacts, mild upper respiratory tract infection, acute asymptomatic walking pneumonia, to symptomatic pneumonia with bilateral multifocal ground-glass opacities on lung imaging studies, and severe pneumonia with acute respiratory distress syndrome and multiorgan failure[7].

A coronavirus test for anyone? In **Iceland**, it's happening[8].As of April 9, Iceland time, the country has detected a total of 32,623 people, accounting for nearly 9% of the total population. During the same period, the **United States** completed approximately 1.1 million tests, accounting for approximately 0.34% of the total population. In **South Korea**, which is also a large-scale free screening, the test volume accounts for 0.9% of the total population.Iceland lab's testing suggests 50% of coronavirus cases have no symptoms[9].

e. No effective cure drugs

1) Hydroxychloroquine

Dr. Fauci, the core member of the White House Outbreak Special Action Team and an NIH authoritative infectious disease expert.

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6 https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa410/5818134

7 Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020.

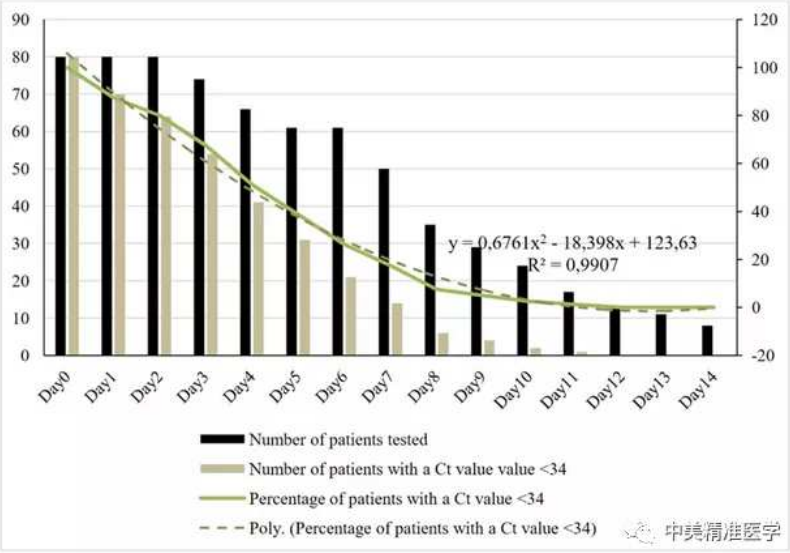
8 https://www.pressdemocrat.com/news/10884442-181/a-coronavirus-test-for-anyone

9 https://edition.cnn.com/2020/04/01/europe/iceland-testing-coronavirus-intl/index.html

"Yeah, of course, particularly if people have no other option" Fauci said. "These drugs (#hydroxychloroquine) are approved drugs, Physicians can prescribe that in off-label way. Which means they can write it for something it was not approved for."

Fauci Would Prescribe Chloroquine to Patient Suffering From COVID-19
Editor's Note: Did you know there is a special column

On March 20, the French scientist Dr. Didier Raoult and his colleagues published the clinical trial paper in the international peer-reviewed journal "International Journal of Antimicrobial", which seems to have the most conclusive results. Their clinical trials verified that the antimalarial drug hydroxychloroquine + azithromycin combined treatment of new coronavirus infection almost reached 100% (see figure below).



Dr. Raoult published the results of 80 cases of hydroxychloroquine + azithromycin in the treatment of new coronavirus infection / new coronary pneumonia (diagram)

Immediately after the publication of the research paper for this clinical trial, many of the fatal flaws were dug by professional peers. For example, the trial group had only 6 patients; the trial design was an observational, open trial, not a randomized controlled trial; participating patients "shed" too much.

International colleagues even believe that if the epidemic is not urgent, the results of such clinical trials data are really embarrassing to come up with, let alone draw any conclusions. However, the "laurel" of hydroxychloroquine for the treatment of new coronavirus infection was put on by President Trump:

Trump Again Promotes Use of Unproven Anti-Malaria Drug; Deaths in Country May Be Undercounted

For the second straight day, the president pushed the use of hydroxychloroquine, which has not been proven to treat the coronavirus (Published April 5, 2020).

At a White House coronavirus briefing Sunday, President Trump continued to push hydroxychloroquine against the advice of doctors and health experts who say its efficacy against the coronavirus is unproven and warn of dangerous side effects.
Mr. Trump suggested he was speaking on gut instinct, and acknowledged he had no expertise on the subject.
“But what do I know? I’m not a doctor,” Mr. Trump said, after recommending the anti-malaria drug’s use for coronavirus patients as well as medical personnel at high risk of infection.
Saying that the drug is “being tested now,” Mr. Trump said “there are some very strong, powerful signs” of its potential, although health experts say the data is limited and that more study of the drug’s effectiveness against the coronavirus is needed.

“If it does work, it would be a shame we did not do it early,” Mr. Trump said, noting again that the federal government has purchased and stockpiled 29 million doses of the drug. Mr. Trump added, “We are sending them to various labs, our military, we’re sending them to the hospitals.”
“What do you have to lose?” Mr. Trump asked, for the second day in a row.
When a reporter asked Dr. Anthony S. Fauci, the director of the National Institute of Allergy and Infectious Diseases, to weigh in on the question of using hydroxychloroquine, Mr. Trump stopped him from answering. As the reporter noted that Dr. Fauci was the president’s medical expert, Mr. Trump made it clear he did not want the doctor to answer.
“He’s answered the question 15 times,” the president said, stepping toward the lectern where Mr. Fauci was standing.
Peter Navarro, the president’s trade adviser who is overseeing supply chain issues related to the coronavirus, plopped a sheaf of folders on the table and said he had seen several studies from various countries, as well as information culled from C.D.C. officials, showing the “clear” efficacy of chloroquines in treating the coronavirus.
Dr. Fauci pushed back, echoing remarks he has made in a series of interviews in the last week that rigorous study is still necessary. Mr. Navarro, an economist by training, shot back that the information he had collected was “science,” according to the people familiar with what took place.
Dr. Megan L. Ranney, an emergency physician at Brown University in Rhode Island and editor for the journal Annals of Emergency Medicine, said in an interview on Sunday night that she had never seen an elected official advertise a miracle cure the way Mr. Trump has done.
“There are side effects to hydroxychloroquine,” Dr. Ranney said. “It causes psychiatric symptoms, cardiac problems and a host of other bad side effects.”
Dr. Ranney said hydroxychloroquine could be effective for some patients, but there wasn’t nearly enough scientific evidence to support Mr. Trump’s claims.
“There may be a role for it for some people,” she said, “but to tell Americans ‘you don’t have anything to lose,’ that’s not true. People certainly have something to lose by taking it indiscriminately.”
Dr. Kenneth B. Klein, a consultant who works for drug companies to design and evaluate their clinical trials, said patients with heart troubles and other underlying conditions are more likely to be severely affected by the coronavirus, so they might also be at higher risk of dangerous side effects from hydroxychloroquine.
“What have we got to lose?” Dr. Klein said, echoing similar remarks Mr. Trump has made in support of the drug. “We’ve got patients to lose from dangerous side effects.”
Other researchers have noted that while future trials may show a benefit, hydroxychloroquine has disappointed in the past, even though it has been tested as a treatment for other viruses, including influenza.
“Hydroxychloroquine has been studied as a possible antiviral therapy for many decades,” said Dr. Luciana Borio, who oversaw public health preparedness for the National Security Council in Mr. Trump’s White House and was previously the acting chief scientist at the Food and Drug Administration under President Barack Obama. “Despite showing evidence of activity against several viruses in the laboratory, it never showed success in randomized clinical trials.”
Mr. Trump defended his constant promotion of the drug, which is also often prescribed for patients with lupus.

“We don’t have time to go and say, ‘Gee, let’s take a couple of years to test it out,’ and test with the test tubes and the laboratories,” Mr. Trump said. “I’d love to be able to do that, but we have people dying today.”
“I’m not acting as a doctor. I’m saying, do what you want,” he added.

Statement on IJAA paper

International Society of Antimicrobial Chemotherapy
www.ISAC.world

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial (Gautret P et al. PMID 32205204)

ISAC shares the concerns regarding the above article published recently in the International Journal of Antimicrobial Agents (IJAA). The ISAC Board believes the article does not meet the Society's expected standard, especially relating to the lack of better explanations of the inclusion criteria and the triage of patients to ensure patient safety.

Despite some suggestions online as to the reliability of the article's peer review process, the process did adhere to the industry's peer review rules. Given his role as Editor in Chief of this journal, Jean-Marc Rolain had no involvement in the peer review of the manuscript and has no access to information regarding its peer review. Full responsibility for the manuscript's peer review process was delegated to an Associate Editor.

Although ISAC recognises it is important to help the scientific community by publishing new data fast, this cannot be at the cost of reducing scientific scrutiny and best practices. Both Editors in Chief of our journals (IJAA and Journal of Global Antimicrobial Resistance) are in full agreement.

Andreas Voss
ISAC President

Hydroxychloroquine-COVID-19 study did not meet publishing society's "expected standard"

Adam Marcus • April 6, 2020

Didier Raoult

The paper that appears to have triggered the Trump administration's obsession with hydroxychloroquine as a treatment for infection with the novel coronavirus has received a statement of concern from the society that publishes the journal in which the work appeared.

The April 3, 2020, notice, from the *International Journal of Antimicrobial Agents*, states that the March 20 article, "Hydroxychloroquine and azithromycin as a treatment of Covid-19: results of an open-label non-randomized clinical trial"

> *does not meet the [International Society of Antimicrobial Chemotherapy's] expected standard, especially relating to the lack of better explanations of the inclusion criteria and the triage of patients to ensure patient safety.*

The notice, which is from the ISAC and not the journal itself, is a bit ambiguous. The society says it "shares the concerns" about the paper, but it doesn't appear to be taking additional action.

The study was led by Didier Raoult, of the University of Marseille, whose publication history has come under scrutiny.

Last month, Elisabeth Bik took a close look at the *IJAA* article and detailed a long list of serious problems with the study, including questions about its ethical underpinnings, messy confounding variables, missing patients, rushed and conflicted peer review, and confusing data.

Others have used PubPeer to report additional issues with the Raoult article.

Raoult has not responded to a request for comment from Retraction Watch.

2) Remdesivir

On April 10th, NEJM published an article reporting the efficacy of Remdesivir sympathetic medication in the treatment of severe COVID-19 patients. This is also the first clinical study result of Remdesivir treatment of COVID-19.


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Compassionate Use of Remdesivir for Patients with Severe Covid-19

The study came from multiple clinical centers in the United States, Canada, Europe, and Japan. The study gave a total of 61 symptomatic patients with "sympathetic medication" from January 25 to March 7. These patients may have a blood oxygen saturation of 94% or less, or receive any oxygen therapy and assisted ventilation. The study applied a method synchronized with China's clinical trials. The course of medication was 10 days, with 200 mg intravenously on the first day and 100 mg daily for the next 9 days.

Of the 61 patients who received at least one Remdesivir treatment, data from 8 patients could not be analyzed (7 of which had no post-treatment data and 1 patient had a dose error). The study eventually collected data from 53 patients. Before applying the drug, a total of 30 patients received ventilator therapy and 4 patients received ECMO.

After receiving treatment (median follow-up of 18 days), 36 patients who received Remdesivir achieved clinical improvement (36/53, 68%), including 17 patients who were extubated (17/30, 57%). Twenty-five patients were discharged (25/53, 47%) and 7 died (7/53, 13%). After receiving Remdesivir, the mortality rate of patients with invasive mechanical ventilation was 18% (6/30 + 4).

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Invasive Ventilation (N=34)	Noninvasive Oxygen Support (N=19)	Total (N=53)
Median age (IQR) — yr	67 (56–72)	53 (41–68)	64 (48–71)
Age category — no. (%)			
<50 yr	6 (18)	8 (42)	14 (26)
50 to <70 yr	14 (41)	7 (37)	21 (40)
≥70 yr	14 (41)	4 (21)	18 (34)
Male sex — no. (%)	27 (79)	13 (68)	40 (75)
Region — no. (%)			
United States	14 (41)	8 (42)	22 (42)
Japan	8 (24)	1 (5)	9 (17)
Europe or Canada	12 (35)	10 (53)	22 (42)
Oxygen-support category — no. (%)			
Invasive ventilation	34 (100)	—	34 (64)
Invasive mechanical ventilation	30 (88)	—	30 (57)
Extracorporeal membrane oxygenation	4 (12)	—	4 (8)
Noninvasive oxygen support	—	19 (100)	19 (36)
Noninvasive positive-pressure ventilation	—	2 (11)	2 (4)
High-flow oxygen	—	5 (26)	5 (9)
Low-flow oxygen	—	10 (53)	10 (19)
Ambient air	—	2 (11)	2 (4)
Median duration of symptoms before remdesivir therapy (IQR) — days	11 (8–15)	13 (10–14)	12 (9–15)
Coexisting conditions — no. (%)			
Any condition	25 (74)	11 (58)	36 (68)
Hypertension	9 (26)	4 (21)	13 (25)
Diabetes	8 (24)	1 (5)	9 (17)
Hyperlipidemia	6 (18)	0	6 (11)
Asthma	5 (15)	1 (5)	6 (11)
Median laboratory values (IQR)			
ALT — IU per liter	48 (31–79)	27 (20–45)	37 (25–61)
AST — IU per liter	39 (30–76)	35 (28–46)	36 (29–67)
Creatinine — mg per deciliter	0.90 (0.66–1.17)	0.79 (0.63–1.00)	0.89 (0.64–1.08)

* ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and IQR interquartile range. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

In terms of safety, mild to moderate increases in liver enzymes (ALT and / or AST) were observed (23%, n = 12/53), and no new safety signals were found.

This study is an observational study of "sympathetic treatment" given to multi-center critically ill patients. Judging from the clinical results compared with the historical cohort, Remdesivir has a good effect, which can greatly improve the clinical manifestations of critically ill patients and significantly reduce the mortality of patients with mechanical ventilation. Therefore, there is an urgent need to uncover blindness in large-scale RCT trials to judge its exact efficacy.

"Although encouraging results were observed in this sympathetic medication analysis, the data is

limited," said Dr. Merdad Parsey, chief medical officer of Gilead. Gilead is conducting multiple clinical trials of Remdesivir, and preliminary data is expected to be released in the next few weeks.