4. *The sponsor provided study size estimates for 1:1 matching for true RR=1, 1.2 and 1.4 in Appendix 1.*

   The sponsor's response is acceptable.

The sponsor submitted C4591021(EU) protocol. Below are the comments:

1. *Page 21. Section 9.1.1.1. Matching process.*

   The sponsor proposed "a 1:1 matching without replacement using a 'rolling cohort' design". A vaccinated individual will be censored if his/her unvaccinated match is vaccinated later.

   If rapid vaccine rollout happens and a large number of individuals receive vaccines within a short period of time, many vaccinated individuals may get censored. This will have a negative impact on the person time. Please clarify how you plan to address this potential issue.

2. *Page 23. Section 9.1.2. Self-controlled risk interval (SCRI) design.*

   Figure 1 illustrated a SCRI example with a risk window of 42 days and a control window of 42 days. Please clarify how the risk interval and control interval are defined for a fully vaccinated individual. For example, for a person who receives the 2nd dose 21 days after the 1st dose, the 1st dose and the 2nd dose risk intervals overlap. Is the risk window 42 days or 42+21=63 days? Is the control window 42 days or 42+21=63 days?

3. *Page 29. Section 9.3.2.1. Safety outcomes*

   Table 1, Heparin-induced thrombocytopenia (HIT)–like event has a risk interval of 15 days. For a person who receives the 2nd dose 21 days after the 1st dose, the 1st dose risk interval and the 2nd dose risk interval do not overlap. Please clarify the HIT-like event risk and control windows for people who receive two doses.

4. *Page 29 Section 9.3.2.1. Safety outcomes*

   Table 1 Cardiovascular system. Myocarditis is one of the AESIs. The risk window was listed as "any". Please specify the length of risk window for myocarditis. Only cohort study was proposed in the Table. Please consider adding SCRI for myocarditis.

5. *Page 32, 9.3.3. Covariate definition*

   "Age will be categorised as age categories in line with published background incidence rates from ACCESS (0-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+)"

Myocarditis is one of the AESIs. Please consider refining the age category 0-19 to include an adolescent age group, such as 10-19 years old.

6. *Page 47, 9.5. Study size*

   The protocol mentioned that "The study will be conducted in a source population of 38.9 million individuals captured in the electronic healthcare data sources."

   Seven data sources are included in the protocol with a total source population of 38.9 million. The data will be analyzed separately by data source. The number of active individuals ranges from 1 million in Pedianet/Health Search Database (IT) to 16 million in Clinical Practice Research Datalink and Hospital Episode Statistics (UK). Some data sources may not have enough study size to detect rare AESIs.

In the Pharmacovigilance Plan, the Sponsor planned three real world post-authorization vaccine effectiveness studies to determine the effectiveness of COMIRNATY when administered outside of the clinical setting: one non-interventional study C4591014 and two low-interventional studies WI235284 and WI255886.

Reviewer comment:

WI235284 COVID-19 vaccine effectiveness (VE) Substudy 6 will enroll healthy women who present at Emory University Hospital or Emory University Hospital Midtown for delivery, regardless of respiratory syncytial virus or COVID-19 status. A test negative case-control design is proposed.

Study WI255886 will be conducted in Bristol, England with approximately 630,000 adults in surveillance population. Real world VE estimates for COVID-19 vaccines will be assessed using a test negative design case control analysis.

Study C4591014 will estimate the VE of 2-doses of Pfizer's COVID-19 vaccine against acute respiratory illness requiring hospitalization due to SARS-CoV-2 infection among Kaiser Permanente Southern California (KPSC) members ≥16 years of age. Two parallel study designs are proposed: a test-negative case-control design and a retrospective cohort design.

Among the three proposed real world post-authorization vaccine effectiveness studies, Study C4591014 has the largest source population. KPSC has significant proportions of adolescent and young adult populations. It would be useful to include this effectiveness study as a postmarketing commitment (PMC) and include individuals 12 through 15 years of age.

In Response to CBER 13 August 2021 Information Request Regarding Safety-Related Postmarketing Requirement/Postmarketing Commitment Studies (STN 125742/0.51; received August 16, 2021), the sponsor addressed questions regarding study C4591014.

Reviewer comment:

The sponsor agreed to include individuals 12 through 15 years of age in Study C4591014.

The sponsor's response is acceptable.

4 OBE REAL WORLD EVIDENCE RECOMMDENDATIONS

Postmarketing requirement (PMR) safety studies under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the known serious risks of myocarditis and pericarditis, using real world evidence study design:

1. Study C4591009, entitled "A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States."
2. Study C4591021, entitled "Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine."
3. Study C4591021 substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY.

OBE will review the final protocols for C4591009 and C4591021 substudy when available (please see approval letter for study milestone dates). The final protocol for Study C4591021 was submitted August 11, 2021 [under STN 125742.0.42] and is currently under review[1].

Postmarketing commitment (PMC) vaccine effectiveness study agreed upon by FDA and the sponsor:

1. Study C4591014, entitled "Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study – Kaiser Permanente Southern California." Include individuals 12 through 15 years of age.

Note that PMR/PMC studies, in addition to the above listed studies, have been described in OBE/Division of Epidemiology pharmacovigilance plan (PVP) review memo and addendum memo.

[1] Note that the FDA review for this protocol will be documented in a separate protocol review memorandum. Additionally, study C4591021 is also a post-conditional approval study for the European Medicines Agency (EMA) and the protocol was approved by the EMA on June 24, 2021.

U.S. FOOD & DRUG ADMINISTRATION

Our STN: BL 125742/0

BLA APPROVAL

BioNTech Manufacturing GmbH
Attention: Amit Patel
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

August 23, 2021

Dear Mr. Patel:

Please refer to your Biologics License Application (BLA) submitted and received on May 18, 2021, under section 351(a) of the Public Health Service Act (PHS Act) for COVID-19 Vaccine, mRNA.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2229 to BioNTech Manufacturing GmbH, Mainz, Germany, under the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product, COVID-19 Vaccine, mRNA, which is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT04368728 and NCT04380701.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture COVID-19 Vaccine, mRNA drug substance at Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC, 1 Burtt Road, Andover, Massachusetts. The final formulated product will be manufactured, filled, labeled and packaged at Pfizer Manufacturing Belgium NV, Rijksweg 12, Puurs, Belgium and at Pharmacia & Upjohn Company LLC, 7000 Portage Road, Kalamazoo, Michigan. The diluent, 0.9% Sodium Chloride Injection, USP, will be manufactured at Hospira, Inc., [redacted] and at Fresenius Kabi USA, LLC, [redacted].

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

You may label your product with the proprietary name, COMIRNATY, and market it in 2.0 mL glass vials, in packages of 25 and 195 vials.
We did not refer your application to the Vaccines and Related Biological Products Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for COVID-19 Vaccine, mRNA shall be 9 months from the date of manufacture when stored between -90ºC to -60ºC (-130ºF to -76ºF). The date of manufacture shall be no later than the date of final sterile filtration of the formulated drug product (at Pharmacia & Upjohn Company LLC in Kalamazoo, Michigan, the date of manufacture is defined as the date of sterile filtration for the final drug product; at Pfizer Manufacturing Belgium NV in Puurs, Belgium, it is defined as the date of the (b) (4) Following the final sterile filtration, , no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for your drug substance shall be when stored at We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center

10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of COVID-19 Vaccine, mRNA, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including Package Insert, submitted under amendment 74, dated August 21, 2021, and the draft carton and container labels submitted under amendment 63, dated August 19, 2021.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the Package Insert submitted on August 21, 2021. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELS

Please electronically submit final printed carton and container labels identical to the carton and container labels submitted on August 19, 2021, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications.

All final labeling should be submitted as Product Correspondence to this BLA STN BL 125742 at the time of use and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80), and you must submit distribution reports at monthly intervals as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports for Vaccines* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports-vaccines. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies for ages younger than 16 years for this application because this product is ready for approval for use in individuals 16 years of age and older, and the pediatric studies for younger ages have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported according to 21 CFR 601.28 and section 505B(a)(4)(C) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Label your annual report as an "**Annual Status Report of Postmarketing Study Requirement/Commitments**" and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. These required studies are listed below:

1. Deferred pediatric Study C4591001 to evaluate the safety and effectiveness of COMIRNATY in children 12 years through 15 years of age.

   Final Protocol Submission: October 7, 2020

   Study Completion: May 31, 2023

   Final Report Submission: October 31, 2023

2. Deferred pediatric Study C4591007 to evaluate the safety and effectiveness of COMIRNATY in infants and children 6 months to <12 years of age.

   Final Protocol Submission: February 8, 2021

   Study Completion: November 30, 2023

   Final Report Submission: May 31, 2024

3. Deferred pediatric Study C4591023 to evaluate the safety and effectiveness of COMIRNATY in infants <6 months of age.

   Final Protocol Submission: January 31, 2022

   Study Completion: July 31, 2024

   Final Report Submission: October 31, 2024

Submit the protocols to your IND 19736, with a cross-reference letter to this BLA STN BL 125742 explaining that these protocols were submitted to the IND. Please refer to the PMR sequential number for each study/clinical trial and the submission number as shown in this letter.

Submit final study reports to this BLA STN BL 125742. In order for your PREA PMRs to be considered fulfilled, you must submit and receive approval of an efficacy or a labeling

supplement. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated as:

- **Required Pediatric Assessment(s)**

We note that you have fulfilled the pediatric study requirement for ages 16 through 17 years for this application.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of myocarditis and pericarditis and identify an unexpected serious risk of subclinical myocarditis.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following studies:

4. Study C4591009, entitled "A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID 19 mRNA Vaccine in the United States," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: August 31, 2021

   Monitoring Report Submission: October 31, 2022

   Interim Report Submission: October 31, 2023

   Study Completion: June 30, 2025

   Final Report Submission: October 31, 2025

5. Study C4591021, entitled "Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus

Disease 2019 (COVID-19) Vaccine," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY.

We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: August 11, 2021

Progress Report Submission: September 30, 2021

Interim Report 1 Submission: March 31, 2022

Interim Report 2 Submission: September 30, 2022

Interim Report 3 Submission: March 31, 2023

Interim Report 4 Submission: September 30, 2023

Interim Report 5 Submission: March 31, 2024

Study Completion: March 31, 2024

Final Report Submission: September 30, 2024

6. Study C4591021 substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY.

We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: January 31, 2022

Study Completion: March 31, 2024

Final Report Submission: September 30, 2024

7. Study C4591036, a prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination (in collaboration with Pediatric Heart Network).

We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: November 30, 2021

Study Completion: December 31, 2026

Final Report Submission: May 31, 2027

8. Study C4591007 substudy to prospectively assess the incidence of subclinical myocarditis following administration of the second dose of COMIRNATY in a subset of participants 5 through 15 years of age.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this assessment according to the following schedule:

   Final Protocol Submission: September 30, 2021

   Study Completion: November 30, 2023

   Final Report Submission: May 31, 2024

9. Study C4591031 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a third dose of COMIRNATY in a subset of participants 16 to 30 years of age.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: November 30, 2021

   Study Completion: June 30, 2022

   Final Report Submission: December 31, 2022

Please submit the protocols to your IND 19736, with a cross-reference letter to this BLA STN BL 125742 explaining that these protocols were submitted to the IND. Please refer to the PMR sequential number for each study/clinical trial and the submission number as shown in this letter.

Please submit final study reports to the BLA. If the information in the final study report supports a change in the label, the final study report must be submitted as a supplement to this BLA STN BL 125742. For administrative purposes, all submissions related to these postmarketing studies required under section 505(o) must be submitted to this BLA and be clearly designated as:

- **Required Postmarketing Correspondence under Section 505(o)**
- **Required Postmarketing Final Report under Section 505(o)**
- **Supplement contains Required Postmarketing Final Report under Section 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise

undertaken to investigate a safety issue. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

You must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will consider the submission of your annual report under section 506B of the FDCA and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in section 505(o) and 21 CFR 601.70. We remind you that to comply with section 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your letter of August 21, 2021 as outlined below:

10. Study C4591022, entitled “Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry.”

    Final Protocol Submission: July 1, 2021

Study Completion: June 30, 2025

Final Report Submission: December 31, 2025

11. Study C4591007 substudy to evaluate the immunogenicity and safety of lower dose levels of COMIRNATY in individuals 12 through <30 years of age.

    Final Protocol Submission: September 30, 2021

    Study Completion: November 30, 2023

    Final Report Submission: May 31, 2024

12. Study C4591012, entitled "Post-emergency Use Authorization Active Safety Surveillance Study Among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine."

    Final Protocol Submission: January 29, 2021

    Study Completion: June 30, 2023

    Final Report Submission: December 31, 2023

13. Study C4591014, entitled "Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California."

    Final Protocol Submission: March 22, 2021

    Study Completion: December 31, 2022

    Final Report Submission: June 30, 2023

Please submit clinical protocols to your IND 19736, and a cross-reference letter to this BLA STN BL 125742 explaining that these protocols were submitted to the IND. Please refer to the PMC sequential number for each study/clinical trial and the submission number as shown in this letter.

If the information in the final study report supports a change in the label, the final study report must be submitted as a supplement. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Correspondence Study Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing commitment;
- the original schedule for the commitment;
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

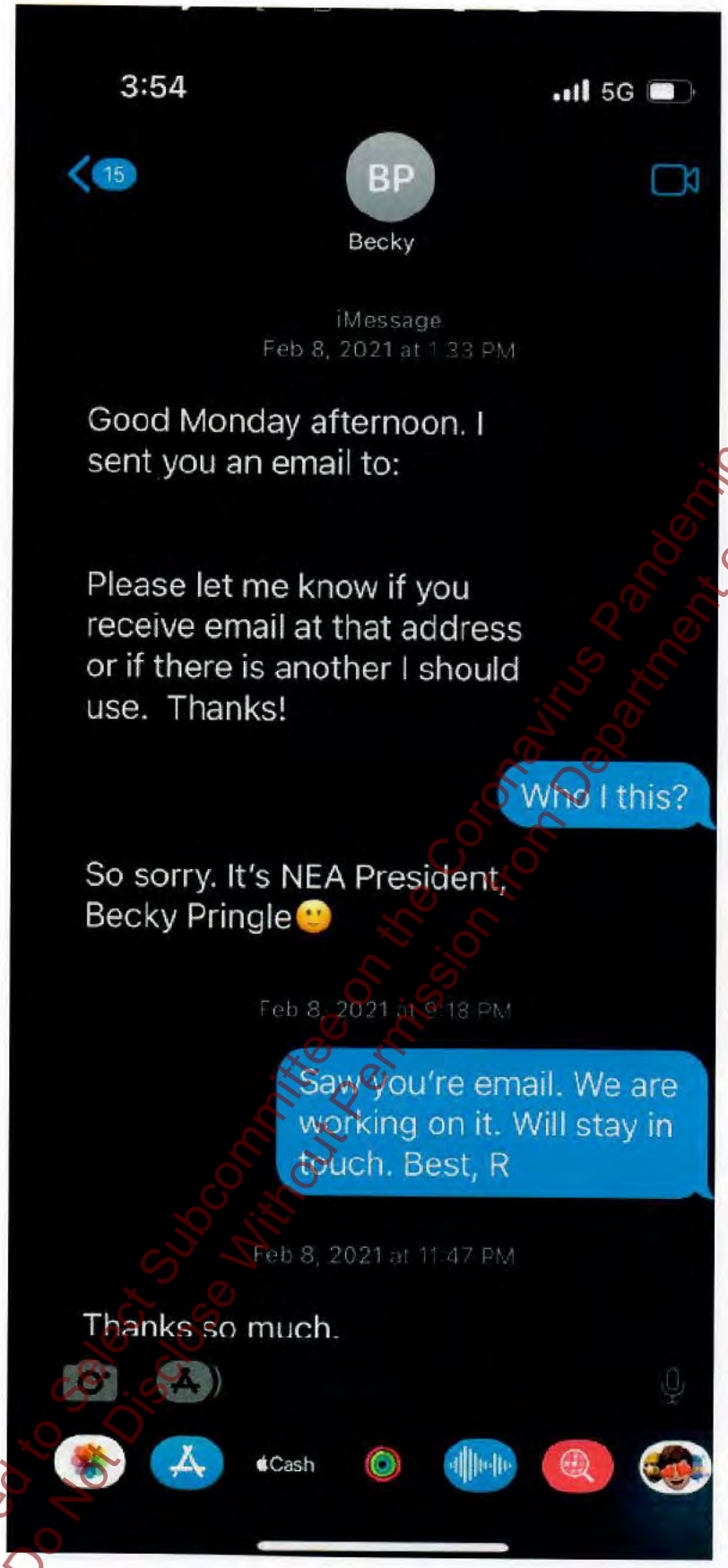
POST APPROVAL FEEDBACK MEETING

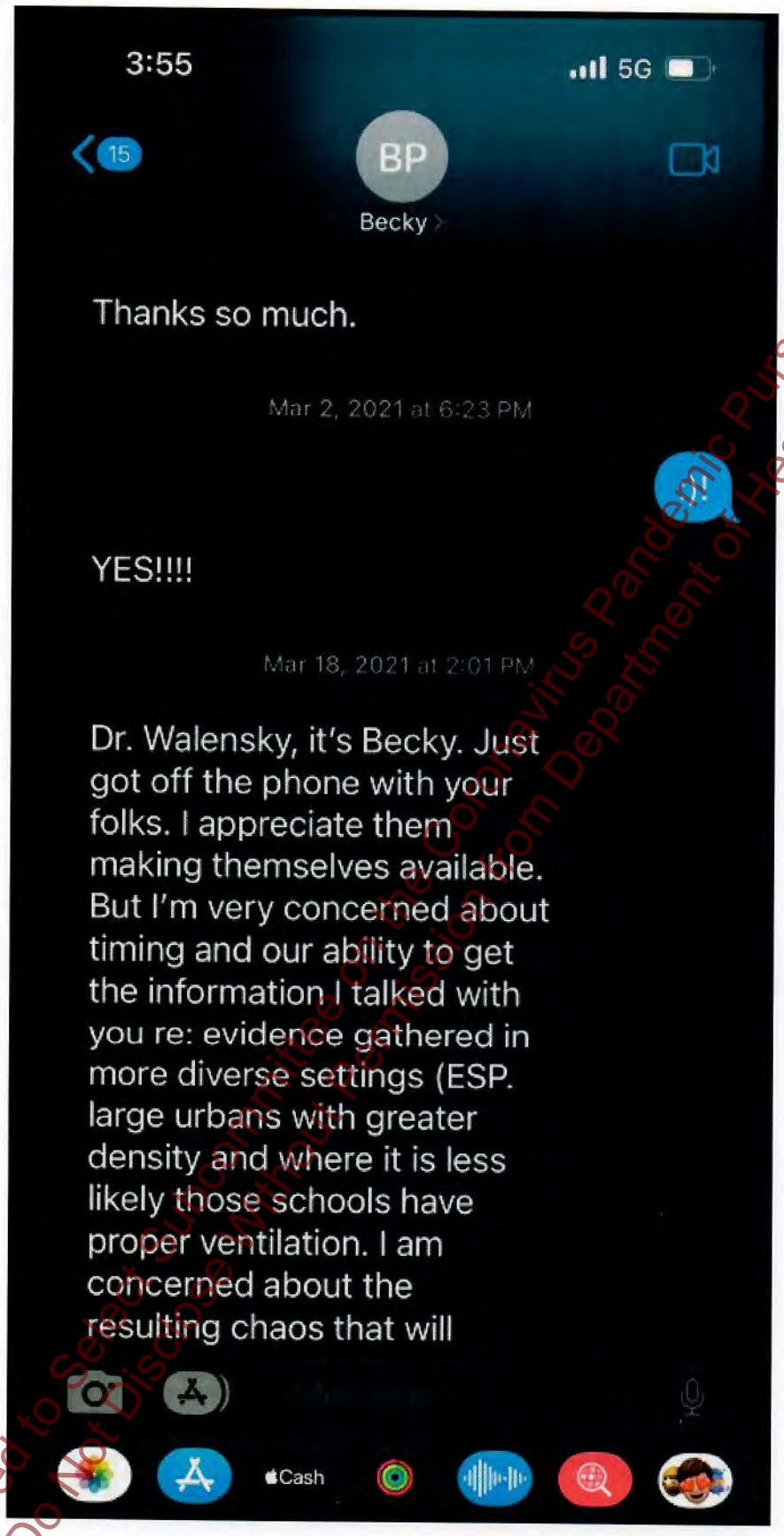
New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

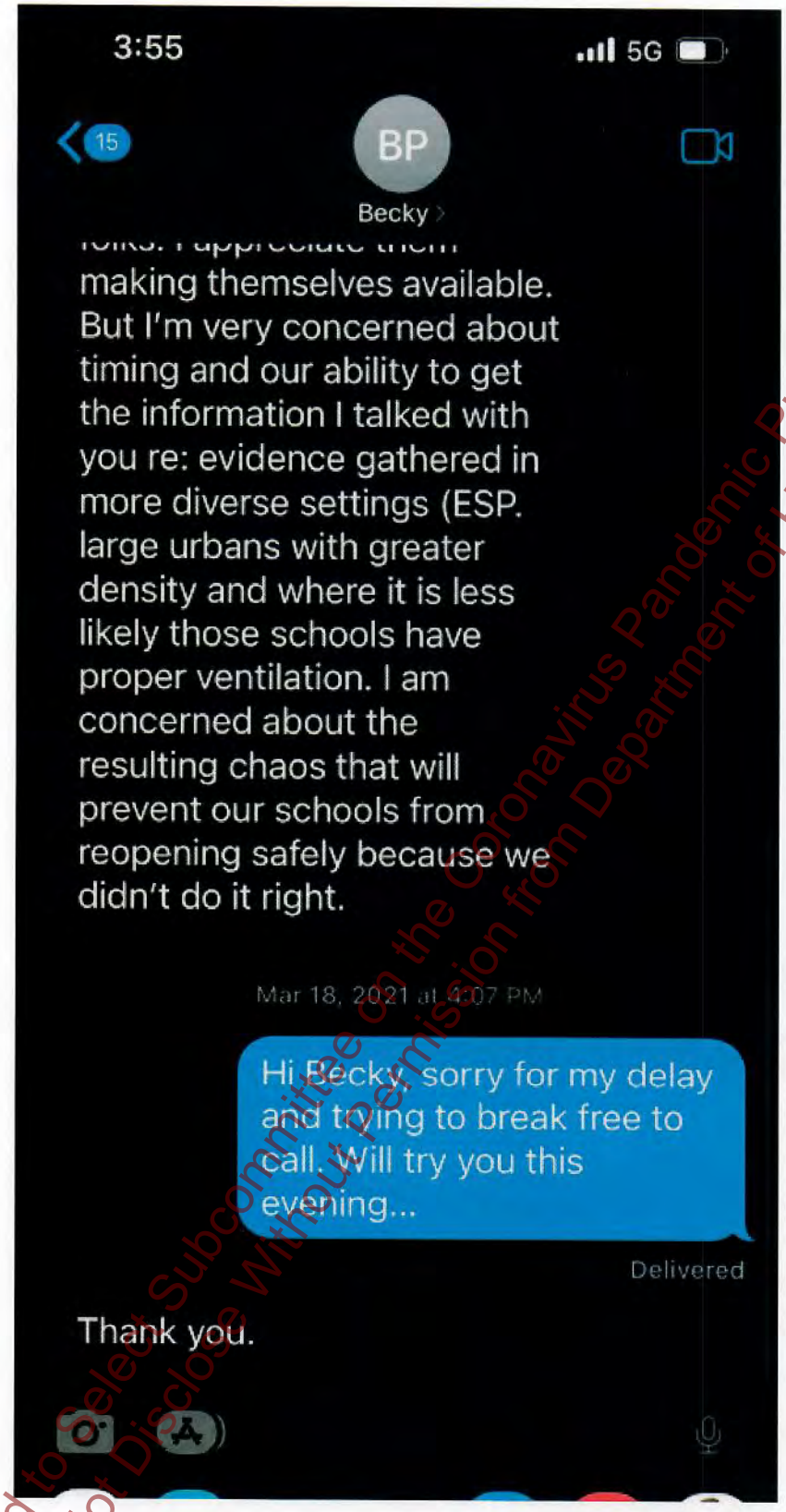
Sincerely,

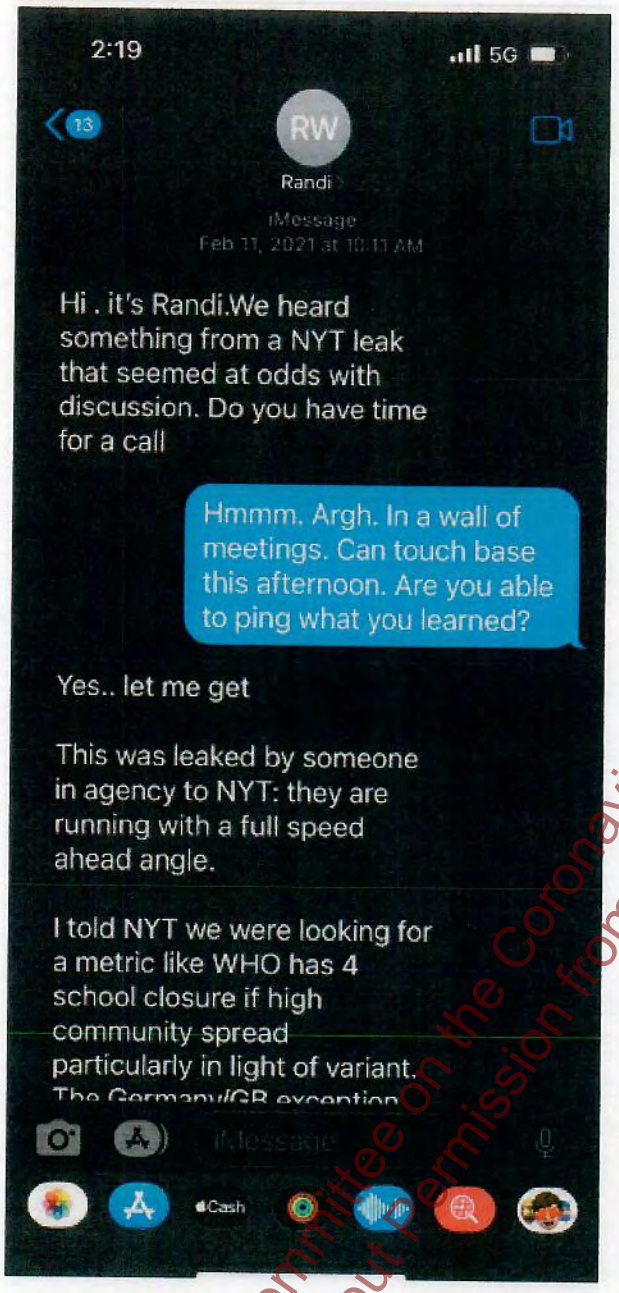
Mary A. Malarkey
Director
Office of Compliance
and Biologics Quality
Center for Biologics
Evaluation and Research

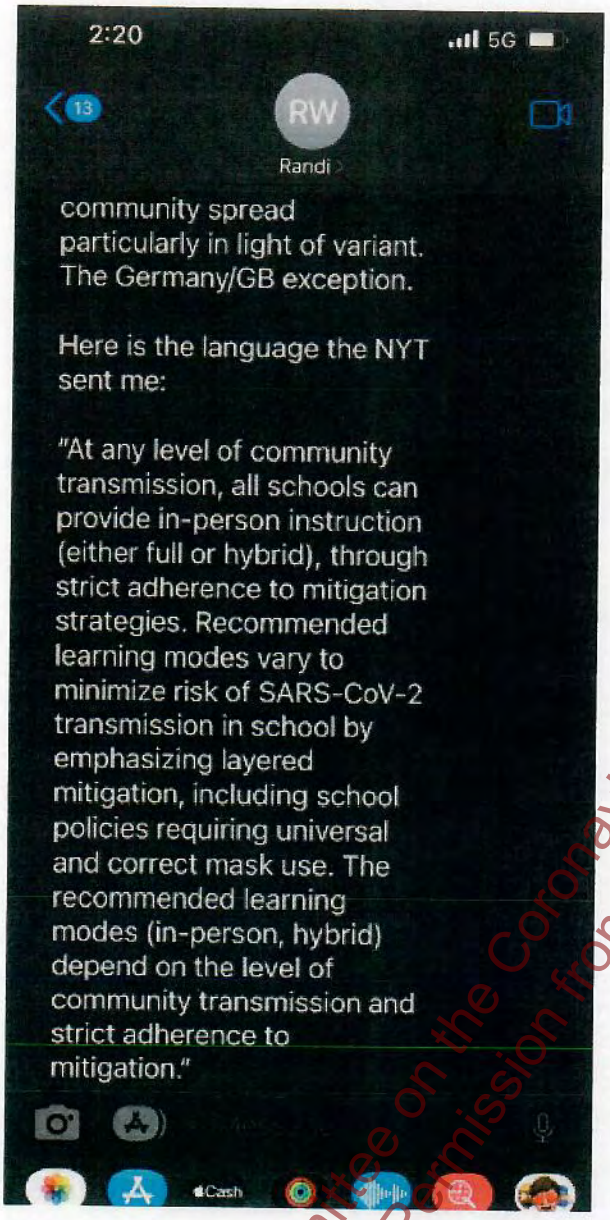
Marion F. Gruber, PhD
Director
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research

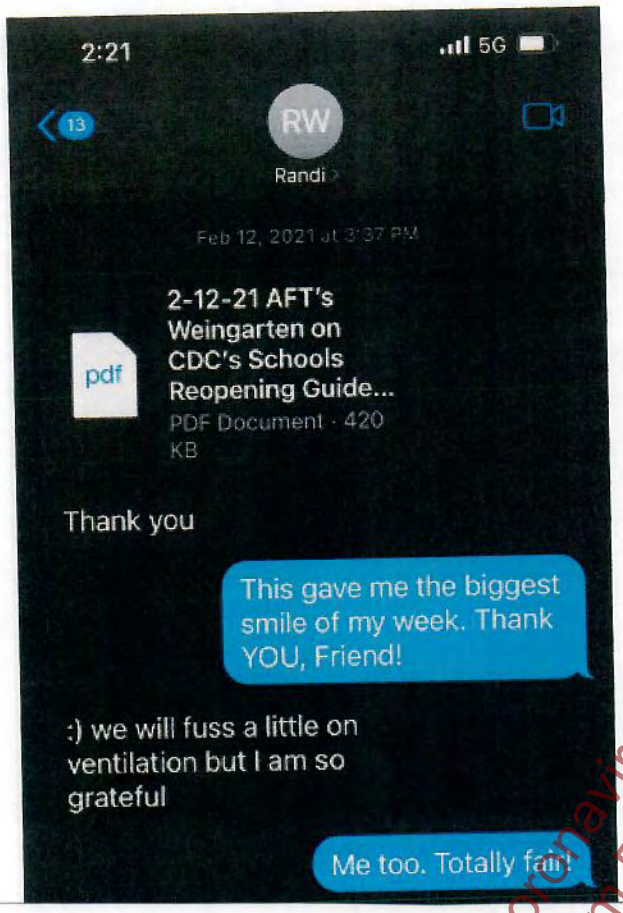












A Union of Professionals

AFT News Release

For Immediate Release
February 12, 2021

Contact:
Andrew Crook
607-262-9431
acrook@aft.org
www.aft.org

AFT's Weingarten on CDC's Schools Reopening Guidelines

'Today, the CDC met fear of the pandemic with facts and evidence.'

WASHINGTON—American Federation of Teachers President Randi Weingarten issued to following statement after the Centers for Disease Control and Prevention issued new guidelines for reopening schools:

"Today, the CDC met fear of the pandemic with facts and evidence. For the first time since the start of this pandemic, we have a rigorous road map, based on science, that our members can use to fight for a safe reopening.

"The CDC has produced an informed, tactile plan that has the potential to help school communities around the country stay safe by defining the mitigation and accommodation measures, and other tools educators and kids need, so classrooms can once again be vibrant places of learning and engagement.

"Of course, this set of safeguards should have been done 10 months ago—and the AFT released its plan recommending a suite of similar reopening measures in April. Instead, the previous administration meddled with the facts and stoked mass chaos and confusion. Now we have the chance for a rapid reset.

"We note the CDC has identified the importance of layered mitigation, including compulsory masking, 6 feet of physical distancing, handwashing, cleaning and ventilation, diagnostic testing and contact tracing. It reinforces vaccine priority for teachers and school staff. Crucially, it emphasizes accommodations for educators with pre-existing conditions and those taking care of others at risk.

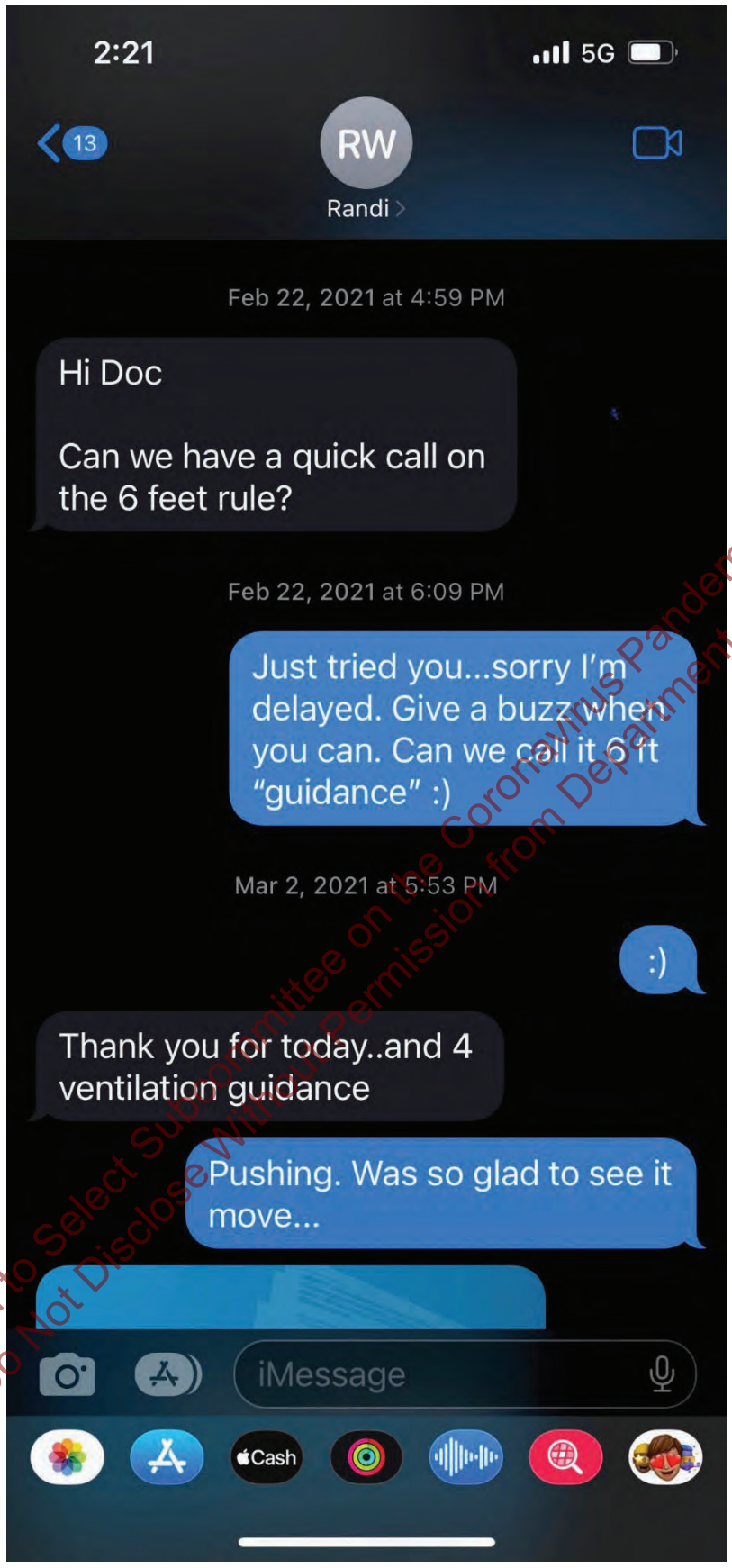
"We remain supportive of widespread testing—especially as mutant strains multiply in areas of uncontrolled community spread—and we urge the CDC to remain flexible as more data comes to light. The guidance is instructive for this moment in time, but this disease is not static.

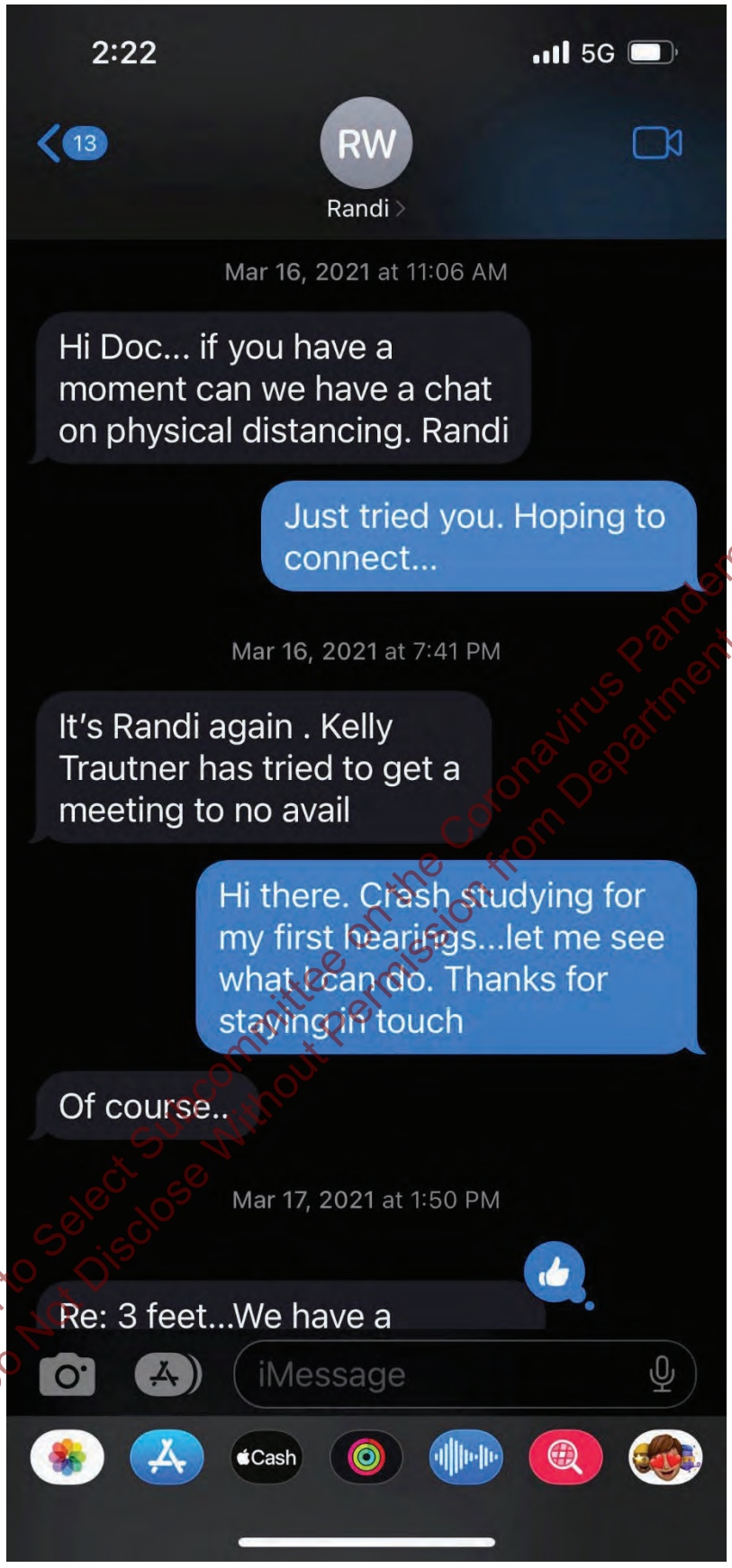
"The stage is now set for Congress and the Education Department to make this guidance real—and that means securing the funding to get this done in the nation's school districts and meet the social, emotional and academic needs of kids. To that end, we are encouraged that the department is citing examples of successful reopening strategies in New York City, Boston and Washington, D.C.

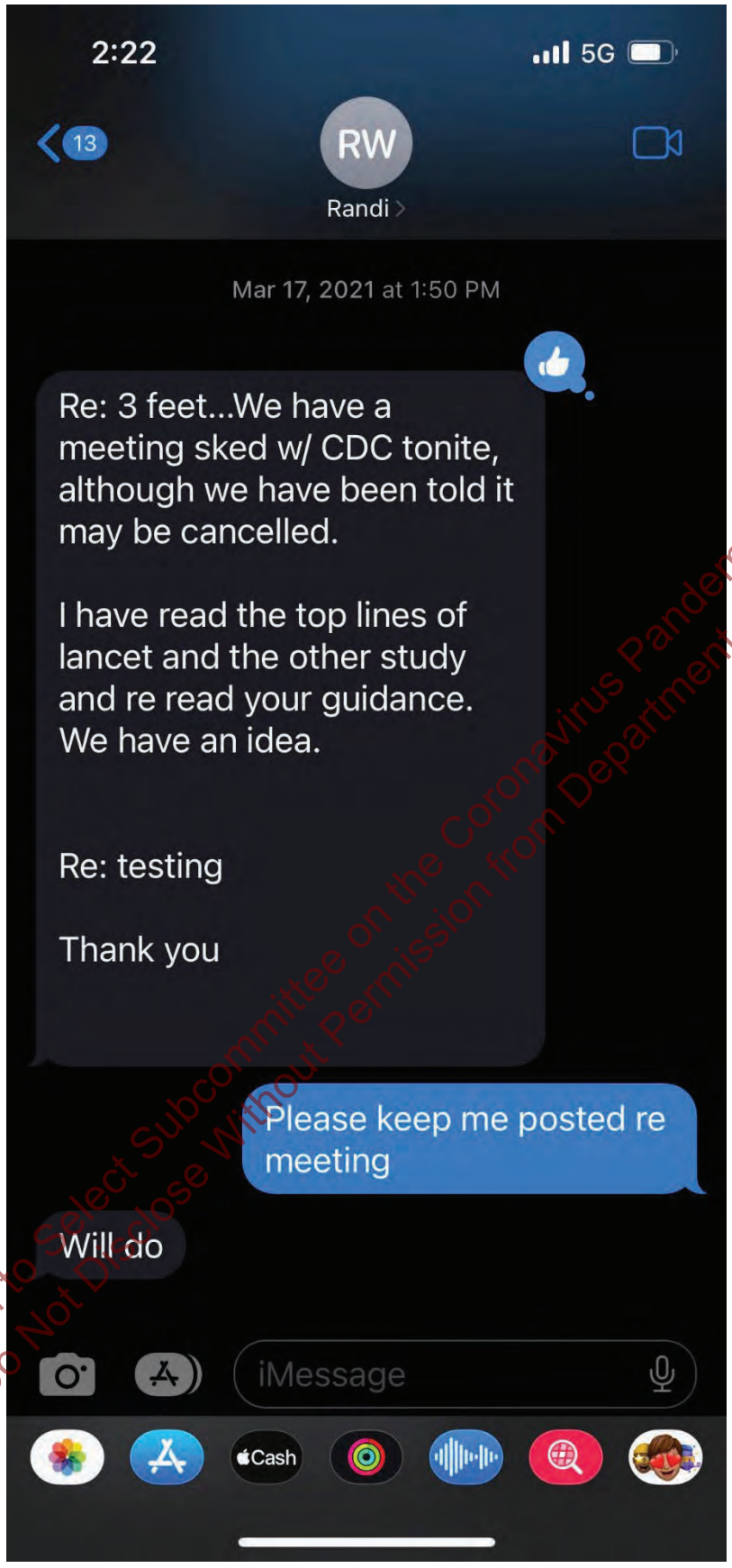
"There's a lot of work ahead to get this done. But the good news is the Biden administration is committed to realizing these recommendations through its $1.9 trillion American Rescue Plan, and to creating a culture of trust and collaboration with educators and parents to get us there."

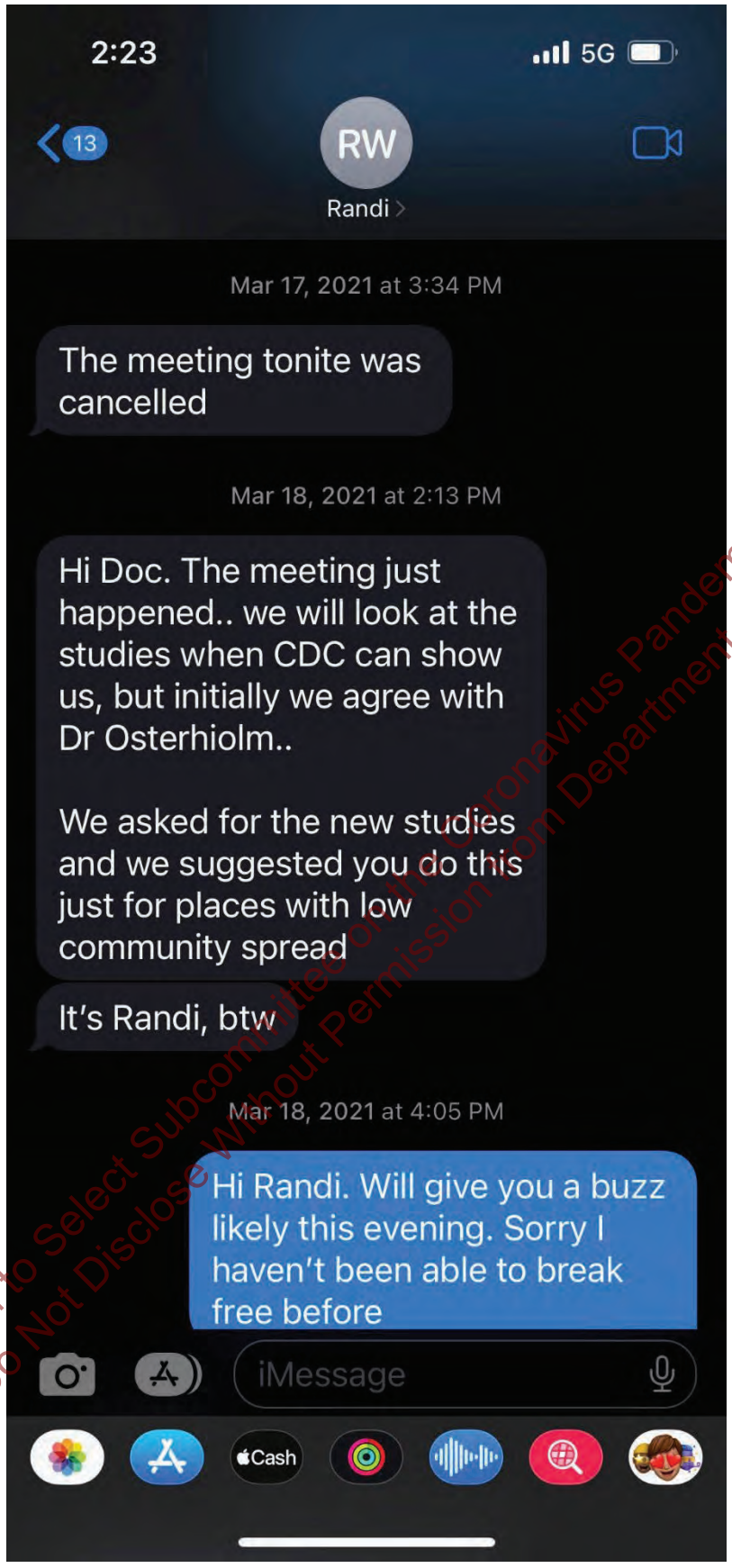
###

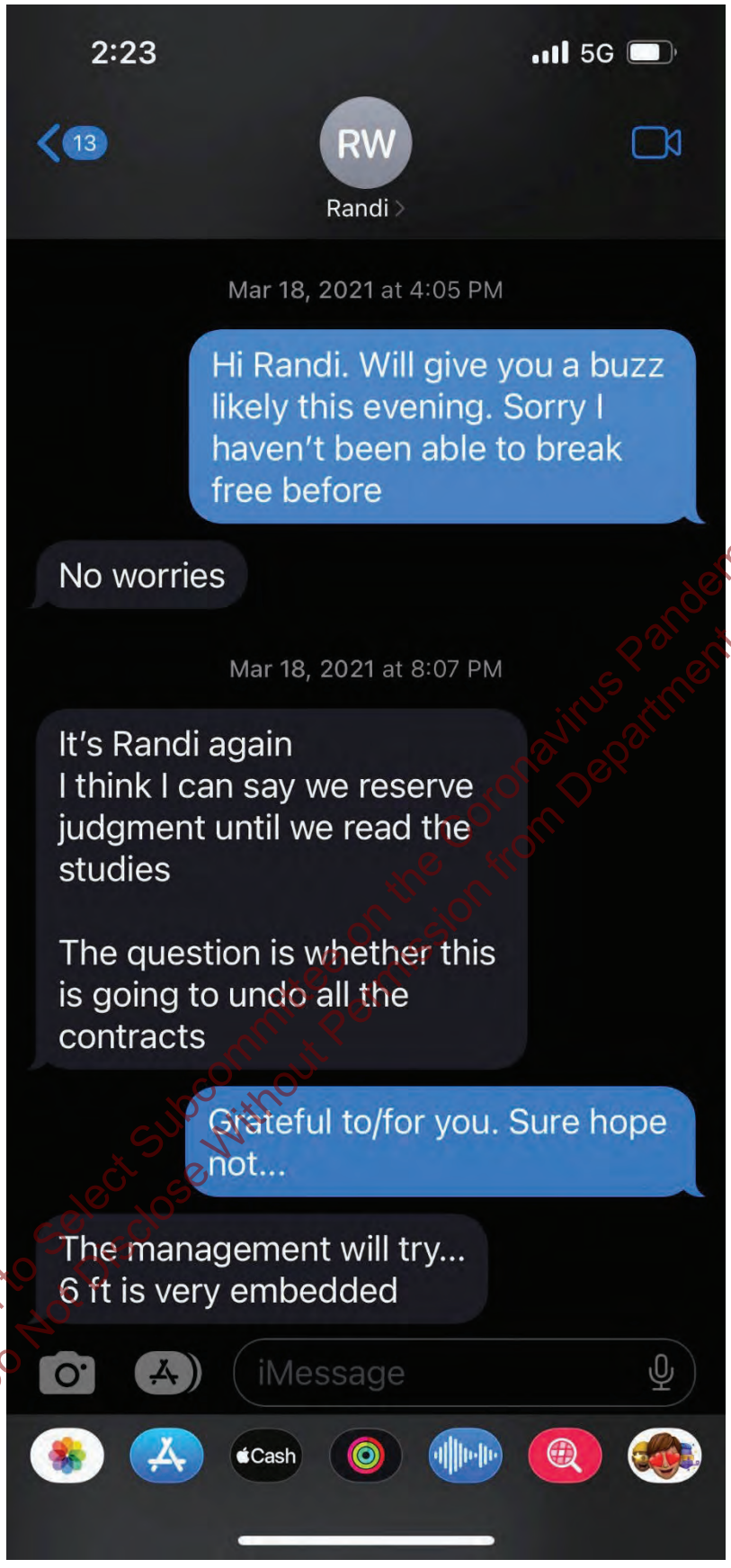
Follow AFT President Randi Weingarten: http://twitter.com/rweingarten

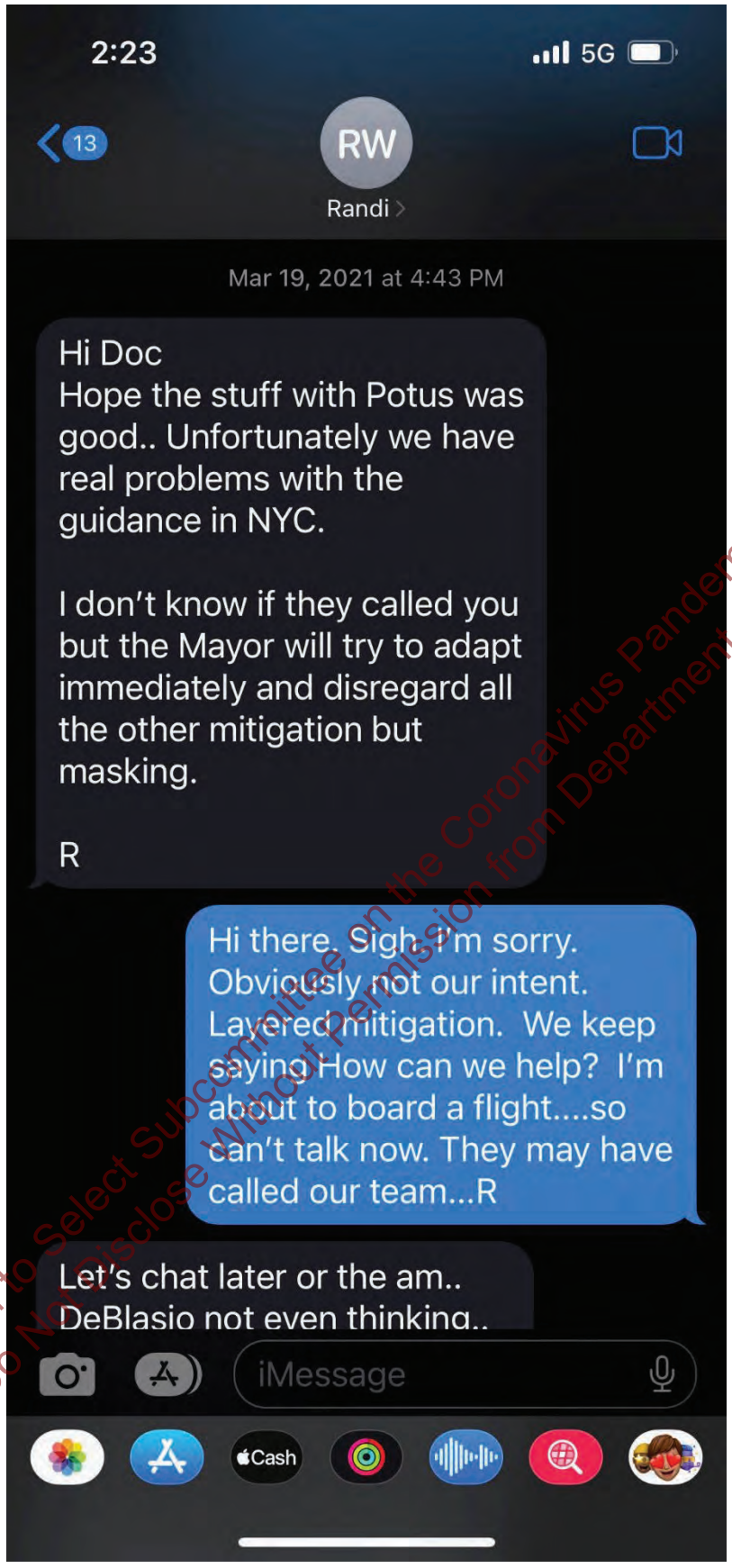


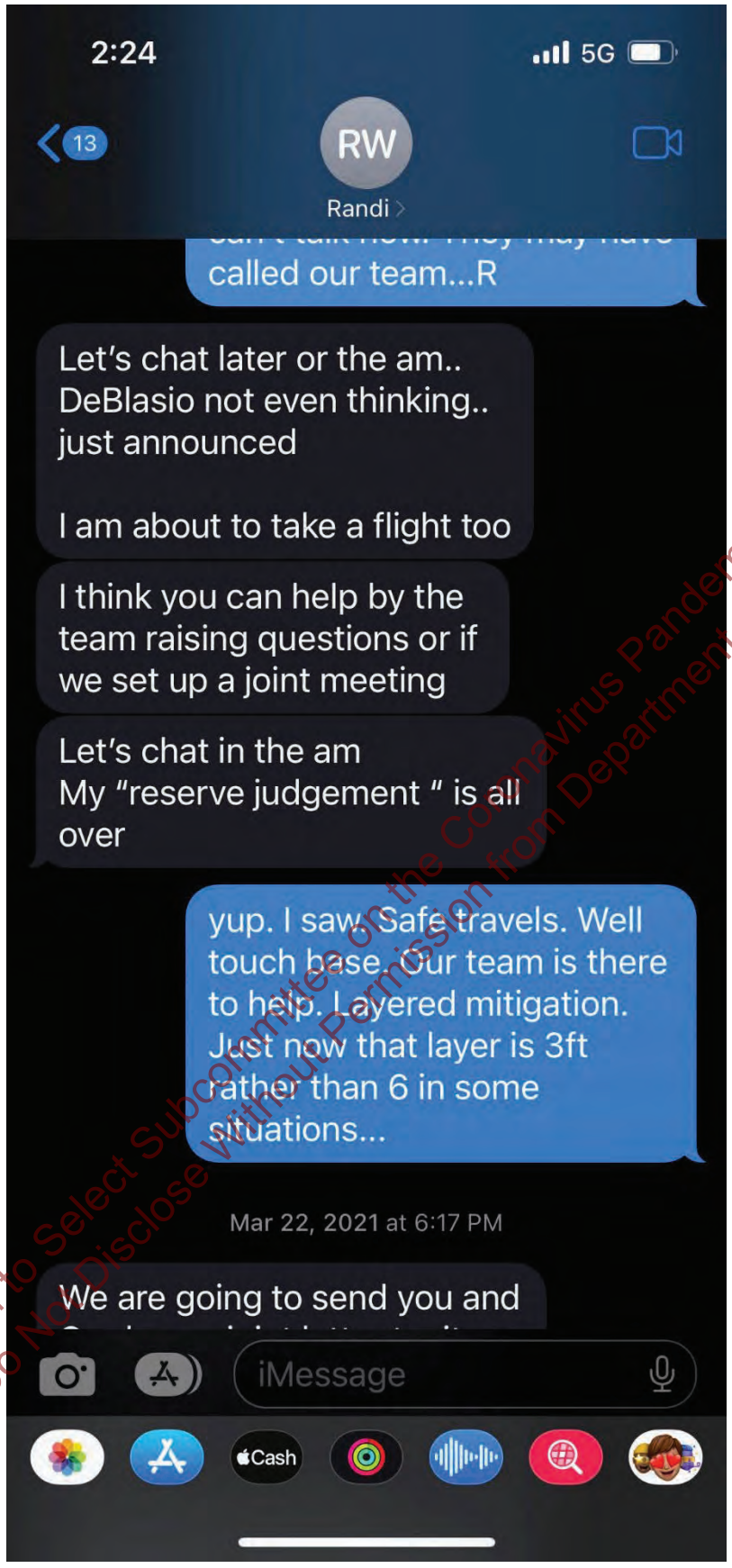


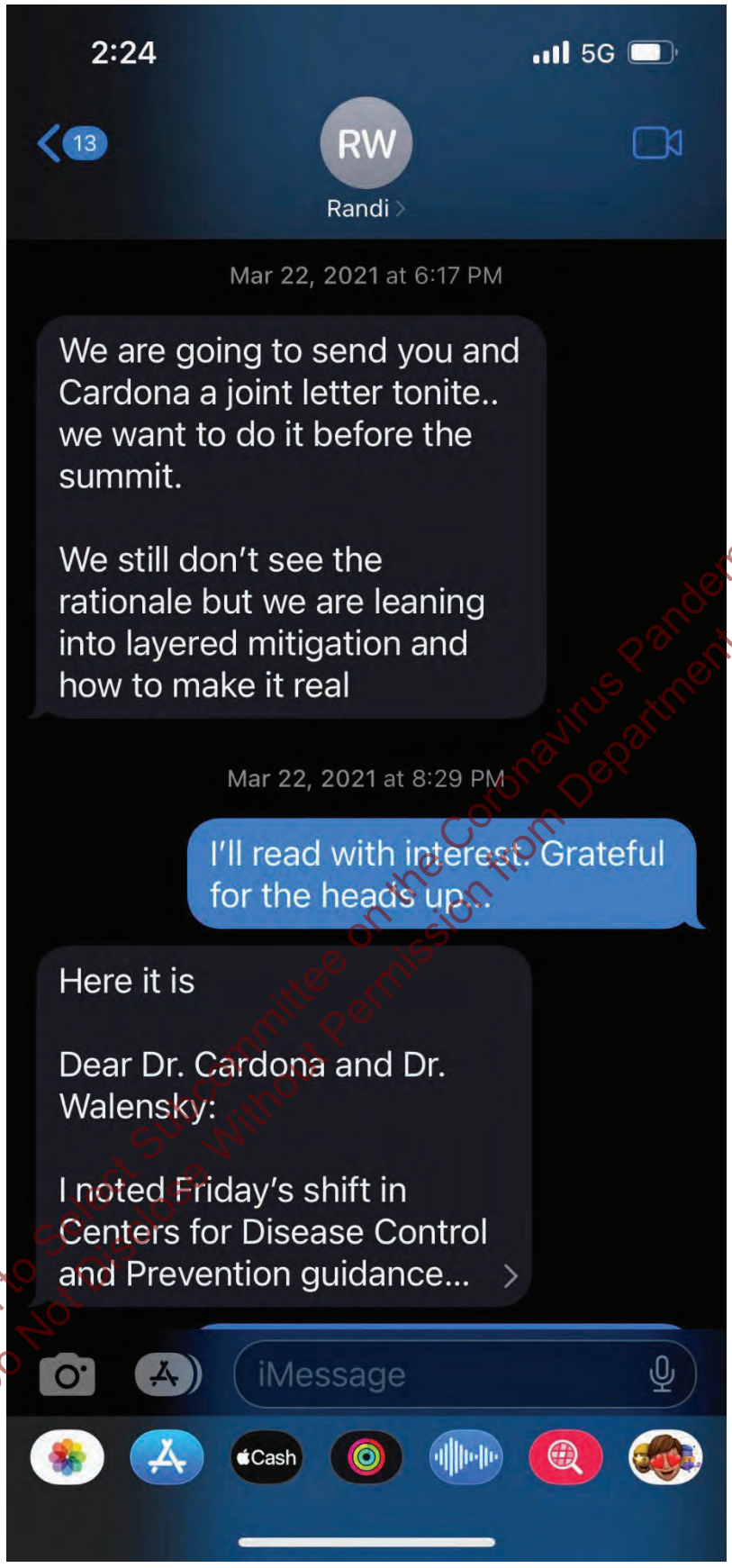


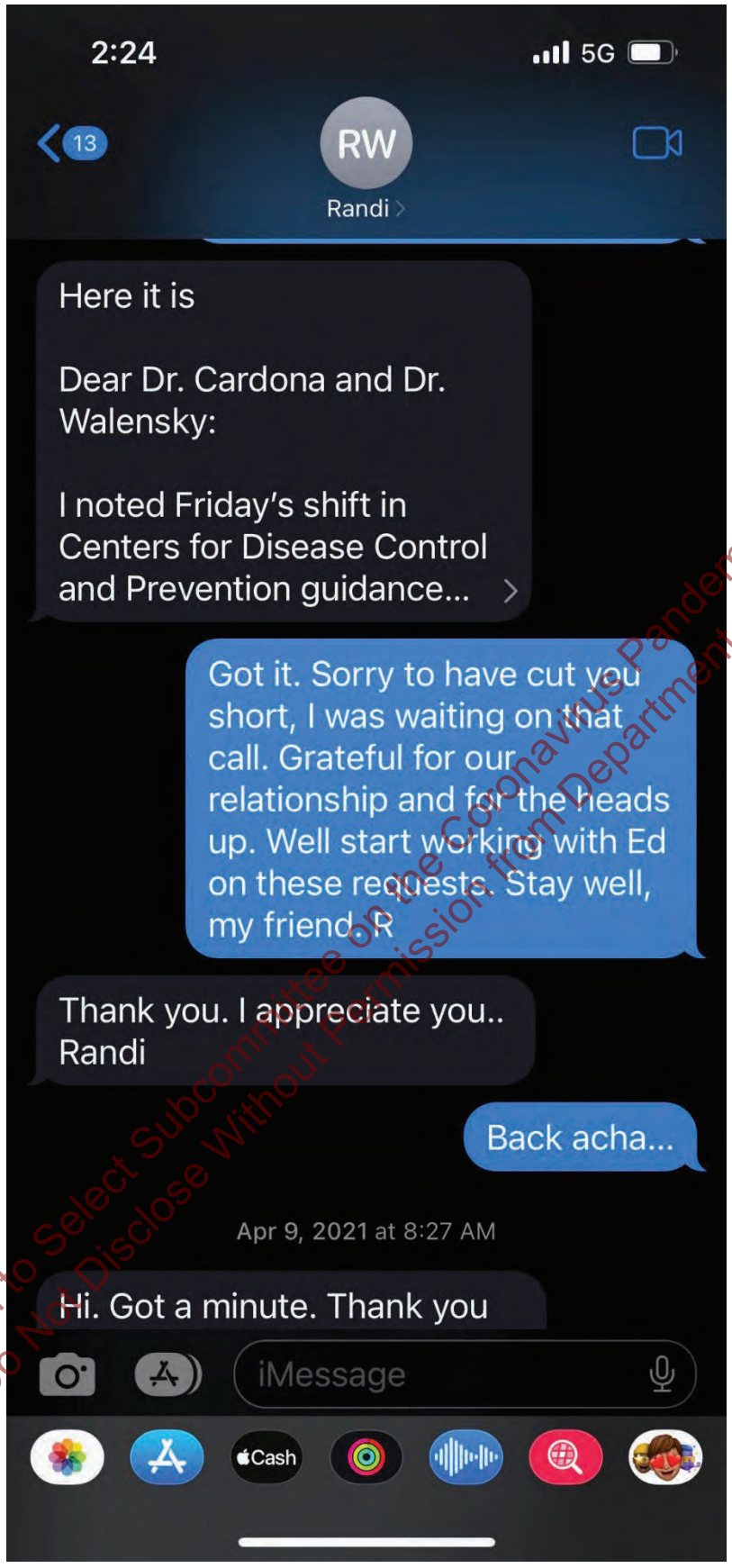


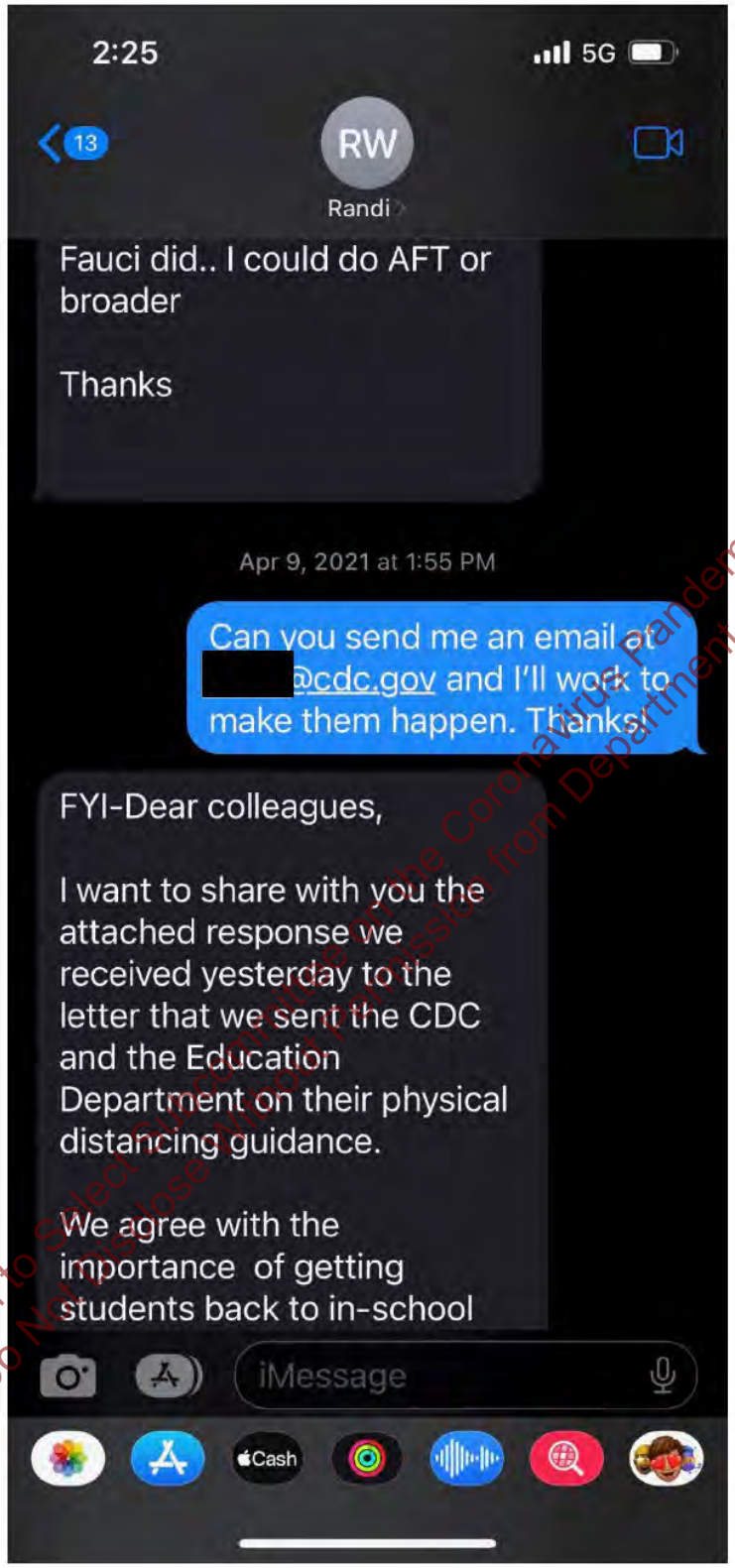


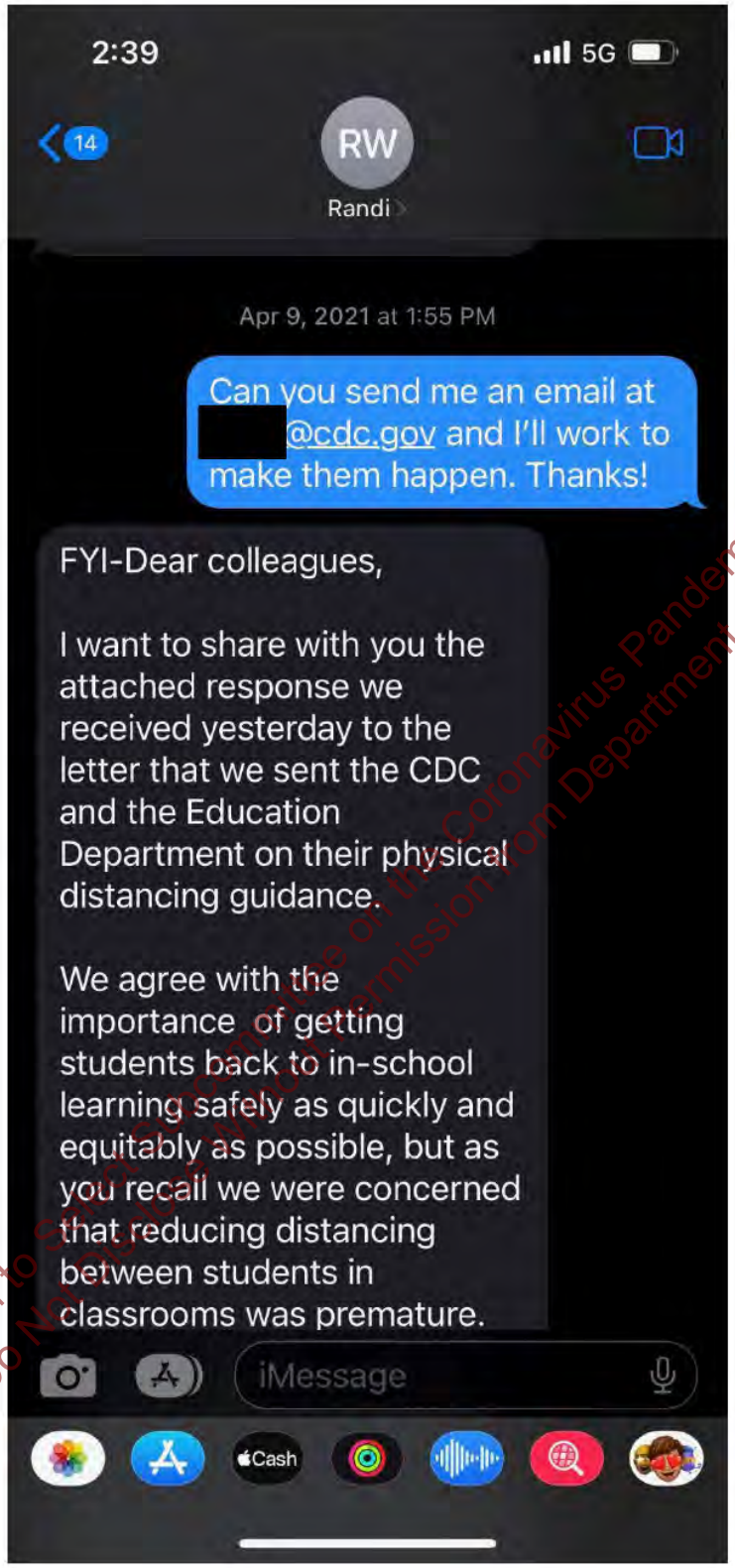


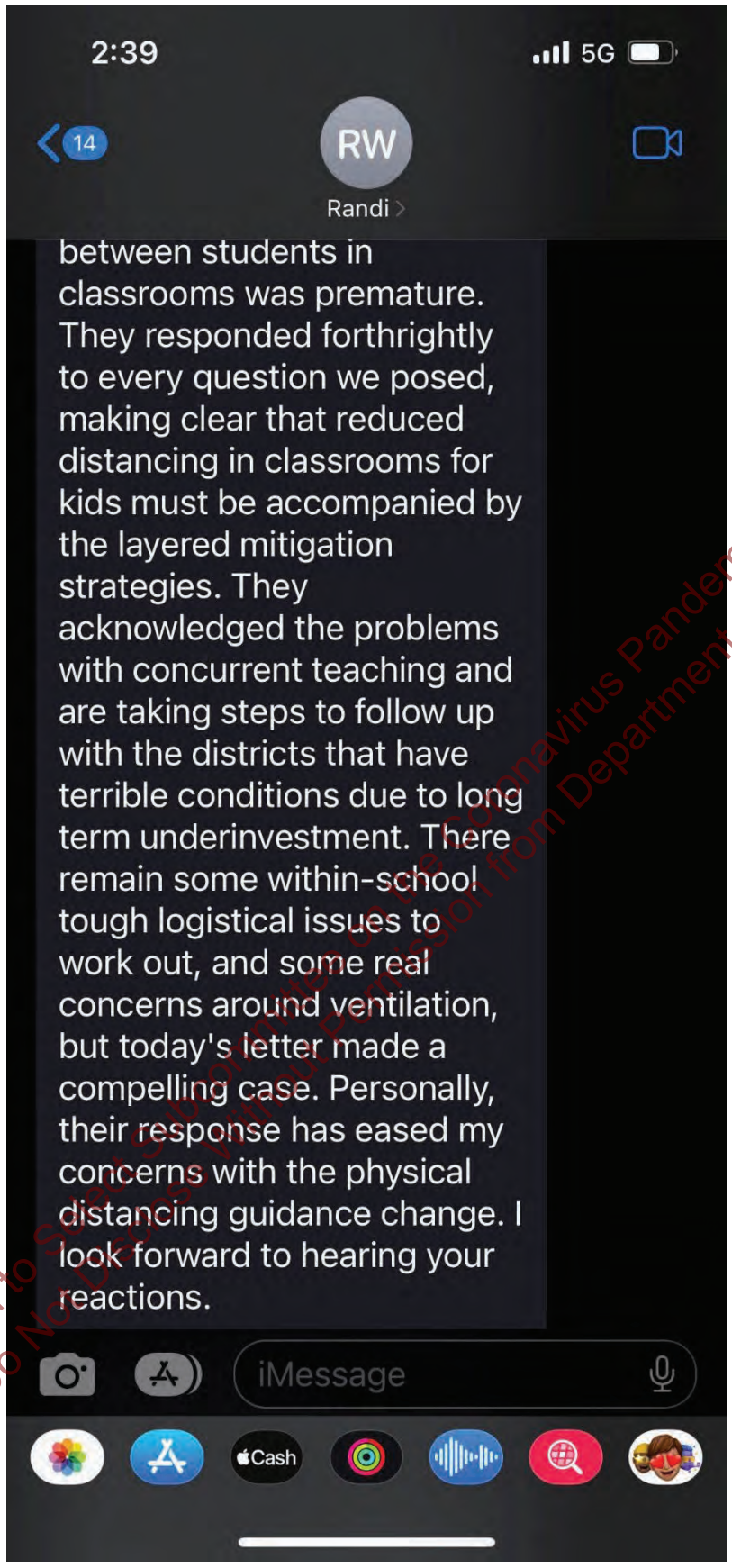


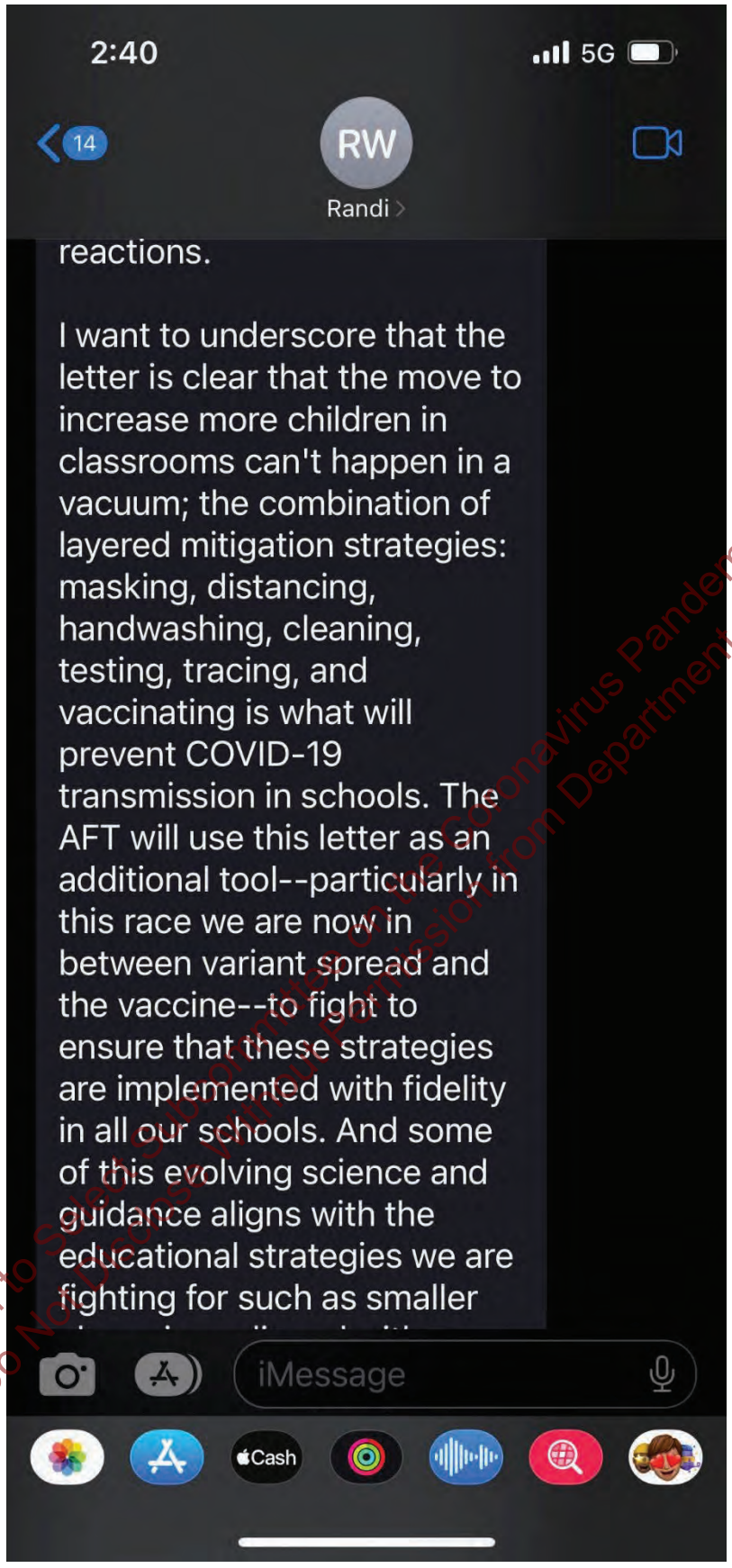


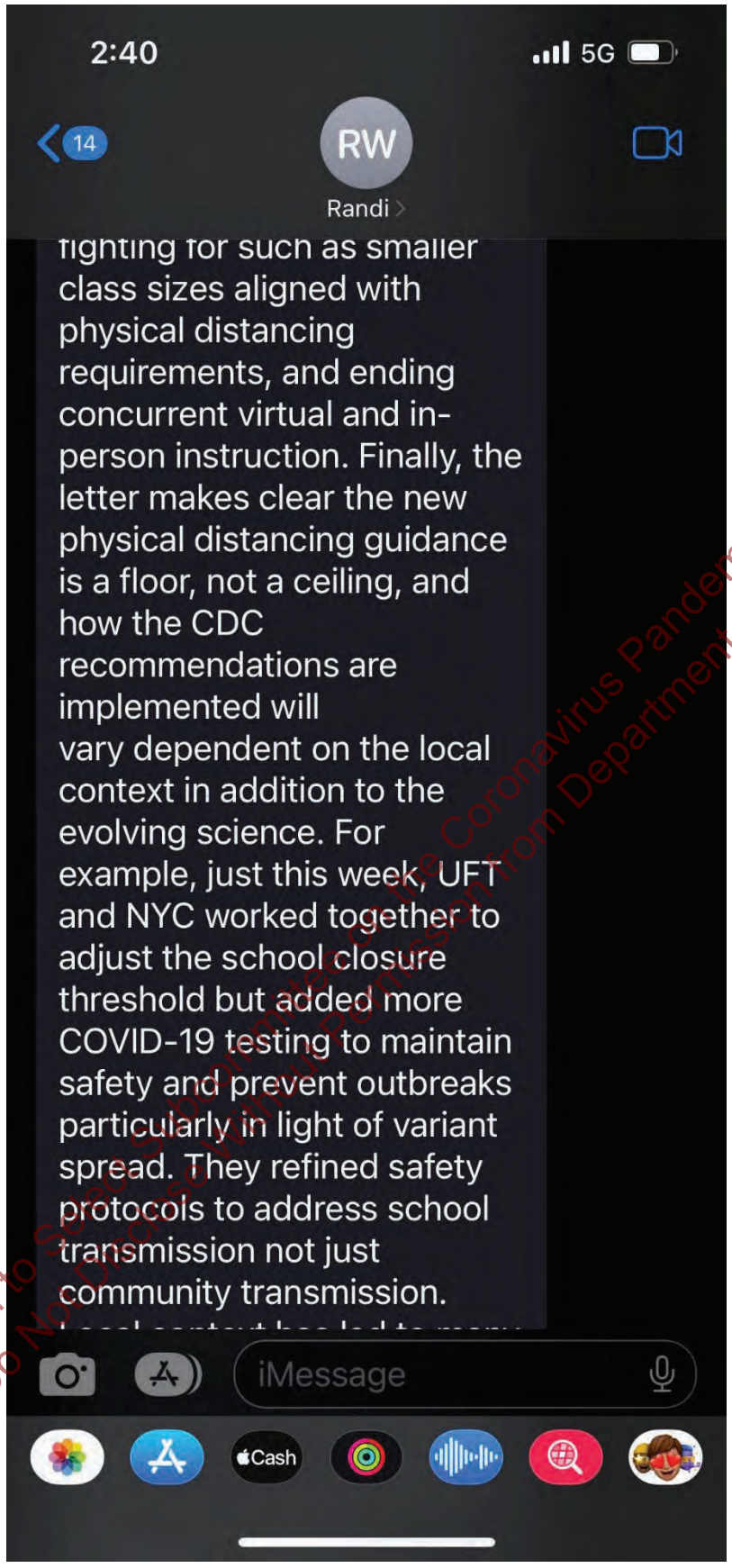


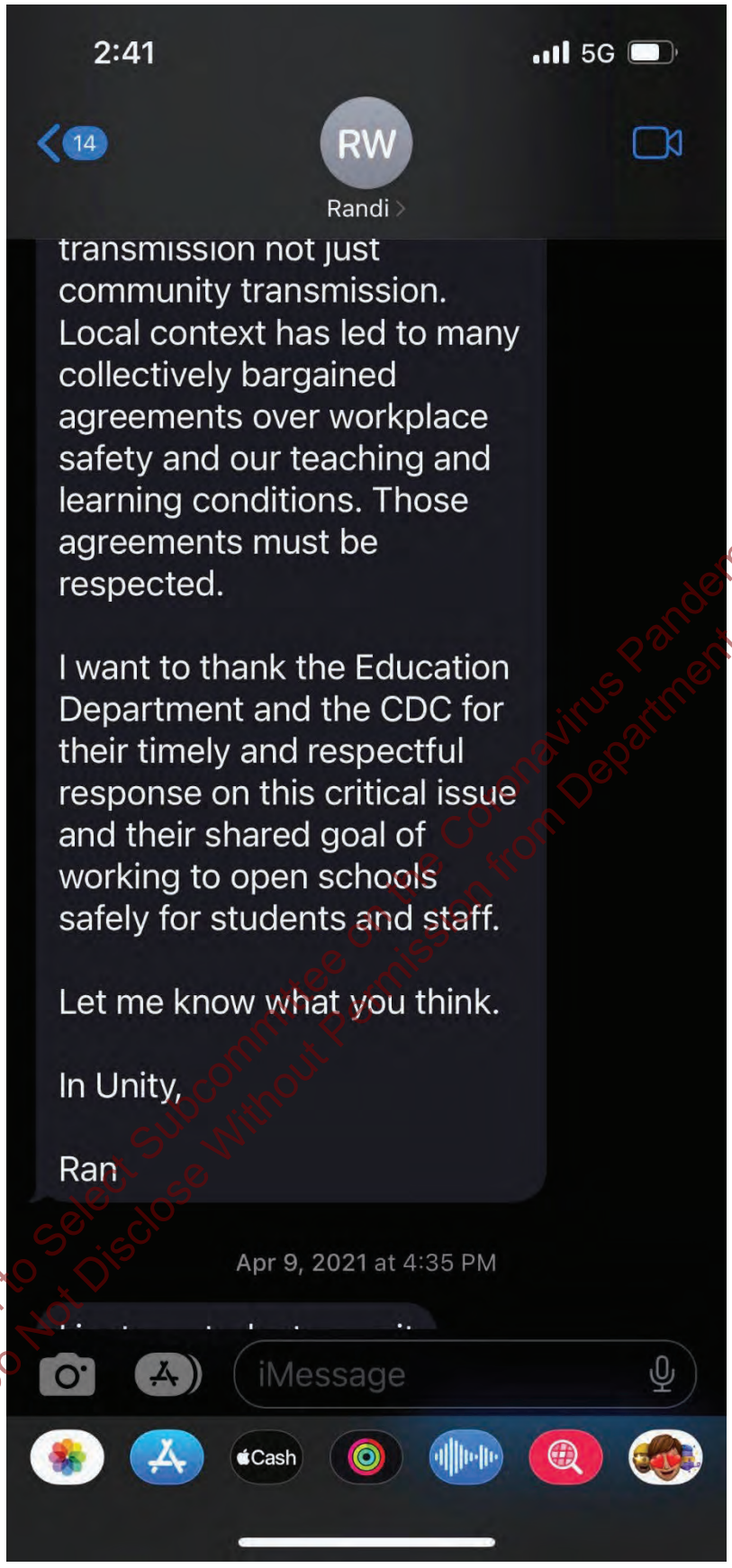


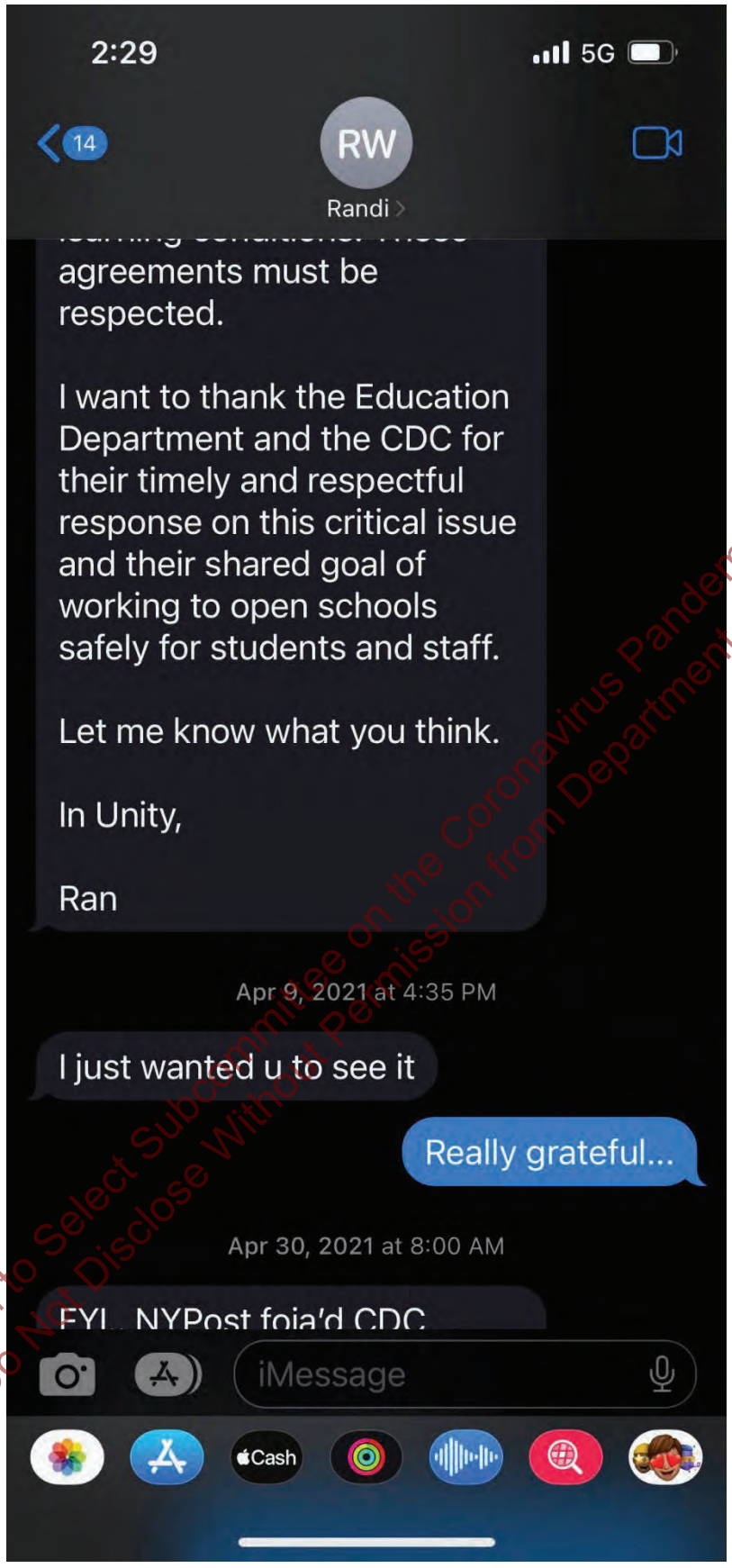


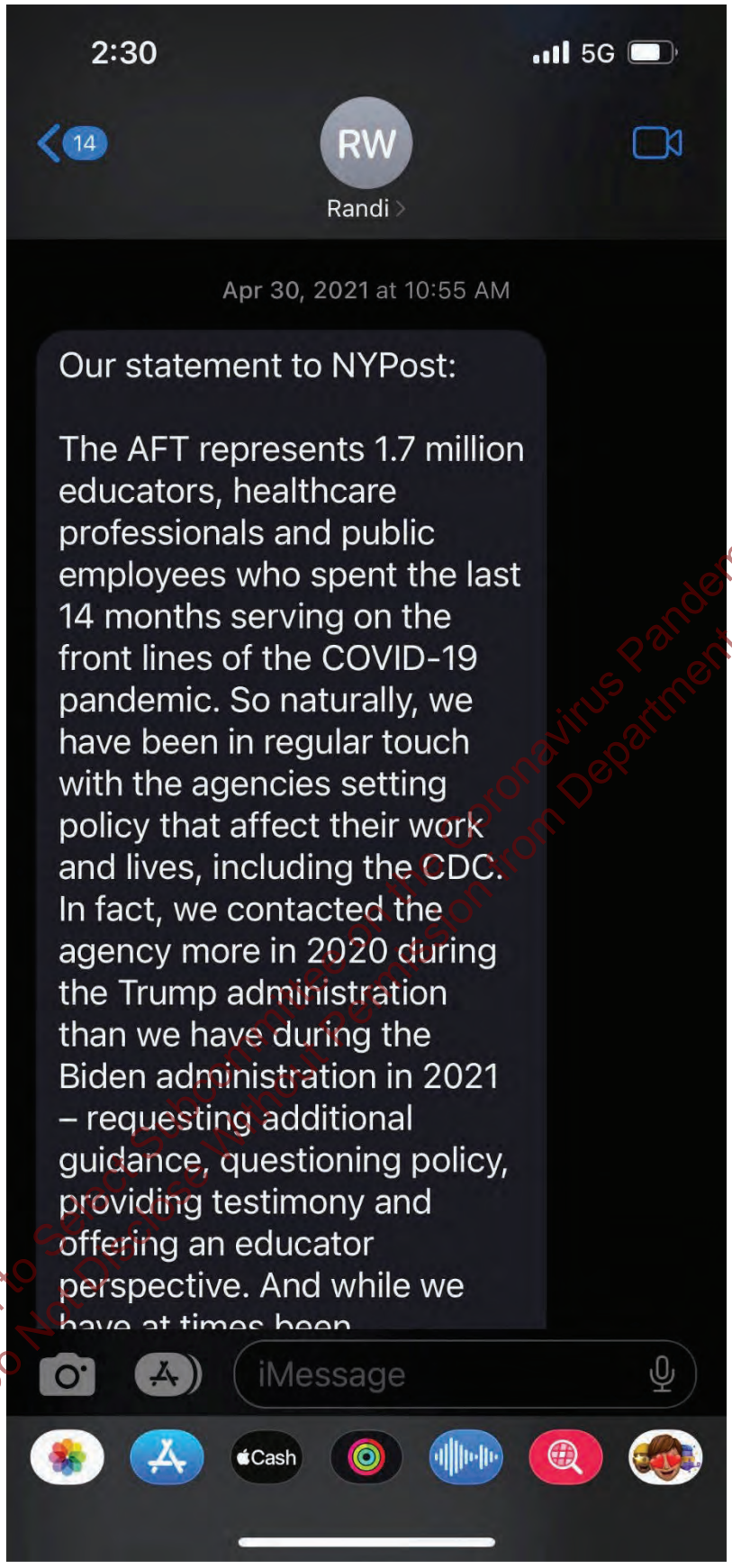


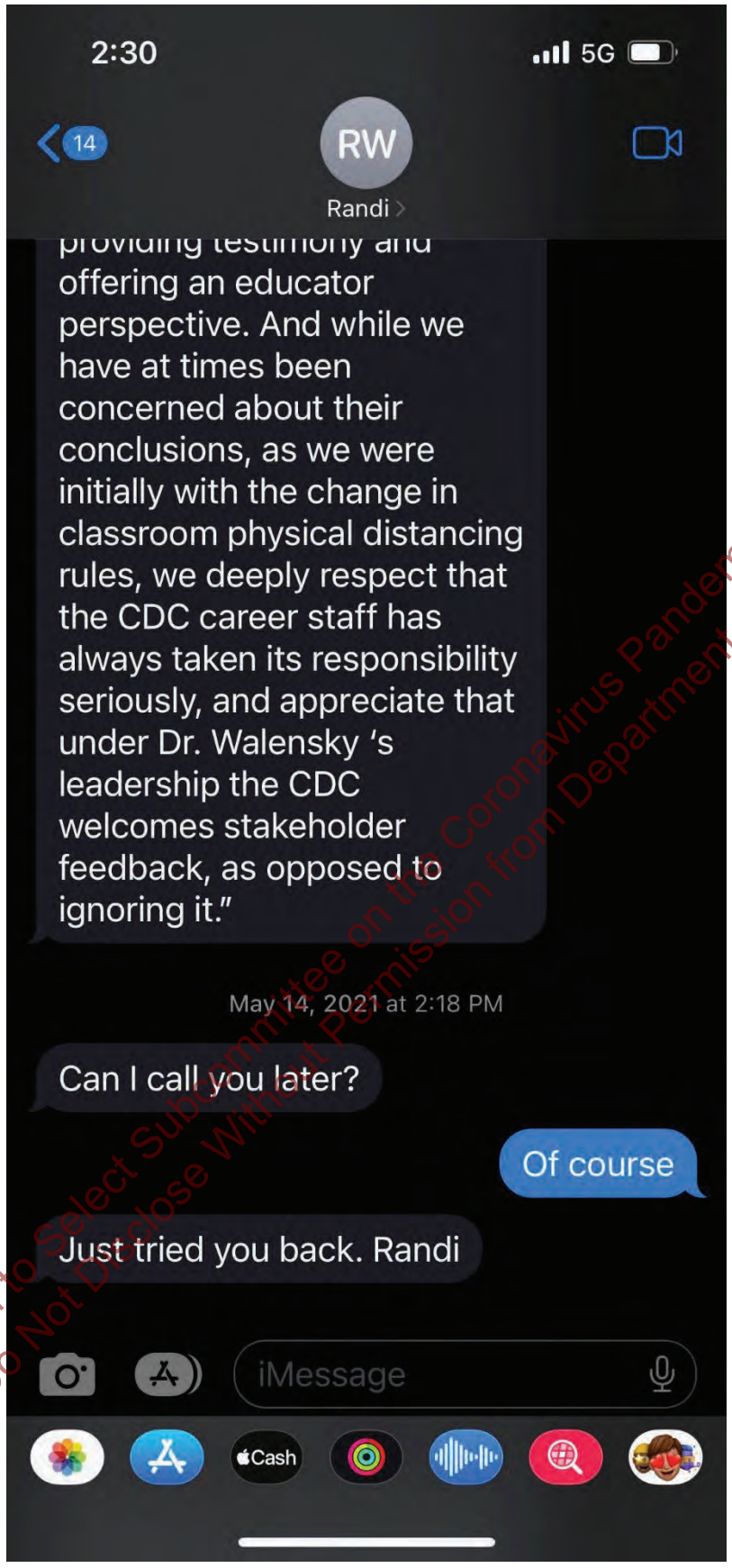












DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

www.nih.gov

MEMORANDUM

DATE: 19 July 2023

TO: David Morens, Ph.D., Senior Scientific Advisor, National Institute of Allergy and Infectious Disease (NIAID), National Institutes of Health (NIH)

CC: Anthony D. Crawley Gibson, NIH Records Officer
Chief, Information Management Branch, Division of Compliance Management (DCM),
Office of Management Assessment (OMA), Office of Management (OM), Office of the Director (OD)

FROM: Jill R. Harper, Ph.D. Deputy Director for Science Management, NIAID, NIH

SUBJECT: TIME SENSITIVE - In accordance with 36 CFR 1230.16(b), the National Archives and Records Administration (NARA) is requesting in an open letter a response to *allegations of unauthorized disposition of NIH records* to assist in its investigation of any potential violations of federal record keeping laws, regulations, or policies.

Dear Dr. Morens,

This memorandum requires your immediate action. By close of business on July 26, I request that you:

1. **Locate, mark for litigation hold and provide a copy to me** of all records, documents, data and information to include working drafts and peer reviewed correspondence, emails, texts, or instant messages ("communications") created and/or received by NIAID personnel at NIH email addresses/devices using:
   - Redacted
   - Redacted or
   - any other associated accounts/mobile devices government sponsored or personal.

   This is to include:

   a. All documents and Communications regarding the drafting, publication, or critical reception of the following publications:
      i. The Correspondence in The Lancet titled, "Statement in support of the scientists, public health professionals, and medical professionals of China combatting COVID-19."
      ii. The Correspondence in Nature Medicine titled, "The proximal origin of SARS-CoV-2."
      iii. The Letter in Science titled, "Investigate the origins of COVID-19."
      iv. The Review in Cell Press titled, "The origins of SARS-CoV-2: A critical review."
      v. The Publication in Science titled, "The Hunan Seafood Wholesale Market in Wuhan was the early epicenter of the COVID-19 pandemic."

vi. The Publication in Science titled, "The molecular epidemiology of multiple zoonotic origins of SARS-CoV-2."
vii. The Publication in The Lancet titled, "The Lancet Commission on lessons for the future from the COVID-19 pandemic."
viii. The Perspective in The Proceedings of the National Academy of Sciences titled, "Pandemic origins and a One Health approach to preparedness and prevention: Solutions based on SARS-CoV-2 and other RNA viruses."
ix. The Report in Zenodo titled, "Genetic evidence of susceptible wildlife in SARS-CoV-2 positive samples at the Huanan Wholesale Seafood Market, Wuhan: Analysis and interpretation of data released by the Chinese Center for Disease Control."
x. The Pre-Print Publication in Nature titled, "Surveillance of SARS-CoV-2 in the environment and animal samples of the Huanan Seafood Market.

b. All documents and Communications regarding the Wuhan Institute of Virology, EcoHealth Alliance, Inc., or the origins of COVID-19 from 1 November 2019 to present.

2. **Provide a detailed list to me of any Communications that were deleted**
Please ensure your report contains a complete description of the records involved, including volume and dates of the records, any salvage, recovery, or restoration efforts, and all safeguards that will be implemented to prevent the future unauthorized disposition of agency records.

3. **Acknowledge the following:**
a. NIH received notification by way of the Chairman of the House Select Subcommittee on the Coronavirus Pandemic that alleged you used a personal email account Redacted as a method of conducting official government business in an apparent effort to evade the strictures of the Freedom of Information Act. Including the statement that you would delete any NIH or personal emails that you "don't want to see in the New York Times".

b. You understand that it is stipulated in the NIH IT General Rules of Behavior that employees must:
- Use only Government Issued Federal Equipment (GFE) to perform official duties or to connect to NIH IT resources (excluding NIH public websites and other public use systems).
- Take all necessary precautions to protect NIH information and IT resources, including but not limited to hardware, software, sensitive information, federal records [media neutral], and other NIH information from unauthorized access, use, modification, destruction, theft, disclosure, loss, damage, or abuse, and in accordance with NIH information handling policies.
- Not use personal email and storage/service accounts to conduct NIH business.
- Never use personal devices to conduct NIH business or store/transmit NIH data without official approval. Using personal phones to take phone calls or attend remote meetings is permitted.
- Only disseminate authorized NIH information related to official job and duties at NIH to internal and external sources. (Note: While teleworking, managers/coworkers are encouraged to use Skype, Microsoft Teams, and ZoomGov to communicate essential NIH business. Other messaging services such as WhatsApp and WeChat are not currently approved.

c. You understand that Federal employees must not remove Federal records from Government custody without proper authorization. Under 36 CFR 1222.24
- Unauthorized Records Destruction: means disposal of an unscheduled or permanent record; disposal prior to the end of the NARA-approved retention period of a temporary record

(other than court-ordered disposal under § 1226.14(d) of this subchapter); and disposal of a record subject to a FOIA request, litigation hold, or any other hold requirement to retain the records.

- The ICO must report promptly any unlawful or accidental removal, defacing, alteration, or destruction of records in their custody to the NIH Records Officer. Title 36 / Chapter XII / Subchapter B / Part 1230
- While it is prohibited for NIH employees to use personal email accounts to conduct official agency business. In the event of an emergency situations when Federal accounts are not accessible or when an employee is initially contacted through a personal account. In these situations, **agency employees must ensure that all Federal records sent or received on personal email systems are captured and managed in accordance with agency recordkeeping practices and procedures** to ensure compliance with other statutes and obligations, such as Litigation Hold, FOIA and discovery.
- The Federal Records Act (44 U.S.C. 2911 as amended by Pub. L. 113-187): Electronic messages created or received in a personal account under the conduct of official NIH business must be forwarded to an official electronic messaging account within 20 days of receipt and/or creation.

4. **Agree to immediately transfer all communications related to your NIH work** or sent with a NIH signature block from your personal email accounts to your official NIH account. This is to be completed no later than Wednesday, July 26.

I, David Morens, acknowledge and agree to the above:

Signature: Redacted

Title: Senior Advisor to the Director, NIAID, NIH

Date: 20 July 2023

From: Handley, Gray (NIH/NIAID) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=1CEB55D4B673477391C9DA8A3EB3C75 C[redacted]
Sent: 1/28/2020 8:56:02 PM
To: Chen, Ping (NIH/NIAID) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e86e86eeeef44552b2918975f5001d13-[redacted]
CC: Dominique, Joyelle (NIH/NIAID) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5c55f75b58f14ab2b2ccbac0a881ccae-[redacted]; Rosa, William (NIH/NIAID) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6ad94c8f809d41ad91b1f78754f60c54-[redacted]; Lu, Tami (NIH/NIAID) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=683d9f298f344f53b273ce527aa15d9a-[redacted]; Bernabe, Gayle (NIH/NIAID) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c78e95b3db24482ba3dcbdedc2d3a003-[redacted]
Subject: RE: 2019-nCoV_PotentialContactsandSites_updated28Jan2020.xlsx

See below suggestions. Good to send it via WeChat. Thanks. G

From: Chen, Ping (NIH/NIAID) [E] [redacted]
Sent: Tuesday, January 28, 2020 3:36 PM
To: Handley, Gray (NIH/NIAID) [E] [redacted]; Dominique, Joyelle (NIH/NIAID) [E] [redacted] Rosa, William (NIH/NIAID) [E] [redacted] Lu, Tami (NIH/NIAID) [E] [redacted] Bernabe, Gayle (NIH/NIAID) [E] [redacted]
Subject: RE: 2019-nCoV_PotentialContactsandSites_updated28Jan2020.xlsx

Gray, here is my draft. I am going to send with some Chinese language (I provided translation). Please let me know if this is acceptable. Thanks
Ping

Hi George, 陈平在NIH给你拜年了。知道你很忙。不想打扰你。现在有任务在身，(translation: Ping is sending her new year's greetings. I know you are incredibly busy, did not want to bother you. Now I have job to do :-)) Would you be interested in having a quick phone call with Dr. Fauci to share information about our respective nCoV research efforts and plans? We think it might be especially useful to update each other about what we are doing here and n China to develop diagnostics, vaccines, and therapeutics. We could set this up in the next few days and also explore any opportunities to work together so the science advances as quickly as possible. Greatly appreciate your response. (I will end with some Chinese New Year's greetings)

From: Handley, Gray (NIH/NIAID) [E] [redacted]
Sent: Tuesday, January 28, 2020 3:25 PM
To: Dominique, Joyelle (NIH/NIAID) [E] [redacted]; Rosa, William (NIH/NIAID) [E] [redacted]; Lu, Tami (NIH/NIAID) [E] [redacted] Bernabe, Gayle (NIH/NIAID) [E] [redacted] Chen, Ping (NIH/NIAID) [E] [redacted]
Subject: RE: 2019-nCoV_PotentialContactsandSites_updated28Jan2020.xlsx

I have asked Ping to reach out to George Gao to see if he is interested in having a research information sharing call with CASF. We will see if he even has time to respond.

From: Dominique, Joyelle (NIH/NIAID) [E] [redacted]
Sent: Tuesday, January 28, 2020 2:47 PM
To: Handley, Gray (NIH/NIAID) [E] [redacted]; Rosa, William (NIH/NIAID) [E] [redacted] Lu, Tami (NIH/NIAID) [E] [redacted]; Bernabe, Gayle (NIH/NIAID) [E] [redacted] Chen, Ping

(NIH/NIAID) [E] [redacted]
Subject: 2019-nCoV_PotentialContactsandSites_updated28Jan2020.xlsx

Hi all,
Updated spreadsheet. If there is other contact we should be tracking, please include or let me know.
Thanks!
Joyelle

T-Mobile 5:32 PM 73%

白玉

Thank you. That is a great news. Tell him we are all welcoming his participation to the banyaviruses conference.

Jan 9, 2020 10:57 AM

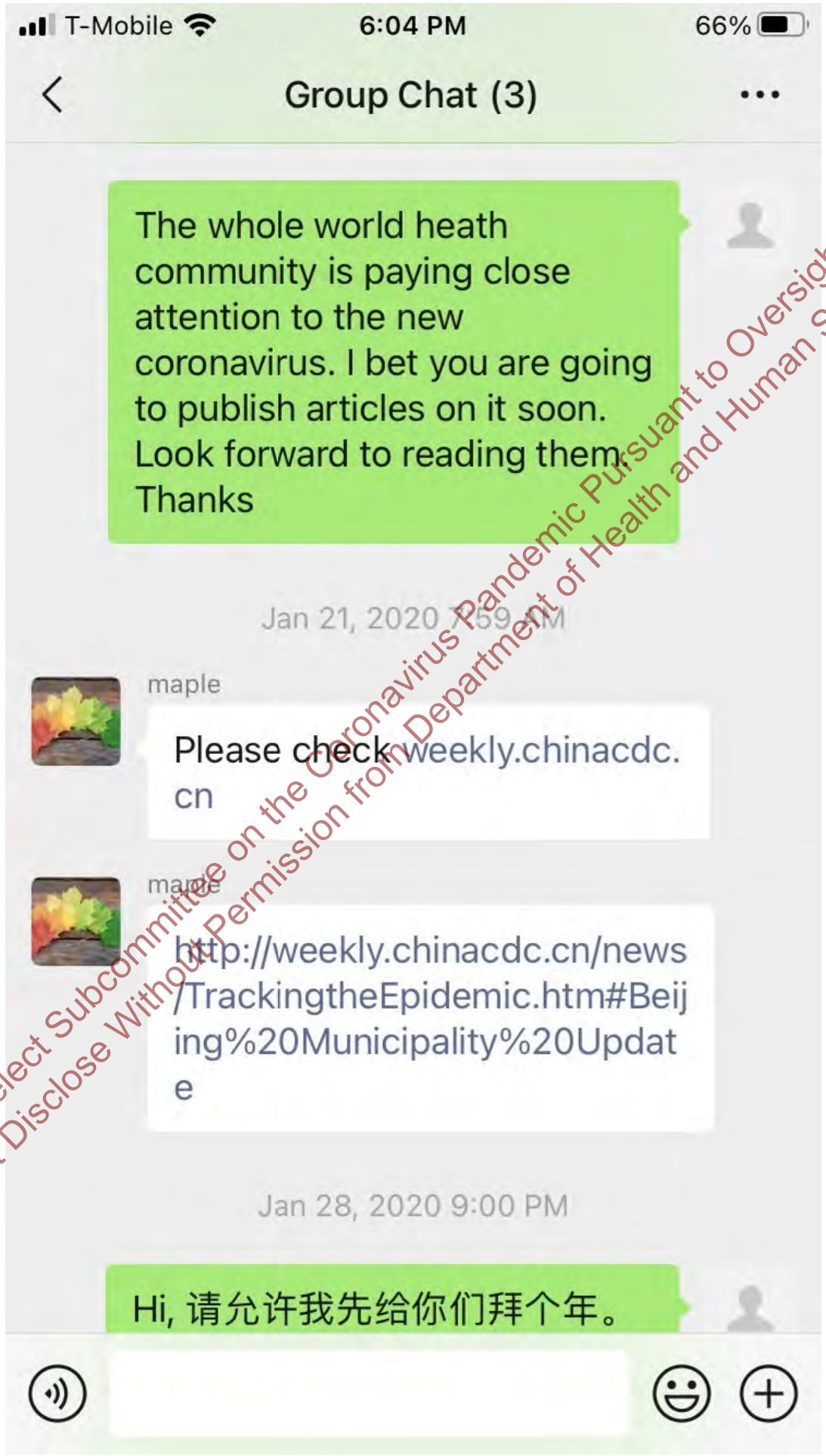
George just told me that he could not come because of the Wuhan pneumonia outbreak

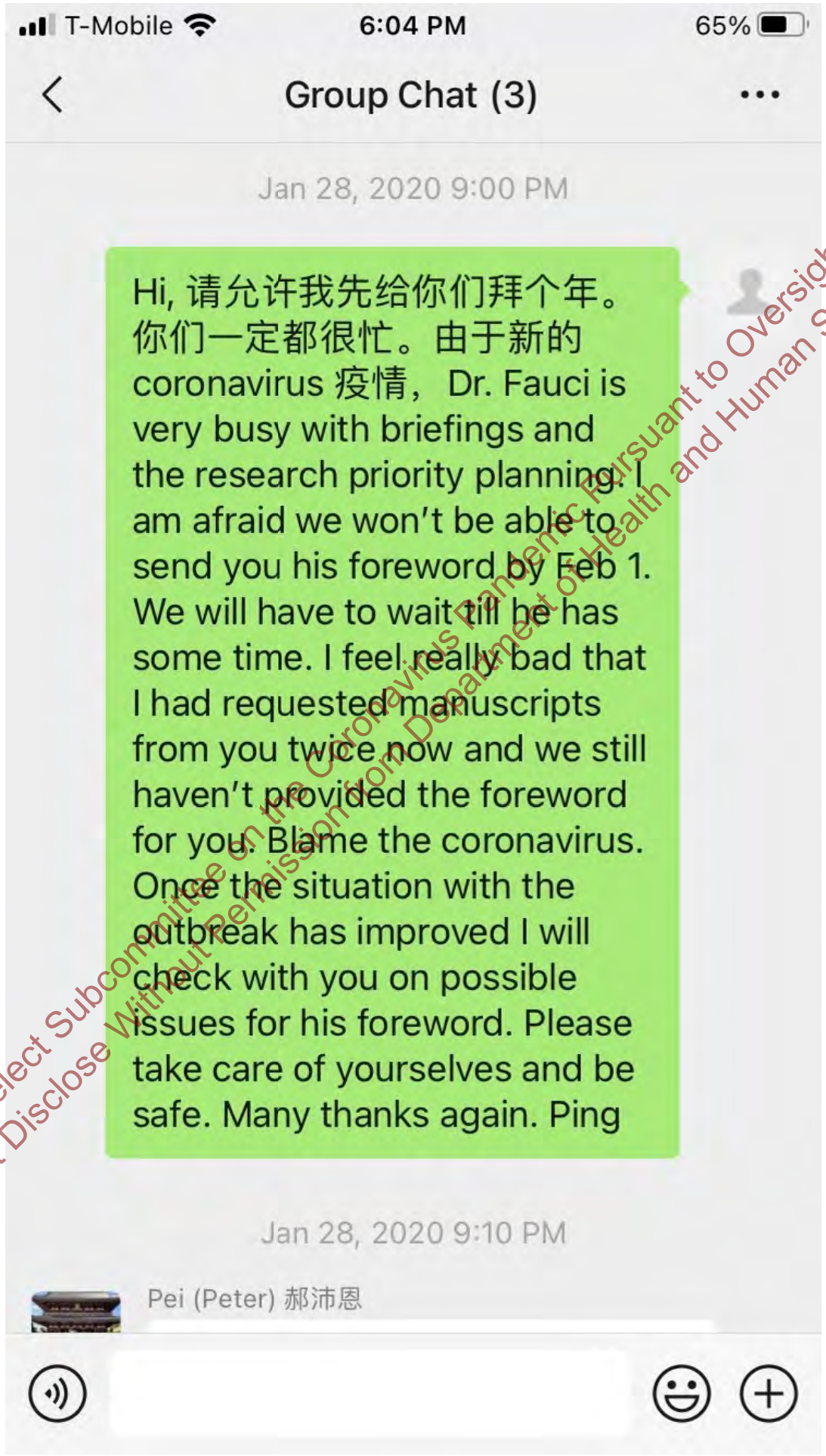
Jan 9, 2020 2:50 PM

抱歉，我少打了一个单词“not”

Jan 9, 2020 3:37 PM

I figured that was what had happened. No worries. Hope he can come another time.





T-Mobile 6:05 PM 65%

Group Chat (3)

Jan 28, 2020 9:10 PM

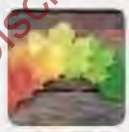
Pei (Peter) 郝沛恩

Happy new year to you too Ping! We understand as we have been working nonstop on the Coronavirus as well. Please keep us updated on when he has time to write something as we are really looking forward to his piece. Otherwise thank you very much and stay safe!!

Jan 28, 2020 9:19 PM

I will definitely follow up on this.

Jan 28, 2020 10:16 PM



maple

JAMA 主编访谈: 国际权威专家谈冠状病毒疫情非同...

美国国立卫生研究院国际感染传染疾病专家

T-Mobile 6:06 PM 65%

Group Chat (3)

maple

JAMA 主编访谈: 国际权威专家谈冠状病毒疫情非同...

美国国立卫生研究院国际感染传染疾病专家 Dr. Fauci 访谈此次...

全球医生组织

maple

Dr.Fauci

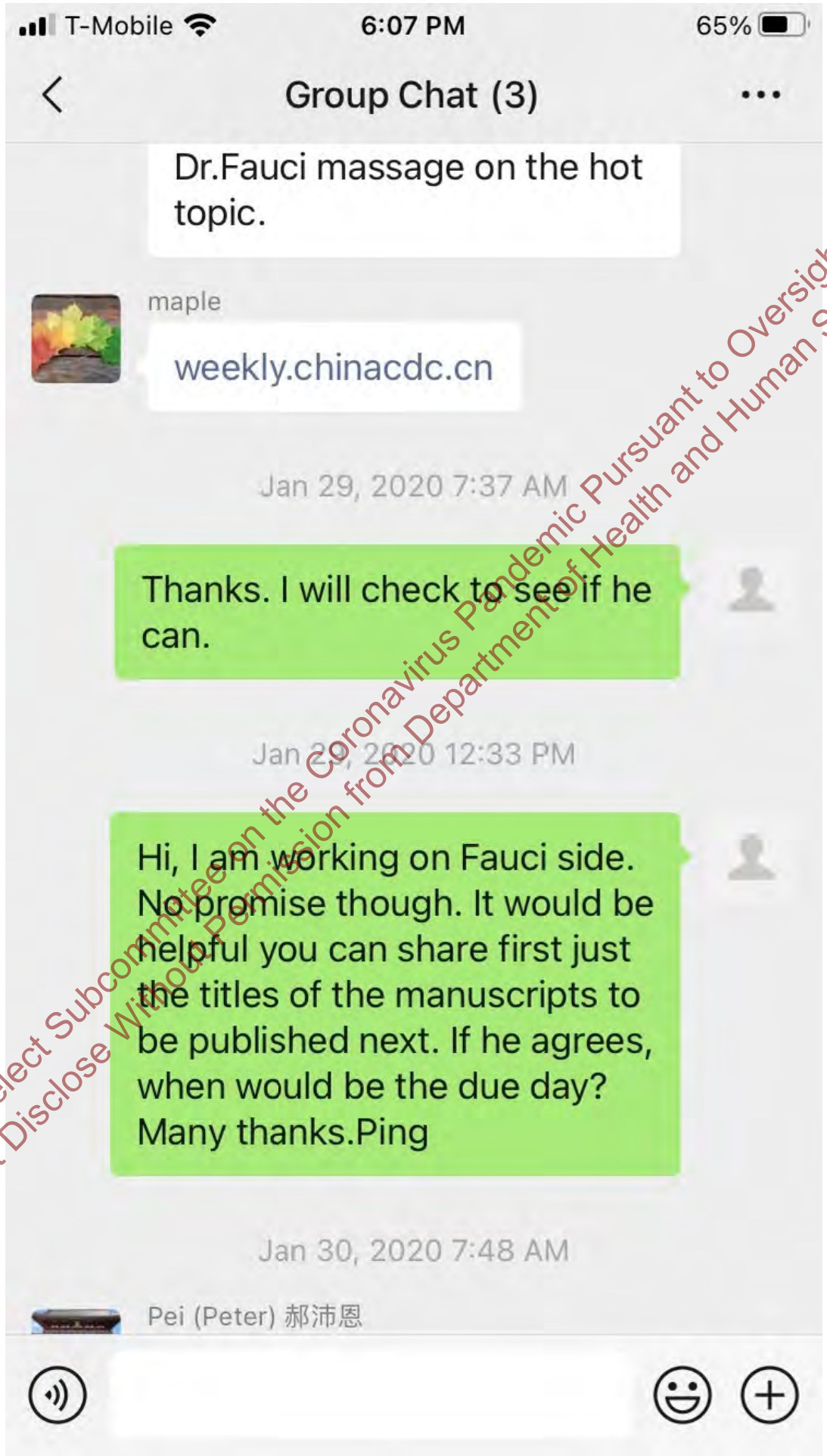
Jan 29, 2020 7:05 AM

Yes. He and NIAID have been following the outbreak closely.

Jan 29, 2020 7:12 AM

maple

The weekly published 2 and will release 2 in the fellowing issues related to the outbreak.We appreciate Dr.Fauci massage on the hot



T-Mobile 6:08 PM 65%

Group Chat (3)

Jan 30, 2020 7:48 AM

Pei (Peter) 郝沛恩

Hi Ping, once we return to the office (likely on Monday) we'll reorganize and send you the titles. Many of the upcoming issues have not been completely set due to the epidemic. We will contact you soon!

Jan 30, 2020 7:54 AM

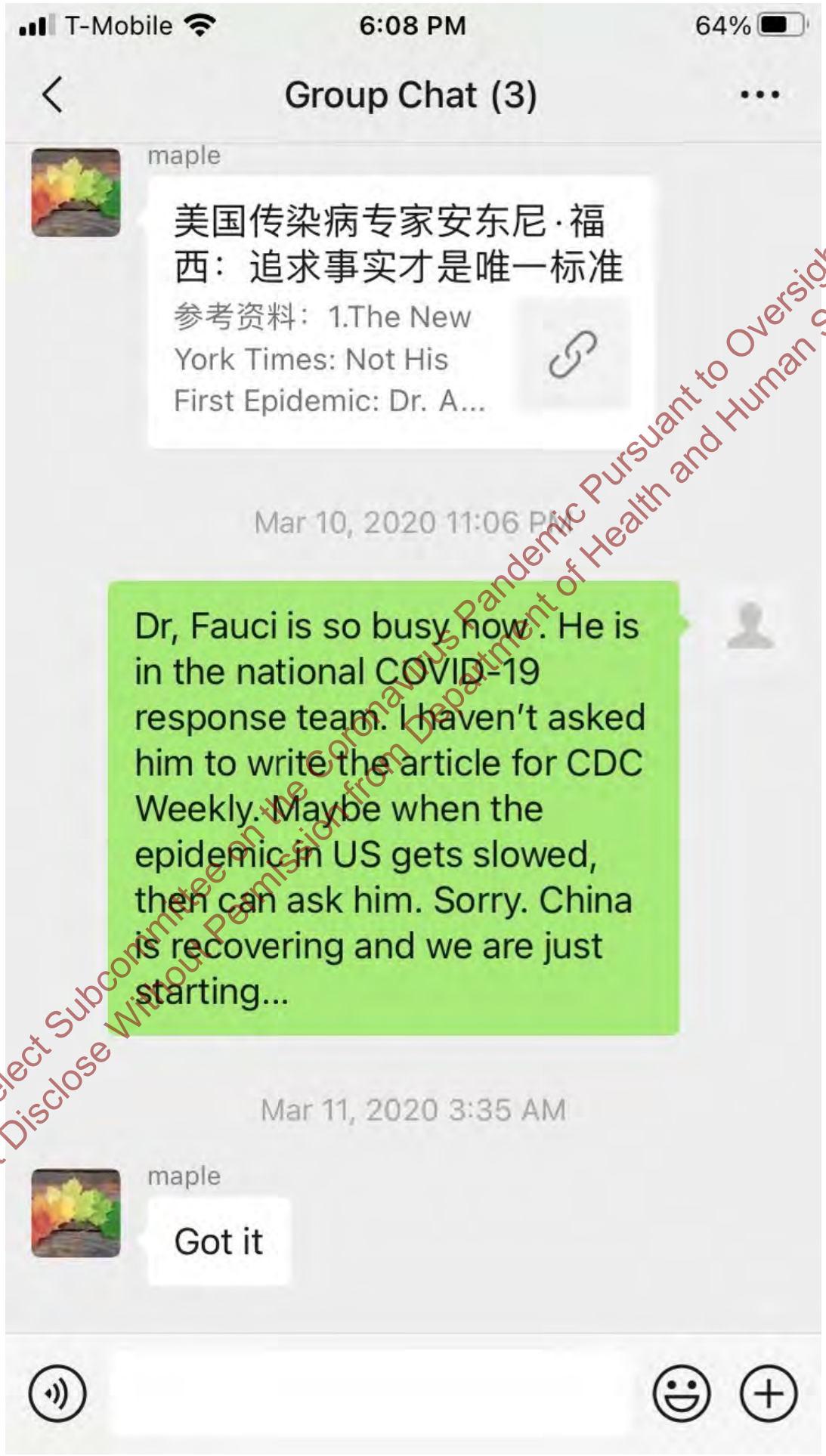
Great. Please do what you can. Best

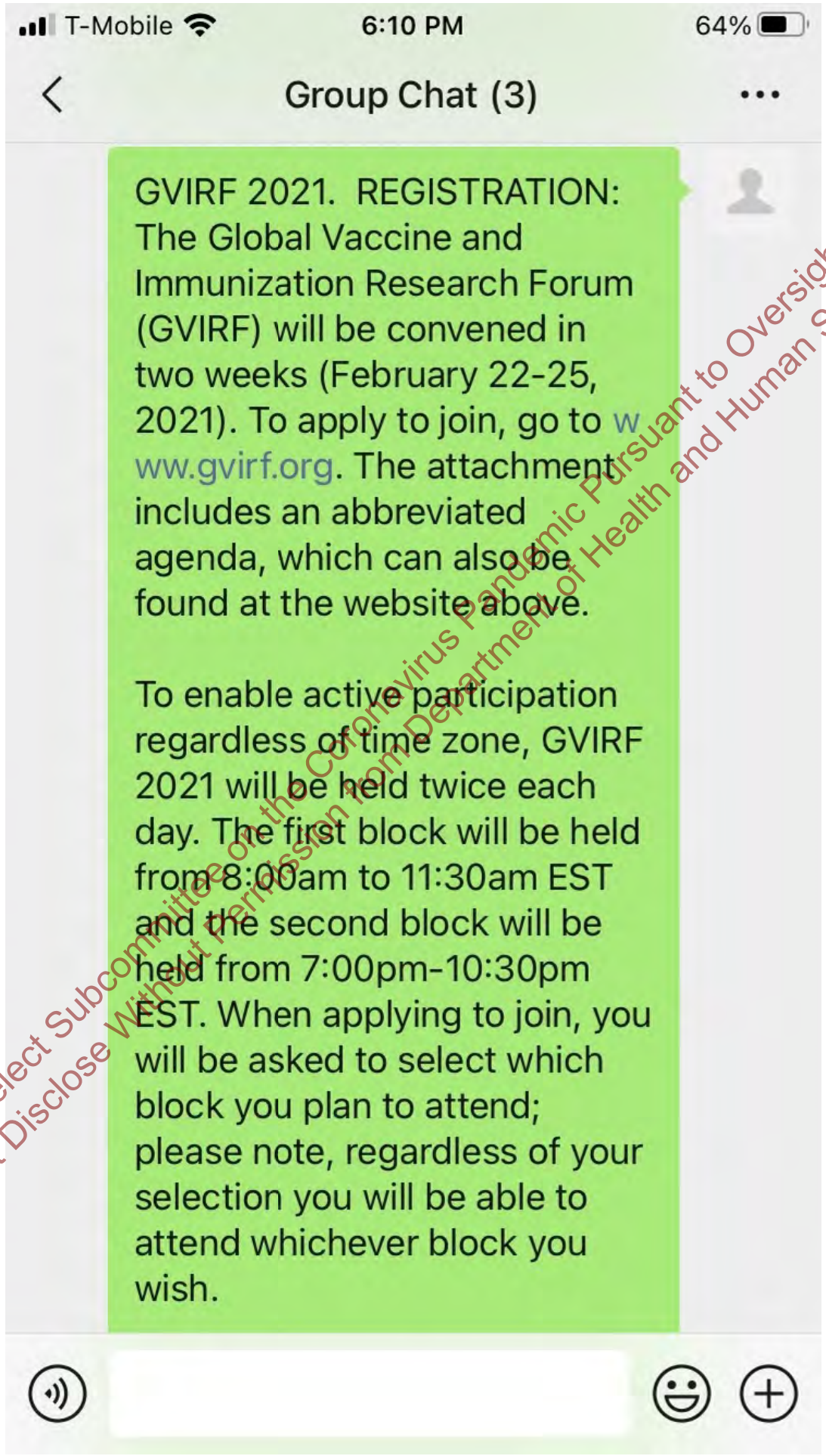
Mar 10, 2020 10:53 PM

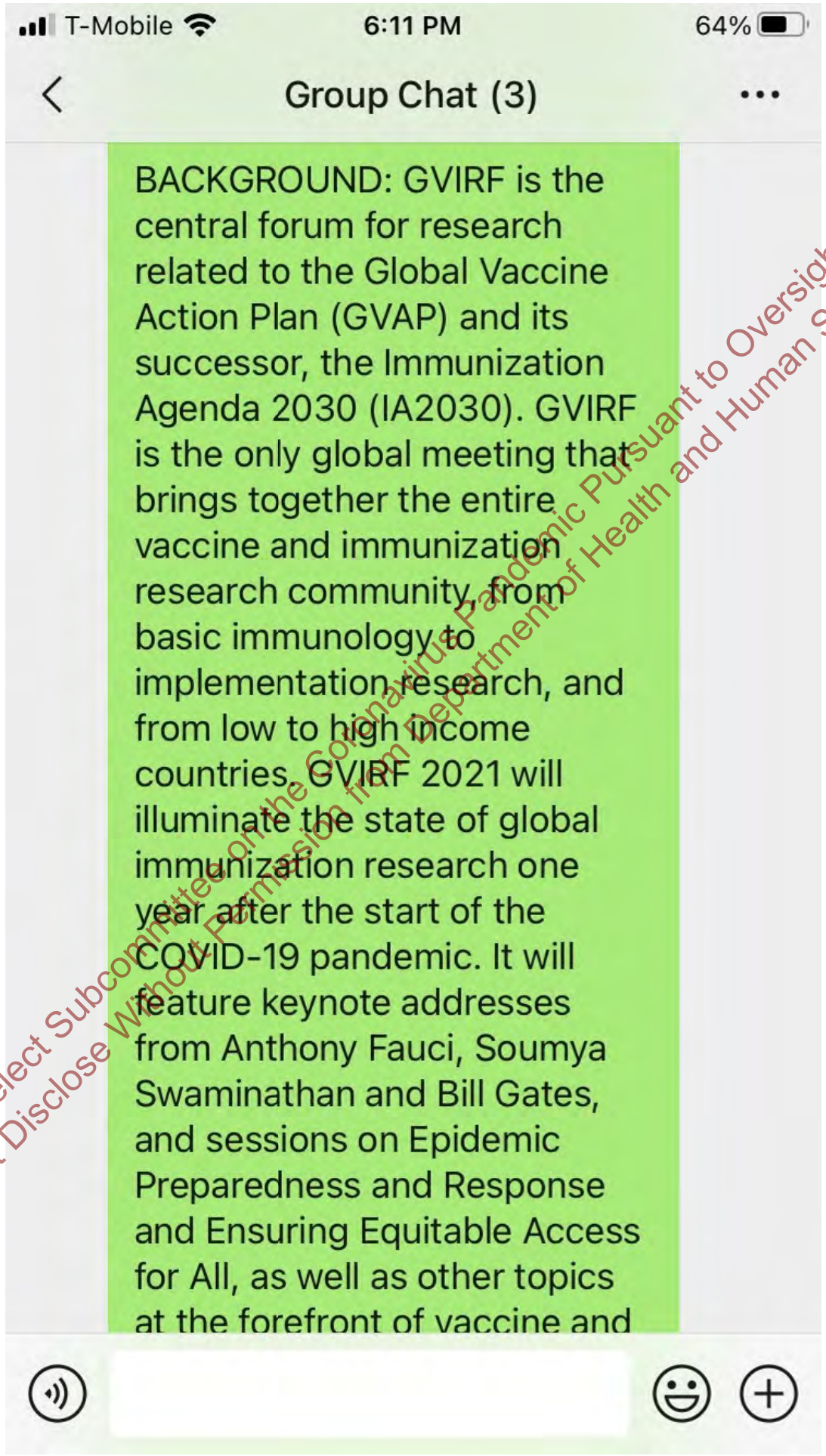
maple

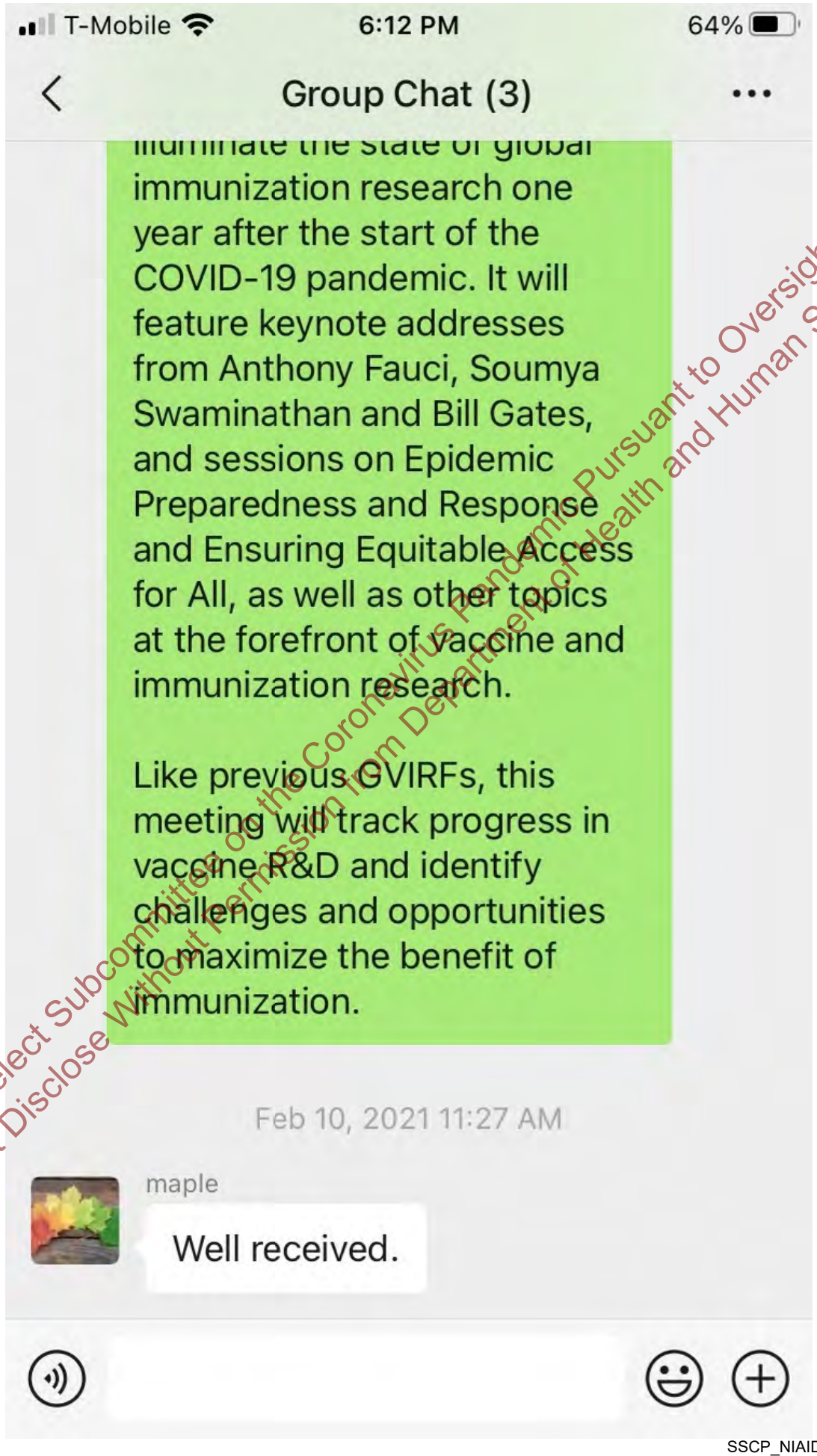
美国传染病专家安东尼·福西：追求事实才是唯一标准

参考资料：1.The New York Times: Not His First Epidemic: Dr. A...









T-Mobile 5:04 PM 78%

李浩

Jan 2, 2020 11:28 PM

对不起。没写完。是 NIAID's Director, Dr. Fauci. Letter to China CDC Weekly

我准备说写一下他对同期发表的文章的 comments. 这是我问你问题的原因

Jan 3, 2020 12:10 AM

嗯嗯，我建个群，把出版部负责同志一起拉进来，以便您确认放在哪一期合适。

Jan 28, 2020 8:33 PM

浩， 刚刚给高福老师发了微信。你也应该收到的。请你一定协助我们了解高老师的决定是否愿意在最近的 1-2 天里和 Dr. Fauci 通电话。 麻烦你了。

T-Mobile 5:05 PM 77%

李浩

Dr. Fauci 通电话。 麻烦你了。祝你鼠年快乐健康幸福. 陈平

我在群里看到了。祝您新春快乐！ 拜年了！

Jan 28, 2020 9:21 PM

拜托了。高老师那边要靠你的帮助了。 谢谢

Jan 28, 2020 9:41 PM

我现在也见不到高老师，派我在委机关对接应急。

Jan 28, 2020 9:48 PM

好吧。我等一两天。你知道这些日子有谁能和高老师接触多? 你能帮我找到CDC Doris (王晓琪?) 的微信吗？ 谢谢了

T-Mobile 5:06 PM 77%

李浩

好吧。我等一两天。你知道这些日子有谁能和高老师接触多？你能帮我找到CDC Doris (王晓琪?)的微信吗？谢谢了

Doris

Contact Card

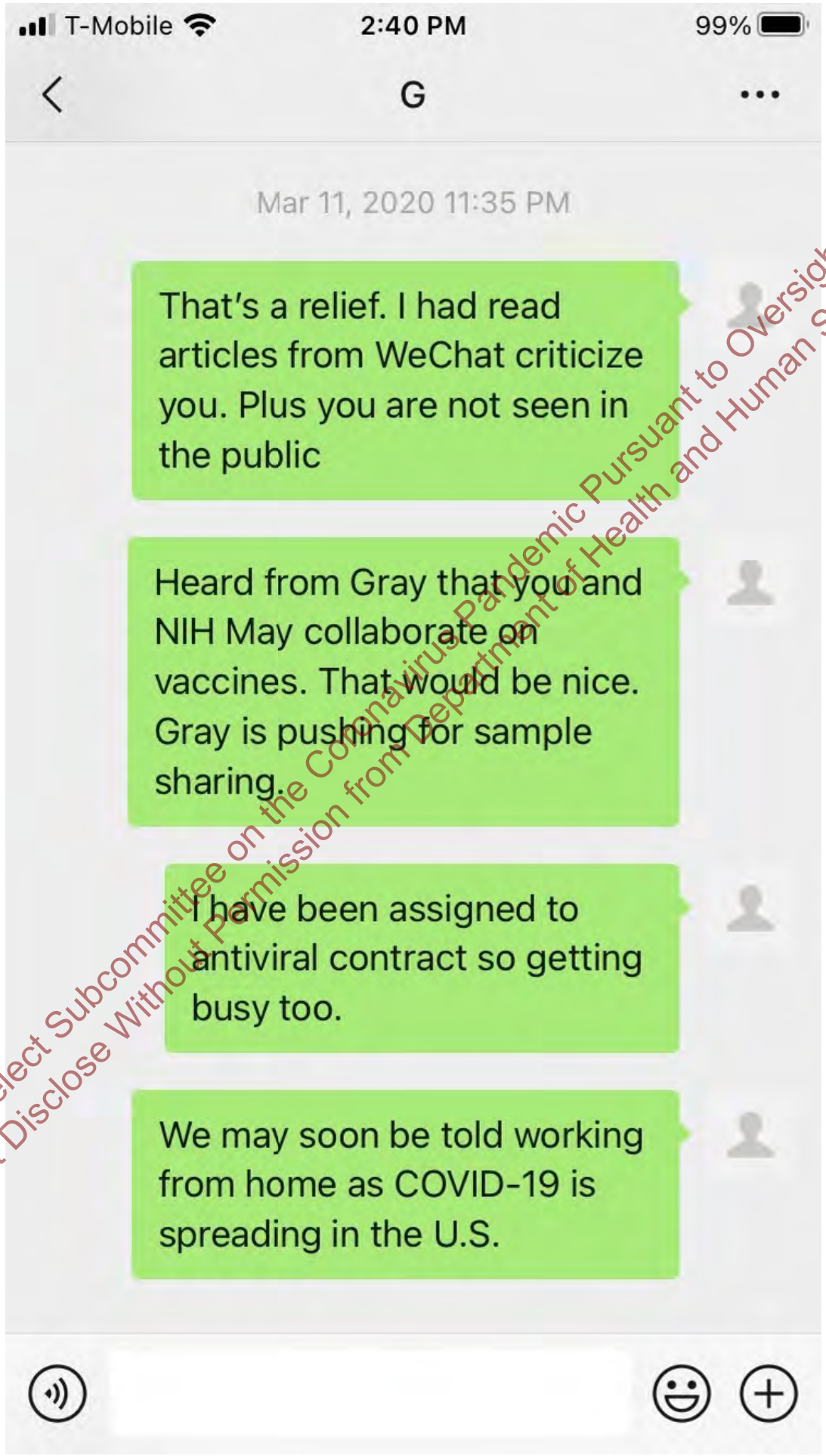
Jan 28, 2020 9:59 PM

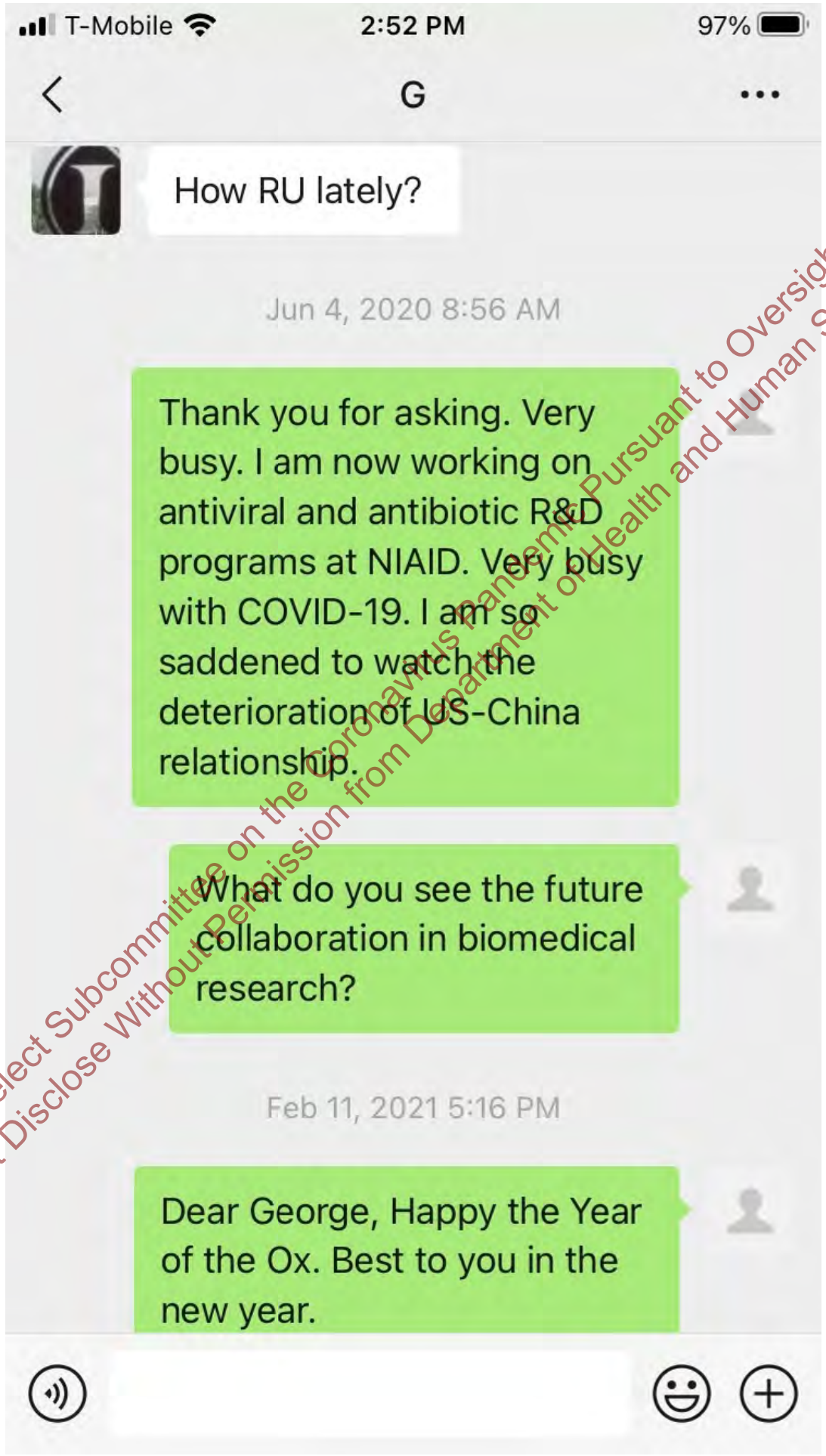
谢谢。我打可the contact card, but no contact info. Me - Doing something incorrectly?

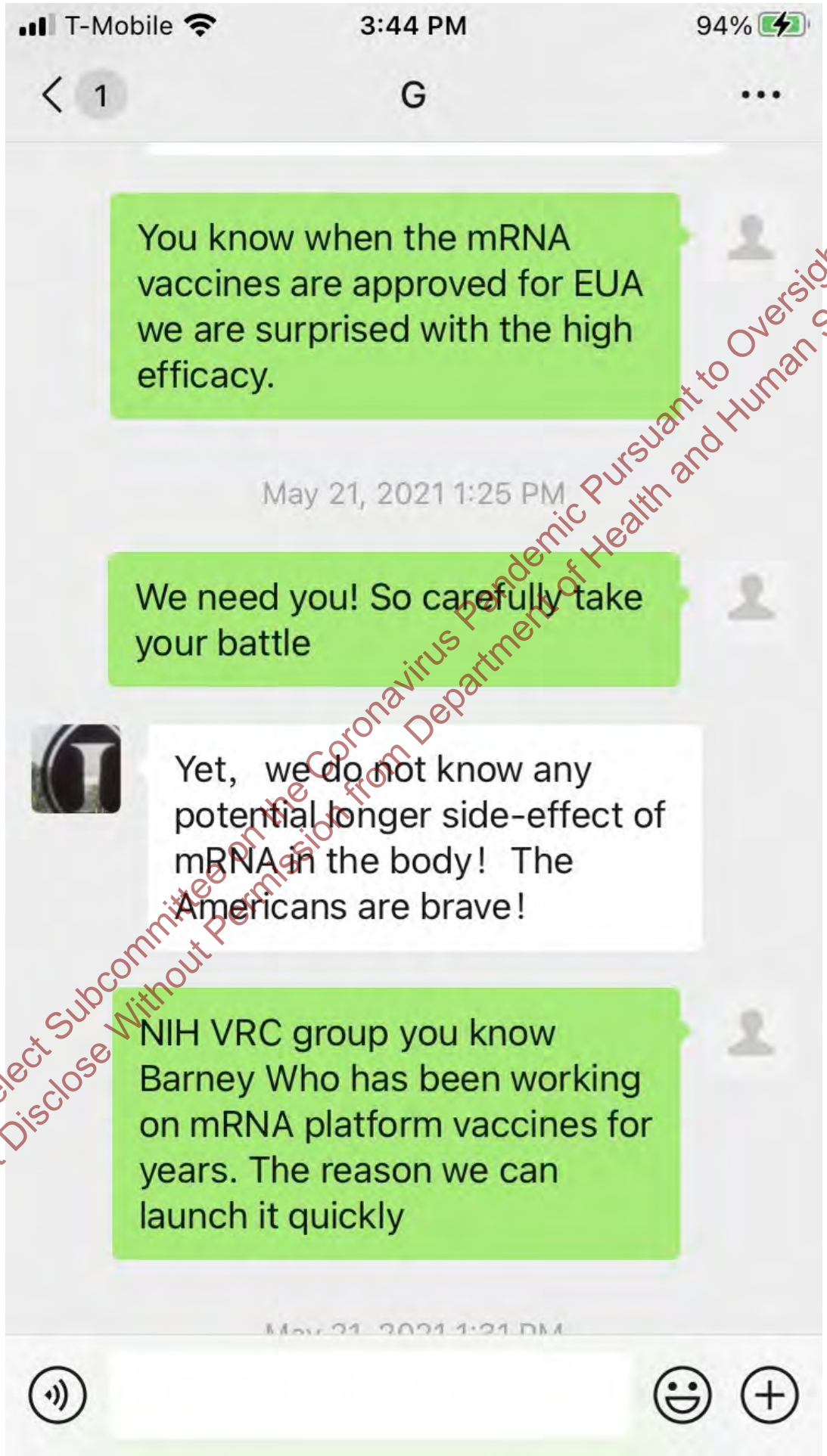
Jan 28, 2020 10:07 PM

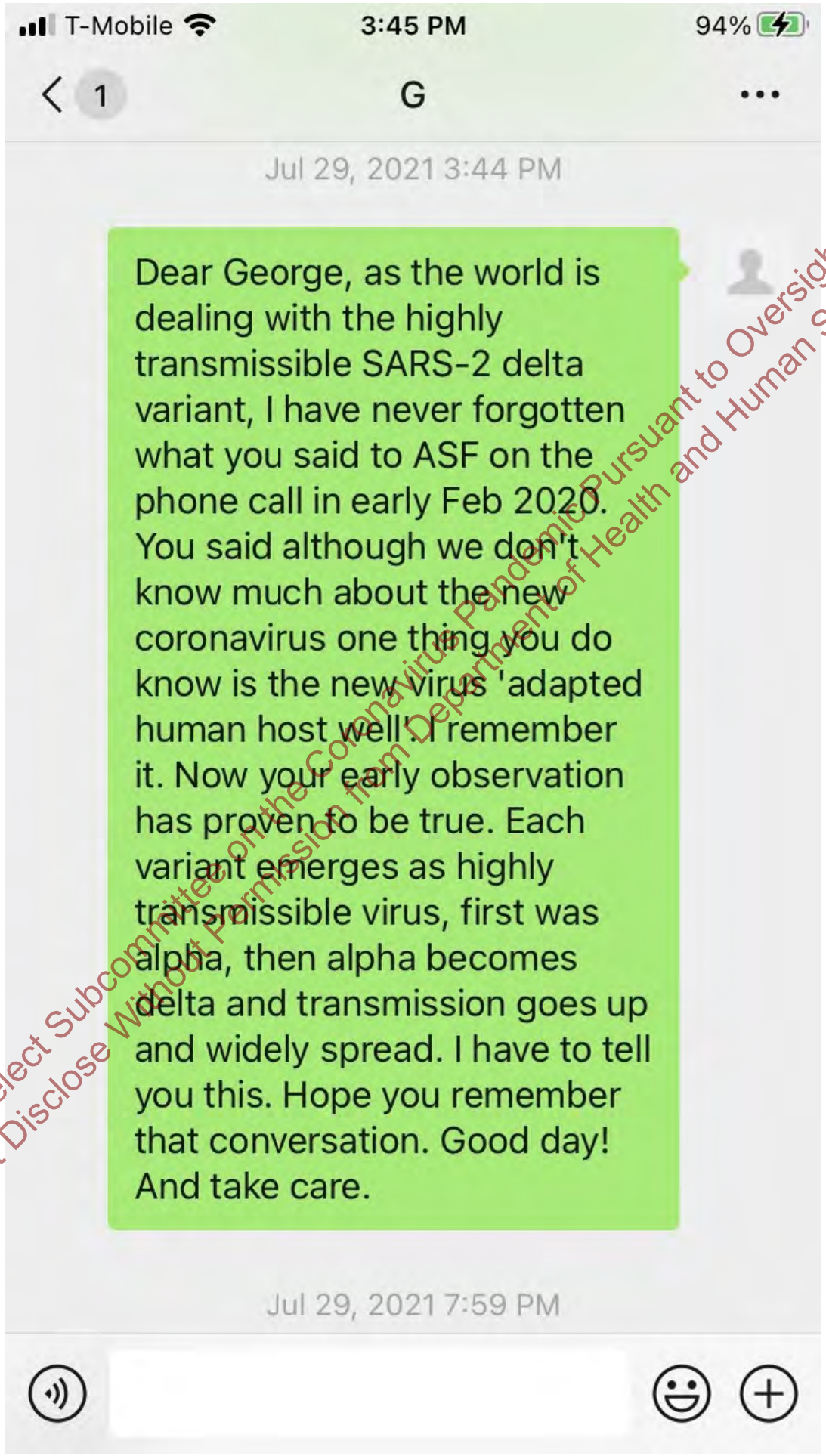
您再等等，现在都是满负荷。
🙏🙏

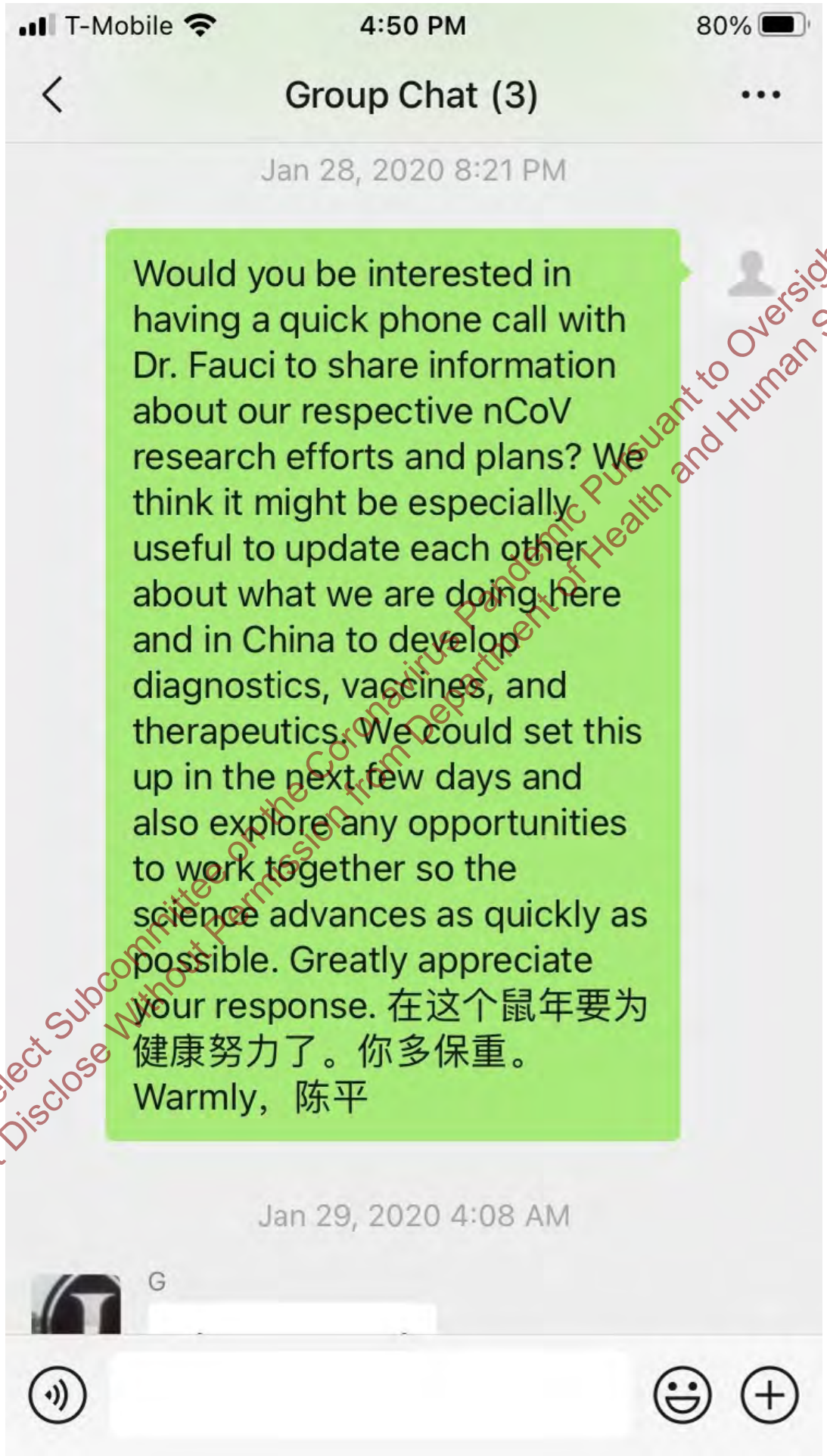
明白

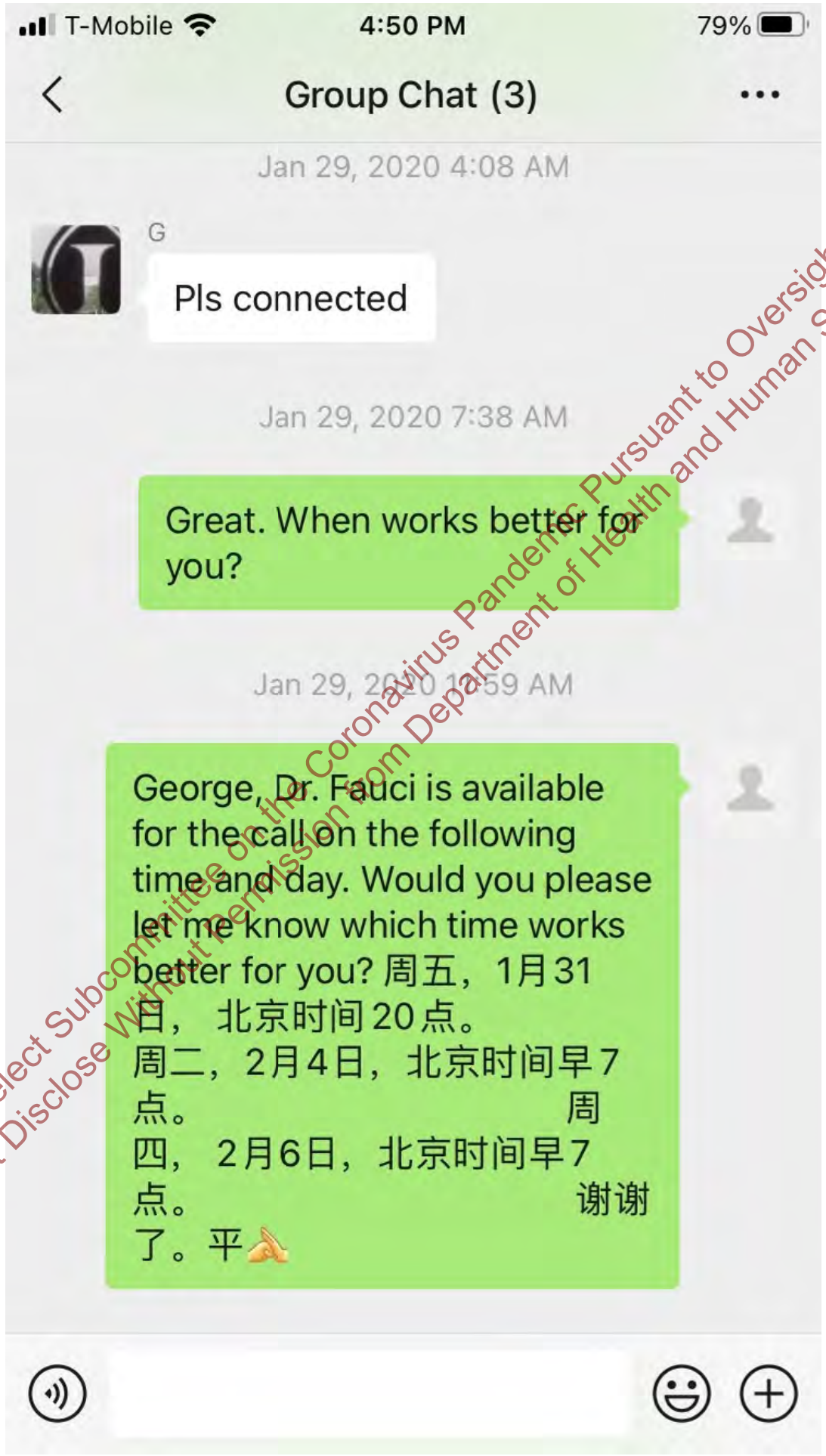


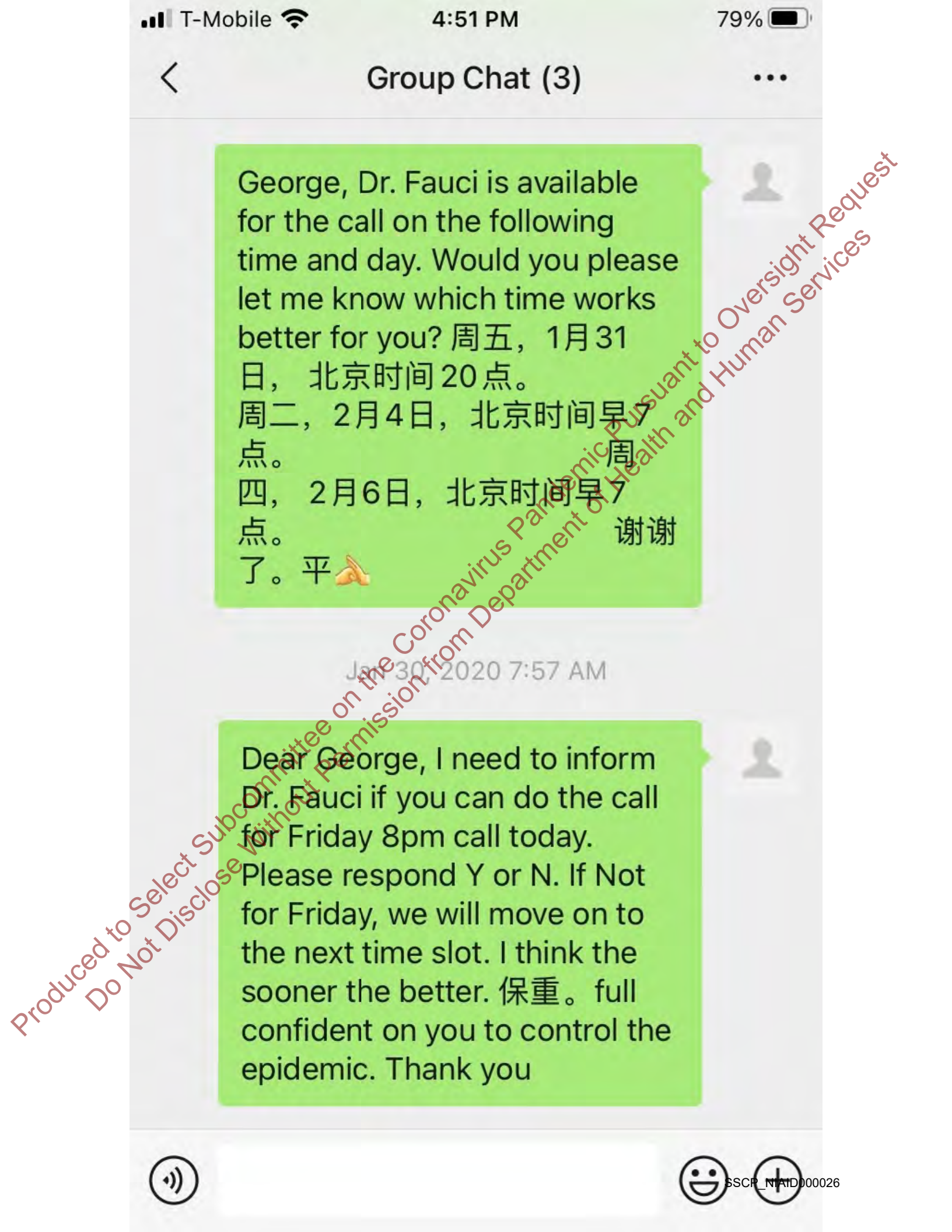












Message

From: [redacted]
Sent: 2/5/2020 1:54:59 AM
To: [redacted]
Subject: Evolution of 2019-nCoV
Attachments: Proposed WHO Discussion on Viral Evolution nCoV 02-02-2020 v3 CLEAN.docx; ATT81809

Hi Soumya,

I hope you are able to get a little shut eye during this turbulent time and the rapidly changing nature of this outbreak.

May I ask for your help please – Secretary Azar has asked me to follow very closely the issue raised to WHO by Drs. Collins and Farrar last weekend. He asks about it daily. We crafted the original request recognizing the extreme sensitivity of the issue, and I was pleased to hear that you would be handling the request.

Proposed WHO Discussion on Vi...

As your plans solidify to address the issue, or if you need any assistance from HHS or the USG, I am happy to help you in any way I can.

Much thanks and best wishes,

Larry
+001 [redacted] text or WhatsApp

Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Office of Global Affairs
Health and Human Services
Switzer Building, Suite 2312
330 C Street, SW
Washington, DC 20201
Phone: [redacted]
Fax: 202-260-8902
[redacted]

www.globalhealth.gov

U.S. Department of Health & Human Services

DRAFT PROPOSAL: WHO-Convened Discussion on Evolutionary Origins of 2019-nCoV

Since the release of the first full genome sequence of 2019-nCoV on January 10, 2020, the global scientific community has been rapidly and diligently analyzing the available sequence information and other data in order to learn more about the origins and properties of this newly emerging virus. Initial analyses have identified phylogenetic linkages to other betacoronaviruses from bats, and we anticipate learning more about the origins of this virus as additional sequences are released and further analyses are performed. However, the combination of the global spotlight on the outbreak, the speed at which the results of these analyses are being released (not all of which have been peer-reviewed) and the creation of rumors by multiple and varied interpretations of the results have fueled rumors and suspicion of potential intentional creation of this new virus. To address responsibly such rumors and more fully understand the potential future risk to human health from this and other coronaviruses of animal origin, we propose that WHO bring together scientific experts that are broadly representative of the global scientific community for the specific purpose of evaluating the evolutionary origins of 2019-nCoV.

On February 1, 2020, U.S. National Institutes of Health Director Francis Collins, U.S. National Institute of Allergy and Infectious Diseases Director Anthony Fauci, and Wellcome Trust Director Jeremy Farrar discussed emerging published analyses on potential evolutionary origins of the virus with several highly esteemed scientists with expertise in evolutionary biology. The group was unanimous in their assessment that the paper by an Indian research group pointing out that there are HIV gene sequences in the 2019-nCoV virus and thus indicating intentional insertion were not credible. However, several in the group noted that the sequences of published isolates of the nCoV included mutations in the virus that have never been seen before in a bat virus. Although there were some who felt such mutations could occur naturally, others felt that they were suggestive of intentional insertion, thus questioning the origin of the virus. Thus, the group agreed that it would be beneficial to gather a larger group of scientific experts broadly representative of the global scientific community convened by WHO to discuss the evolutionary origins of 2019-nCoV and its lessons for future risk assessment and understanding of animal/human coronaviruses.

Participants in the call included:

- Francis Collins, Director of the U.S. National Institutes of Health, U.S.;
- Anthony Fauci, Director of the U.S. National Institute of Allergy and Infectious Diseases, U.S.;
- Jeremy Farrar, Director of the Wellcome Trust;
- Patrick Vallance, U.K. Chief Scientific Adviser and Head of the Government Science and Engineering;
- Kristian Anderson, Director of Infectious Disease Genomics, Scripps Research Translational Institute, CA, U.S.;
- Christian Drosten, Director of Human Virology at the German Center for Infection Research at Charité – Universitätsmedizin, Germany;
- Edward Holmes, Professor of Viral Evolution at University of Sydney;
- Andrew Rambaut, Professor of Molecular Evolution, University of Edinburgh's Institute of Evolutionary Biology, U.K.;
- Ron Fouchier, Deputy Head of Department of Viroscience, Erasmus Medical Center, NL;
- Robert Garry, Professor of Virology, Tulane University School of Medicine, Louisiana, U.S. ;
- Mike Ferguson, Professor of Life Sciences at University of Dundee, U.K.; and
- M.P.G. Koopmans, Head of Department of ViroScience, Erasmus Medical Center, NL.

Message

From: Linde, Emily (NIH/NIAID) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=B2FD661421CD499B8F7FAD6A196F6B02-LINDEE]
Sent: 2/17/2021 4:18:13 PM
To: Erbelding, Emily (NIH/NIAID) [E] [redacted]
CC: Fenton, Matthew (NIH/NIAID) [E] [redacted] Auchincloss, Hugh (NIH/NIAID) [E] [redacted] Harper, Jill (NIH/NIAID) [E] [redacted] Stemmy, Erik (NIH/NIAID) [E] [redacted]
Subject: RE: Status of R01AI110964-6 Understanding the Risk of Bat Coronavirus Emergence

To follow-up NIH/OD OPERA has confirmed that there has been *no change* to the restrictive terms on 2R01AI110964-06.

From: Linde, Emily (NIH/NIAID) [E]
Sent: Wednesday, February 17, 2021 8:19 AM
To: Erbelding, Emily (NIH/NIAID) [E] [redacted]
Cc: Fenton, Matthew (NIH/NIAID) [E] [redacted] Auchincloss, Hugh (NIH/NIAID) [E] [redacted] Harper, Jill (NIH/NIAID) [E] [redacted] Stemmy, Erik (NIH/NIAID) [E] [redacted]
Subject: RE: Status of R01AI110964-6 Understanding the Risk of Bat Coronavirus Emergence

Hi Emily E.,

As I read the email string below Dr. Daszak's question more closely I believe it pertains only to the Freedom of Information Act (FOIA) investigations. I have sent note to NIH OD to see if there is any movement on lifting the terms of award and will let you know the outcome.

Thanks,

Emily L.

From: Linde, Emily (NIH/NIAID) [E]
Sent: Wednesday, February 17, 2021 7:52 AM
To: Erbelding, Emily (NIH/NIAID) [E] [redacted]
Cc: Fenton, Matthew (NIH/NIAID) [E] [redacted] Auchincloss, Hugh (NIH/NIAID) [E] [redacted] Harper, Jill (NIH/NIAID) [E] [redacted] Stemmy, Erik (NIH/NIAID) [E] [redacted]
Subject: RE: Status of R01AI110964-6 Understanding the Risk of Bat Coronavirus Emergence

Thank you for letting me know. When I asked OER last week, nothing had changed. I will reach out to OER today and see if we can lift the terms.

From: Erbelding, Emily (NIH/NIAID) [E] [redacted]
Sent: Tuesday, February 16, 2021 6:05 PM
To: Linde, Emily (NIH/NIAID) [E] [redacted]
Cc: Fenton, Matthew (NIH/NIAID) [E] [redacted] Auchincloss, Hugh (NIH/NIAID) [E] [redacted] Harper, Jill (NIH/NIAID) [E] [redacted] Stemmy, Erik (NIH/NIAID) [E] [redacted]
Subject: FW: Status of R01AI110964-6 Understanding the Risk of Bat Coronavirus Emergence
Importance: High

Emily L-
See below.
What is the meaning of this? Pretty awesome if we are allowed to move forward with funding good science that was previously blocked.
Thanks
Emily E

From: Peter Daszak <[redacted]>
Sent: Tuesday, February 16, 2021 5:59 PM
To: Stemmy, Erik (NIH/NIAID) [E] [redacted]
Cc: Aleksei Chmura <[redacted]>; Erbelding, Emily (NIH/NIAID) [E] <[redacted]>; Cassetti, Cristina (NIH/NIAID) [E] <[redacted]>
Subject: Status of R01AI110964-6 Understanding the Risk of Bat Coronavirus Emergence
Importance: High

Hi Erik,

We received an email (below) from Garcia-Malone Gorka of the Office of Director letting us know that they have confirmed there are no pending investigations into the Wuhan Institute of Virology, and that the grant is funded. Because of that email, I'm writing to ask if you can confirm that we can move ahead with a continuation of our 5-yr award R01AI110964 and spend funds against the budget.

We're really hopeful that this is the case, and everyone at EcoHealth Alliance is looking forward to continuing this critical work.

Looking forward to hearing news from you!

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance
520 Eighth Avenue, Suite 1200
New York, NY 10018-6507
USA

Tel.: +1-212-380-4474
Website: www.ecohealthalliance.org
Twitter: @PeterDaszak

EcoHealth Alliance develops science-based solutions to prevent pandemics and promote conservation

From: Garcia-Malene, Gorka (NIH/OD) [E] [redacted]
Sent: Tuesday, January 26, 2021 12:20:51 PM

To: Matthew R.Torsiello
Cc: Nels T. Lippert; Andrew N. Krinsky; Bartok, Lauren (NIH/NIAID) [E]; NIH FOIA
Subject: [EXT] FW: FOIA Case No. 55702 re: EcoHealth Alliance & Grant No. R01AI110964-6

Good afternoon, Mr. Torsiello –

I'd like to insert myself into the unfolding FOIA conversation in hopes of providing some helpful context. Our records show that this competing renewal has in fact been funded. In addition, any indication from my program that there is an ongoing investigation into WIV can now be disregarded, as we recently confirmed there are no pending investigations into that organization. If we can agree on the above, all that would remain is to receive your proposed redactions to the records sought under the FOIA request.

Please let me know if there are any questions. I look forward to facilitating the Pre-Disclosure Notification process as efficiently as possible.

Best regards.

Gorka Garcia-Malene | FOIA Officer for the National Institutes of Health

From: Matthew R.Torsiello [redacted]
Sent: Monday, January 25, 2021 5:21 PM
To: Bartok, Lauren (NIH/NIAID) [E] [redacted]
Cc: Nels T. Lippert [redacted] Andrew N. Krinsky [redacted]
Subject: FOIA Case No. 55702 re: EcoHealth Alliance & Grant No. R01AI110964-6

Dear Ms. Bartok:

As you may recall, this firm represents EcoHealth Alliance, Inc. ("EcoHealth Alliance"), with respect to certain FOIA requests, including the instant request, FOIA Case No. 55702. The instant request seeks the same documents sought last year in FOIA Case No. 53996, regarding the research project *Understanding the Risk of Bat Coronavirus Emergence*, funded under grant 2R01AI110964. A copy of our prior letter regarding FOIA 53996 is available via the link provided below using the password NIH12345. On the grounds set forth in the letter, FOIA 53996 was denied in its entirety.

Likewise, FOIA 55702 should be denied and the grant documents should be withheld. First, grant 2R01AI110964-06 remains an unfunded competing renewal grant that is the subject of a pending first-level appeal and, thus, the materials are not subject to disclosure under NIH Grants Policy Statement §2.3.11.2.2. Moreover, in the context of the appeal, NIH has made multiple requests for further information regarding The Wuhan Institute of Virology ("WIV"), which requests indicate that a law enforcement investigation concerning WIV remains ongoing. Second, as demonstrated by the recent attack on the US Capital fueled by disinformation and conspiracy theories, the need to protect the privacy of EcoHealth Alliance's employees and affiliates is more important than ever. Last, while EcoHealth Alliance did not initially identify that the grant proposal contained confidential-commercial and propriety information, this is not dispositive. Moreover, since the filing of the renewal application, there has been a global COVID-19 pandemic, which has sparked international and highly competitive research in the area of bat coronaviruses.

At the very least, the responsive documents will require significant redactions. While the grant documents were previously reviewed and redacted in connection with FOIA 53996, we require a further opportunity to review the documents to confirm, *inter alia*, that all personnel information has been removed given the heightened risk of harm in this unprecedented political environment. Accordingly, EcoHealth Alliance respectfully requests a forty-five (45) day extension of time to respond to FOIA 55702, to allow sufficient time for EcoHealth Alliance to

conduct a further review of the responsive documents and provide an updated letter response that incorporates recent developments and specific justifications for additional redactions.

Please confirm that NIH will deny FOIA 55702 in its entirety or that NIH is agreeable to EcoHealth Alliance's request for an extension of time to provide a particularized response to FOIA 55702. Please also confirm NIH's receipt of this email.

Thank you.

Best,
Matthew R. Torsiello

FOIA Case No. 53996 - EcoHealth Alliance's Letter Response to FOIA Request, dated June 5, 2020 (With Exhibits)
https://tarterkrinsky-my.sharepoint.com/:b:/p/mtorsiello/EYHsvmSBaINAk6mAgJ4yl-gByaIrZFhCEBLGOnHjfTjMOw?e=mZHyA8

Matthew R.Torsiello | Associate
D: 212-216-1156 | F: 212-216-8001
[redacted] | Bio
Tarter Krinsky & Drogin LLP
1350 Broadway | New York | NY | 10018
www.tarterkrinsky.com | LinkedIn
COVID-19 RESOURCE CENTER

Tarter Krinsky & Drogin is fully operational. All attorneys and staff have been and will continue to be working remotely and TKD has put measures in place to ensure our services continue uninterrupted. However, because of anticipated delays in receiving regular mail and other deliveries, please e-mail copies of anything you send by regular mail or delivery, including issuing remittances electronically, until further notice. Please contact Katrinia Soares at reception@tarterkrinsky.com or by phone at 212-216-8000 with any questions. Thank you in advance for your courtesies during these unprecedented times.

NOTE: If regular mailing or other specific transmission type is required by terms of a contract, order or statute, please comply with those obligations and transmit the materials by the means set forth in the agreement, order or statute as well as by email.

RE: From Dr. Fauci's Office - Schedule Briefing

From: "Barasch, Kimberly (NIH/NIAID) [E]" <"/o=exchangelabs/ou=exchange administrative group (fydibohf23spdlt)/cn=recipients/cn=ea5fad4c52f64f80b7daee4982ae495f-baraschk">
To: Alison Andre <[redacted]>
Cc: Peter Daszak <[redacted]>, Aleksei Chmura <[redacted]>, "Conrad, Patricia (NIH/NIAID) [E]" <[redacted]>, "Folkers, Greg (NIH/NIAID) [E]" <[redacted]>, "Carver, Trea (NIH) [C]" <[redacted]>
Date: Thu, 25 Feb 2021 19:17:20 +0000

Dear Alison:
Thank you for your reply and confirming Friday, February 26th at 5:00pm – 5:30pm ET for this briefing between Drs. Fauci, Lane and Daszak. We will use the below Zoom meeting link for this meeting.

Join ZoomGov Meeting
https://www.zoomgov.com/j[redacted]
Meeting ID: [redacted]
One tap mobile
+16692545252,[redacted] US (San Jose)
+16468287666,[redacted] US (New York)
Dial by your location
+1 669 254 5252 US (San Jose)
+1 646 828 7666 US (New York)
+1 833 568 8864 US Toll-free
Meeting ID: [redacted]
Find your local number: https://www.zoomgov.com/u/aol6cMGf2

Best regards,
Kim

Kim Barasch [C]
Office of the Director
National Institute of Allergy & Infectious Diseases
301.496.2263
[redacted]

From: Alison Andre <[redacted]>
Sent: Thursday, February 25, 2021 12:51 PM
To: Barasch, Kimberly (NIH/NIAID) [E] <[redacted]>
Cc: Peter Daszak <[redacted]>; Aleksei Chmura <[redacted]>
Subject: Re: From Dr. Fauci's Office - Schedule Briefing

Dear Kimberly,

Tomorrow, Friday February 26th at 5:00pm would work very well for Peter if Dr. Fauci and Dr. Lane are still available. Please let me know.

Thank you,
Alison

Alison Andre
Executive Assistant to the President

EcoHealth Alliance
520 Eighth Ave – Suite 1200
New York, NY 10018

1.212.380.4462 (direct)
1.212.380.4465 (fax)
www.ecohealthalliance.org

EcoHealth Alliance develops science-based solutions to prevent pandemics and promote conservation.

---------- Forwarded message ---------
From: **Barasch, Kimberly (NIH/NIAID) [E]** <[redacted]>
Date: Tue, Feb 23, 2021 at 1:36 PM
Subject: From Dr. Fauci's Office - Schedule Briefing
To: [redacted] <[redacted]>

Dear Dr. Daszak:
Dr. Fauci would like to schedule a 30 minute zoom meeting for a briefing on your recent time in China with the WHO Team. He has asked Dr. Cliff Lane to join as well. Below are some options that Drs. Fauci and Lane are available. Please let me know if one of these times will work for your schedule.

Friday, February 26:	3:00pm – 4:00pm, 5:00pm ET
Monday, March 1:	8:00am, 2:00pm – 3:00pm ET
Tuesday, March 2:	11:30am, 3:30pm ET

Best regards,
Kim

Kim Barasch [C]
Office of the Director
National Institute of Allergy & Infectious Diseases
301.496.2263
[redacted]

RE: Daszak briefing Tony?

From: "Morens, David (NIH/NIAID) [E]" <[redacted]>
To: "Conrad, Patricia (NIH/NIAID) [E]" <[redacted]>, "Folkers, Greg (NIH/NIAID) [E]" <[redacted]>
Cc: NIAID OD AM <[redacted]>
Bcc: "Barasch, Kimberly (NIH/NIAID) [E]" <[redacted]>
Date: Tue, 23 Feb 2021 16:58:40 +0000

Peter Daszak's email is: [redacted]

He's based in NYC and thus is on East Coast time. He is just back in the States from China and catching up on stuff.

David M. Morens, M.D.
CAPT, United States Public Health Service
Senior Advisor to the Director
Office of the Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Building 31, Room 7A-03
31 Center Drive, MSC 2520
Bethesda, MD 20892-2520
☎ 301 496 2263 (assistant: Whitney Robinson)
301 496 4409
[redacted]

From: Conrad, Patricia (NIH/NIAID) [E] <[redacted]>
Sent: Tuesday, February 23, 2021 11:50 AM
To: Folkers, Greg (NIH/NIAID) [E] <[redacted]>; Morens, David (NIH/NIAID) [E] <[redacted]>
Cc: NIAID OD AM <[redacted]>
Subject: RE: Daszak briefing Tony?

David – ASF would like to be briefed.

Please send contact details to Kim and she will schedule.

Kim – pls ask ASF who else he would like to participate in this. thx

From: Folkers, Greg (NIH/NIAID) [E] <[redacted]>
Sent: Monday, February 22, 2021 10:53 AM
To: Morens, David (NIH/NIAID) [E] <[redacted]>
Cc: NIAID OD AM <[redacted]>
Subject: RE: Daszak briefing Tony?

Let us discuss

From: Morens, David (NIH/NIAID) [E] <[redacted]>
Sent: Monday, February 22, 2021 10:29 AM
To: Folkers, Greg (NIH/NIAID) [E] <[redacted]>
Subject: Daszak briefing Tony?

Greg, as you may remember, when Peter Daszak was in China on the WHO team, he offered to brief Tony either then or when he returned. Tomy apparently said when he returned. He is now back, and emailed last night that he is willing to brief Tony in a short Zoom or phone call, whenever convenient.

Could you bring that up at a morning meeting? Ty,

David M. Morens, M.D.
CAPT, United States Public Health Service
Senior Advisor to the Director
Office of the Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Building 31, Room 7A-03
31 Center Drive, MSC 2520
Bethesda, MD 20892-2520
☎ 301 496 2263 (assistant: Whitney Robinson)
301 496 4409
[redacted]

DMM Portrait B 12 29 15 P0923

Message

From: Linde, Emily (NIH/NIAID) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=B2FD661421CD499B8F7FAD6A196F6B02-LINDEE]
Sent: 6/7/2021 5:14:39 PM
To: Auchincloss, Hugh (NIH/NIAID) [E] [redacted] Fenton, Matthew (NIH/NIAID) [E] [redacted]
Subject: RE: How much

Glad it was helpful!

From: Auchincloss, Hugh (NIH/NIAID) [E] [redacted]
Sent: Monday, June 7, 2021 1:13 PM
To: Linde, Emily (NIH/NIAID) [E] [redacted] Fenton, Matthew (NIH/NIAID) [E] <[redacted]>
Subject: RE: How much

Extremely helpful. Very grateful.

From: Linde, Emily (NIH/NIAID) [E] [redacted]
Sent: Monday, June 7, 2021 12:45 PM
To: Auchincloss, Hugh (NIH/NIAID) [E] [redacted] Fenton, Matthew (NIH/NIAID) [E] [redacted]
Subject: RE: How much

Hi Hugh,

There are two sets of numbers and both are correct. The first set of numbers detailed below is what NIAID awarded to EcoHealth for WIV, and the second is what EcoHealth reports they issued in subawards to WIV. They are detailed below in green.

The first the number of funds NIAID awarded to Ecohealth for WIV:

For the first competitive segment:
subcontract/consortium activity with Wuhan Institute of Virology, CHINA – totaling $749,976

-Yr 1	-Yr 2	-Yr 3	-Yr 4	-Yr 5
$123,699	$128,718	$147,335	$147,335	$147,335
)C) $9,896	$10,297	$11,787	$11,787	$11,787
$133,595	$139,015	$159,122	$159,122	$159,122

For the second competitive segment: only the -06 year has been awarded:

$76,301 **($70,649 direct costs +** $5,652 **F&A costs)**

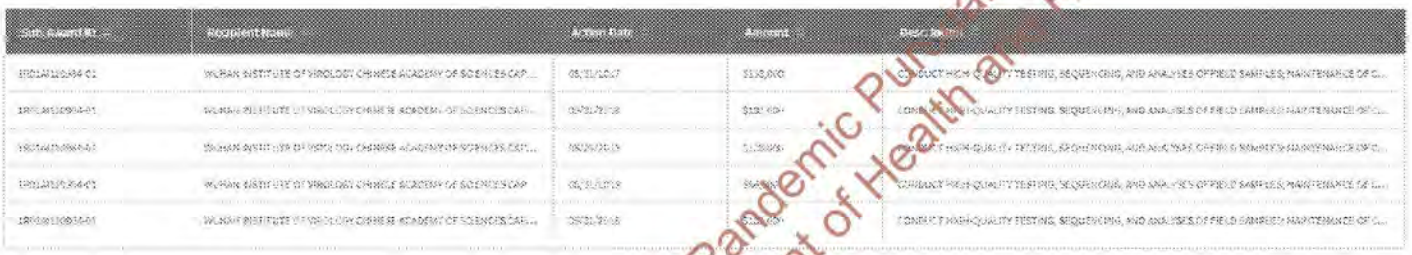
Combined total awarded by NIAID to Ecohealth for WIV for both segments is $826,277

Grantees have authority to rebudget, so they can issue the subawards for more or less money as they deem appropriate without prior approval as long as the rebudgeting does not result in a change of scope or add new foreign sites.

Grantees are required under Federal Funding Accountability and Transparency Act of 2006 (FFATA) to report subawards in excess of $25,000 in the FFATA Subaward Reporting System (FSRS). These numbers are available to the public in USASpending.gov.

The second set of numbers are amounts for the Ecohealth subawards to WIV reported by Ecohealth in USASpending (taken directly from USASpending).

For the first competitive segment subawards are reported as follows:



Sub-Award ID	Recipient Name	Action Date	Amount	Description
[redacted]	WUHAN INSTITUTE OF VIROLOGY CHINESE ACADEMY OF SCIENCES CAP...	05/31/2017	$[redacted]	CONDUCT HIGH QUALITY TESTING, SEQUENCING, AND ANALYSES OF FIELD SAMPLES; MAINTENANCE OF C...
[redacted]	WUHAN INSTITUTE OF VIROLOGY CHINESE ACADEMY OF SCIENCES CAP...	03/31/2018	$[redacted]	CONDUCT HIGH QUALITY TESTING, SEQUENCING, AND ANALYSES OF FIELD SAMPLES; MAINTENANCE OF C...
[redacted]	WUHAN INSTITUTE OF VIROLOGY CHINESE ACADEMY OF SCIENCES CAP...	06/29/2019	$[redacted]	CONDUCT HIGH QUALITY TESTING, SEQUENCING, AND ANALYSES OF FIELD SAMPLES; MAINTENANCE OF C...
[redacted]	WUHAN INSTITUTE OF VIROLOGY CHINESE ACADEMY OF SCIENCES CAP...	05/31/2019	$[redacted]	CONDUCT HIGH QUALITY TESTING, SEQUENCING, AND ANALYSES OF FIELD SAMPLES; MAINTENANCE OF C...
[redacted]	WUHAN INSTITUTE OF VIROLOGY CHINESE ACADEMY OF SCIENCES CAP...	03/31/2018	$[redacted]	CONDUCT HIGH QUALITY TESTING, SEQUENCING, AND ANALYSES OF FIELD SAMPLES; MAINTENANCE OF C...

The total provided to WIV by Ecohealth as reported by Ecohealth for the first competitive segment is $598,500

EcoHealth has not reported any subawards for the second competitive segment. They also stated in letter of 8/13/2020 to Dr. Lauer no that subaward was issued to WIV; therefore, **the combined total provided to WIV by EcoHealth as reported by Ecohealth for both segments is** $598,500

Please let me know if you require any additional information.

Thanks.

From: Auchincloss, Hugh (NIH/NIAID) [E] [redacted]
Sent: Monday, June 7, 2021 12:08 PM
To: Fenton, Matthew (NIH/NIAID) [E] [redacted] Linde, Emily (NIH/NIAID) [E] <[redacted]>
Subject: How much
Importance: High

Very important that we check the number of how much NIH money actually went to WIV. 600? 800? What's the right number.

Hugh Auchincloss, M.D.
Deputy Director, NIAID
National Institutes of Health
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Message

From: Kristian G. Andersen [redacted]
Sent: 2/1/2020 3:32:13 AM
To: Fauci, Anthony (NIH/NIAID) [E] [redacted]
CC: Jeremy Farrar [redacted]
Subject: Re: FW: Science: Mining coronavirus genomes for clues to the outbreak's origins

Hi Tony,

Thanks for sharing. Yes, I saw this earlier today and both Eddie and myself are actually quoted in it. It's a great article, but the problem is that our phylogenetic analyses aren't able to answer whether the sequences are unusual at individual residues, except if they are completely off. On a phylogenetic tree the virus looks totally normal and the close clustering with bats suggest that bats serve as the reservoir. The unusual features of the virus make up a really small part of the genome (<0.1%) so one has to look really closely at all the sequences to see that some of the features (potentially) look engineered.

We have a good team lined up to look very critically at this, so we should know much more at the end of the weekend. I should mention that after discussions earlier today, Eddie, Bob, Mike, and myself all find the genome inconsistent with expectations from evolutionary theory. But we have to look at this much more closely and there are still further analyses to be done, so those opinions could still change.

Best,
Kristian

On Fri, Jan 31, 2020 at 18:47 Fauci, Anthony (NIH/NIAID) [E] [redacted] wrote:

> Jeremy/Kristian:
>
> This just came out today. You may have seen it. If not, it is of interest to the current discussion.
>
> Best,
>
> Tony

From: Folkers, Greg (NIH/NIAID) [E] <[redacted]>
Sent: Friday, January 31, 2020 8:43 PM
Subject: Science: Mining coronavirus genomes for clues to the outbreak's origins

As part of a long-running effort to see what viruses bats harbor, researchers in China collect one from a cave in Guandong.

EcoHealth Alliance

Mining coronavirus genomes for clues to the outbreak's origins

By Jon CohenJan. 31, 2020 , 6:20 PM

attaaaggtt tataccttcc caggtaacaa accaaccaac tttcgatctc ttgtagatct …

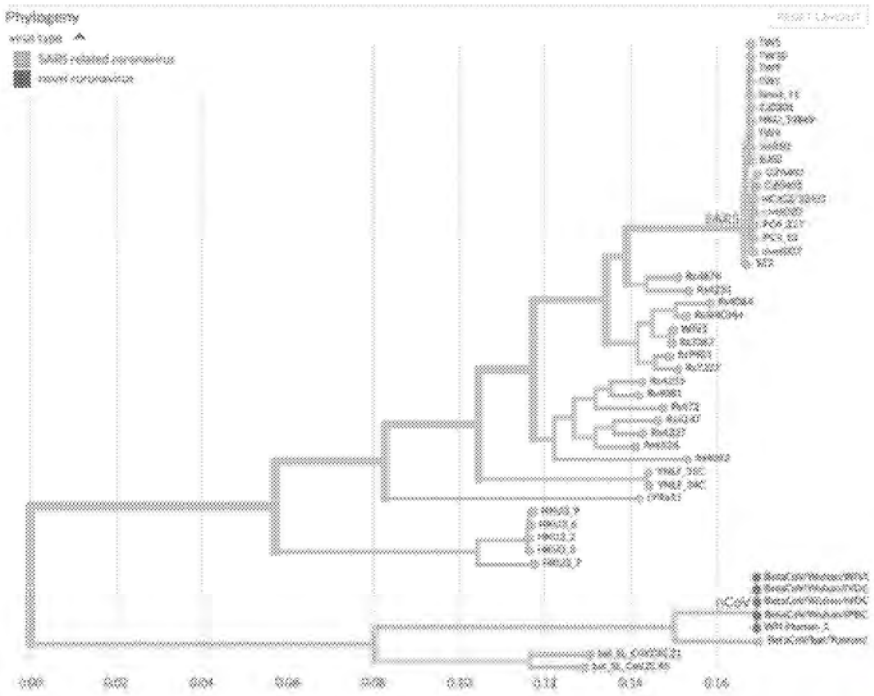
That string of apparent gibberish is anything but: It's a snippet of a DNA sequence from the viral pathogen, dubbed 2019 novel coronavirus (2019-nCoV), that is overwhelming China and frightening the entire world. Scientists are publicly sharing an ever-growing number of full sequences of the virus from patients—83 at last count in the Global Initiative on Sharing All Influenza Data database. These viral genomes are being intensely studied to try to understand the origin of 2019-nCoV and how it fits on the family tree of related viruses found in bats and other species. They have also given glimpses into what this newly discovered virus physically looks like, how it's changing, and how it might be stopped.

"One of the biggest takeaway messages [from the viral sequences] is that there was a single introduction into humans and then human-to-human spread," says Trevor Bedford, a bioinformatics specialist at the University of Washington, Seattle. The role of Huanan Seafood Wholesale Market in Wuhan, China, in spreading 2019-nCoV remains murky, though such sequencing, combined with sampling the market's environment for the presence of the virus, is clarifying that it indeed had an important early role in amplifying the outbreak. The viral sequences, most researchers say, also knock down the idea the pathogen came from a virology institute in Wuhan.

In all, 2019-nCoV has nearly 29,000 nucleotides bases that hold the genetic instruction book to produce the virus. Although it's one of the many viruses whose genes are in the form of RNA, scientists convert the viral genome into DNA, with bases known in shorthand as A, T, C, and G, to make it easier to study. Many analyses of 2019-nCoV's sequences have already appeared on virological.org, nextstrain.org, preprint servers like bioRxiv, and even in peer-reviewed journals. The sharing of the sequences by Chinese researchers allowed public health labs around the world to develop their own diagnostics for the virus, which now has been found in 18 other countries. (*Science*'s news stories on the outbreak can be found here.)

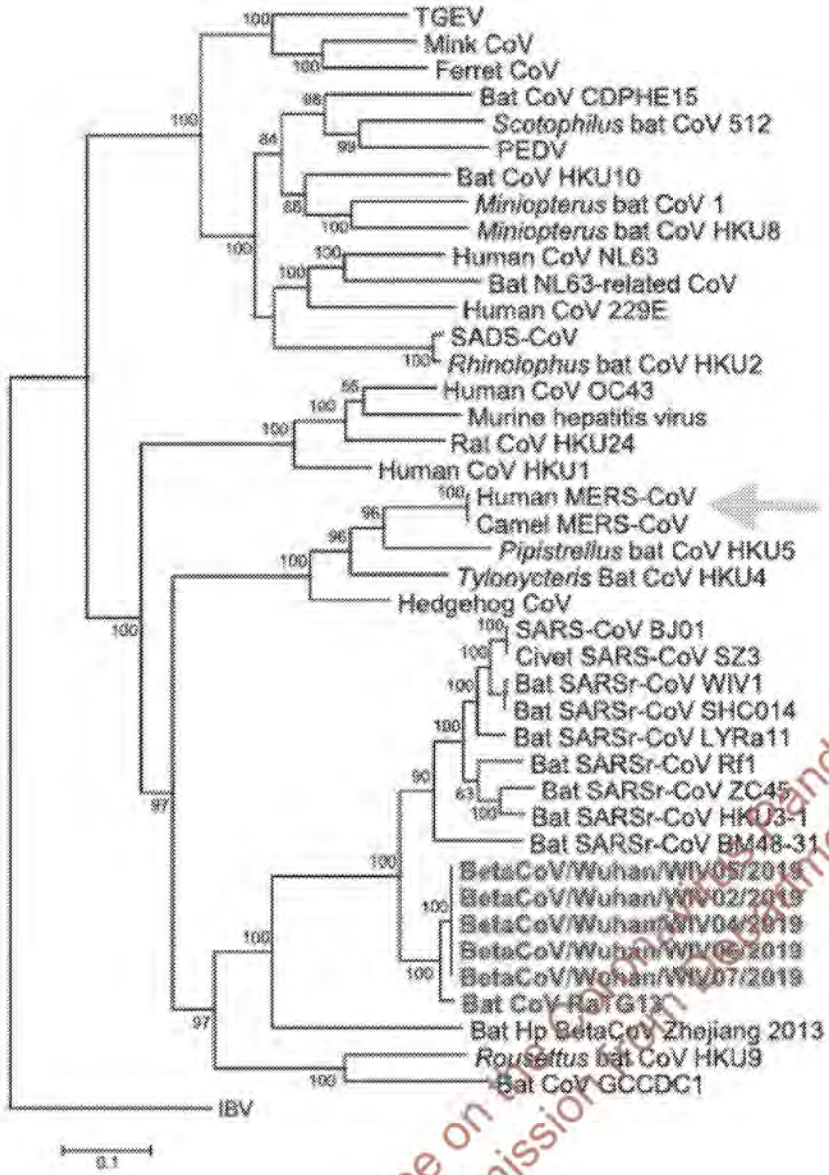
When the first 2019-nCoV sequence became available, researchers placed it on a family tree of known coronaviruses—which are abundant and infect many species—and found that it was most closely related to relatives found in bats. A team led by Shi Zheng-Li, a coronavirus specialist at the Wuhan Institute of Virology, reported on 23 January on bioRxiv that 2019-nCoV's sequence was 96.2% similar to a bat virus and had 79.5% similarity to the coronavirus that causes severe acute respiratory syndrome (SARS), a disease whose initial outbreak was also in China more than 15 years ago. But the SARS coronavirus has a similarly close relationship to bat viruses, and sequence data make a powerful case that it jumped into people from a coronavirus in civets that differed from human SARS viruses by as few as 10 nucleotides. That's one reason why many scientists suspect there's an "intermediary" host species—or several—between bats and 2019-nCoV.

According to Bedford's analysis, the bat coronavirus sequence that Shi Zheng-Li's team highlighted, dubbed RaTG13, differs from 2019-nCoV by nearly 1100 nucleotides. On nextstrain.org, a site he co-founded, Bedford has created coronavirus family trees (example below) that include bat, civet, SARS, and 2019-nCoV sequences. (The trees are interactive—by dragging a computer mouse over them, it's easy to see the differences and similarities between the sequences.)



Bedford's analyses of RaTG13 and 2019-nCoV suggest that the two viruses shared a common ancestor 25 to 65 years ago, an estimate he arrived at by combining the difference in nucleotides between the viruses with the presumed rates of mutation in other coronaviruses. So it likely took decades for RaTG13-like viruses to mutate into 2019-nCoV.

Middle East respiratory syndrome (MERS), another human disease caused by a coronavirus, similarly has a link to bat viruses. But studies have built a compelling case it jumped to humans from camels. And the phylogenetic tree from Shi's bioRxiv paper (below) makes the camel-MERS link easy to see.



The longer a virus circulates in a human populations, the more time it has to develop mutations that differentiate strains in infected people, and given that the 2019-nCoV sequences analyzed to date differ from each other by seven nucleotides at most, this suggests it jumped into humans very recently. But it remains a mystery which animal spread the virus to humans. "There's a very large gray area between viruses detected in bats and the virus now isolated in humans," says Vincent Munster, a virologist at the U.S. National Institute of Allergy and Infectious Diseases who studies coronaviruses in bats, camels, and others species.

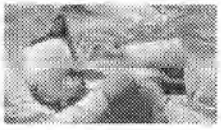
Strong evidence suggests the marketplace played an early role in spreading 2019-nCoV, but whether it was the origin of the outbreak remains uncertain. Many of the initially confirmed 2019-nCoV cases—27 of the first 41 in one report, 26 of 47 in another—were connected to the Wuhan market, but up to 45%, including the earliest handful, were not. This raises the possibility that the initial jump into people happened elsewhere.

According to Xinhua, the state-run news agency, "environmental sampling" of the Wuhan seafood market has found evidence of 2019-nCoV. Of the 585 samples tested, 33 were positive for 2019-nCoV and all were in the huge market's western portion, which is where wildlife were sold. "The positive tests from the wet market are hugely important," says Edward Holmes, an evolutionary biologist at the University of Sydney who

collaborated with the first group to publicly release a 2019-nCoV sequence. "Such a high rate of positive tests would strongly imply that animals in the market played a key role in the emergence of the virus."

Yet there have been no preprints or official scientific reports on the sampling, so it's not clear which, if any, animals tested positive. "Until you consistently isolate the virus out of a single species, it's really, really difficult to try and determine what the natural host is," says Kristian Andersen, an evolutionary biologist at Scripps Research.

One possible explanation for the confusion about where the virus first entered humans is if there was a batch of recently infected animals sold at different marketplaces. Or an infected animal trader could have transmitted the virus to different people at different markets. Or, Bedford suggests, those early cases could have been infected by viruses that didn't easily transmit and sputtered out. "It would be hugely helpful to have just a sequence or two from the marketplace [environmental sampling] that could illuminate how many zoonoses occurred and when they occurred," Bedford says.



A research group sent fecal and other bodily samples from bats they trapped in caves to the Wuhan Institute of Virology to search for coronaviruses.

EcoHealth Alliance

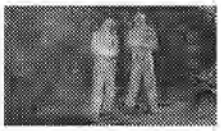
In the absence of clear conclusions about the outbreak's origin, theories thrive, and some have been scientifically shaky. A sequence analysis led by Wei Ji of Peking University and published online by the *Journal of Medical Virology* received substantial press coverage when it suggested that "snake is the most probable wildlife animal reservoir for the 2019-nCoV." Sequence specialists, however, pilloried it.

Conspiracy theories also abound. A CBC News report about the Canadian government deporting Chinese scientists who worked in a Winnipeg lab that studies dangerous pathogens was distorted on social media to suggest that they were spies who had smuggled out coronaviruses. The Wuhan Institute of Virology, which is the premier lab in China that studies bat and human coronaviruses, has also come under fire. "Experts debunk fringe theory linking China's coronavirus to weapons research," read a headline on a story in *The Washington Post* that focused on the facility.

Concerns about the institute predate this outbreak. *Nature* ran a story in 2017 about it building a new biosafety level 4 lab and included molecular biologist Richard Ebright of Rutgers University, Piscataway, expressing concerns about accidental infections, which he noted repeatedly happened with lab workers handling SARS in Beijing. Ebright, who has a long history of raising red flags about studies with dangerous pathogens, also in 2015 criticized an experiment in which modifications were made to a SARS-like virus circulating in Chinese bats to see whether it had the potential to cause disease in humans. Earlier this week, Ebright questioned the accuracy of Bedford's calculation that there are at least 25 years of evolutionary distance between RaTG13—the virus held in the Wuhan virology institute—and 2019-nCoV, arguing that the mutation rate may have been different as it passed through different hosts before humans. Ebright tells *Science*Insider that the 2019-nCoV data are "consistent with entry into the human population as a natural accident."

Shi did not reply to emails from *Science*, but her longtime collaborator, disease ecologist Peter Daszak of the EcoHealth Alliance, dismissed Ebright's conjecture. "Every time there's an emerging disease, a new virus, the same story comes out: This is a spillover or the release of an agent or a bioengineered virus," Daszak says. "It's just a shame. It seems humans can't resist controversy and these myths, yet it's staring us right in the face.

There's this incredible diversity of viruses in wildlife and we've just scratched the surface. Within that diversity, there will be some that can infect people and within that group will be some that cause illness."



A team of researchers from the Wuhan Institute of Virology and the EcoHealth Alliance have trapped bats in caves all over China, like this one in Guangdong, to sample them for coronaviruses.

EcoHealth Alliance

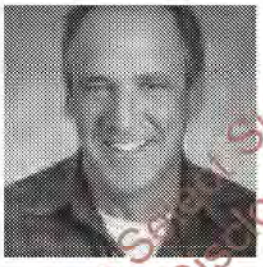
Daszak and Shi's group have for 8 years been trapping bats in caves around China to sample their feces and blood for viruses. He says they have sampled more than 10,000 bats and 2000 other species. They have found some 500 novel coronaviruses, about 50 of which fall relatively close to the SARS virus on the family tree, including RaTG13—it was fished out of a bat fecal sample they collected in 2013 from a cave in Moglang in Yunnan province. "We cannot assume that just because this virus from Yunnan has high sequence identity with the new one that that's the origin," Daszak says, noting that only a tiny fraction of coronaviruses that infect bats have been discovered. "I expect that once we've sampled and sampled and sampled across southern China and central China that we're going to find many other viruses and some of them will be closer [to 2019-nCoV]."

It's not just a "curious interest" to figure out what sparked the current outbreak, Daszak says. "If we don't find the origin, it could still be a raging infection at a farm somewhere, and once this outbreak dies, there could be a continued spillover that's really hard to stop. But the jury is still out on what the real origins of this are."

Posted in:

- Asia/Pacific
- Health
- Coronavirus

doi:10.1126/science.abb1256



Jon Cohen

Jon is a staff writer for *Science*.

- Email Jon
- Twitter

Message

From: Fauci, Anthony (NIH/NIAID) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=DF38103D75134F658AE2D356F0396B94-AFAUCI]
Sent: 2/6/2020 2:55:19 AM
To: Kerr, Lawrence (HHS/OS/OGA) [redacted]
CC: Grigsby, Garrett (HHS/OS/OGA) [redacted]
Subject: RE: Spoke with Soumya re: evolutionary origin of nCoV

I do not see any problem with your doing this. Go for it.
Best,
Tony

From: Kerr, Lawrence (HHS/OS/OGA) <[redacted]>
Sent: Wednesday, February 5, 2020 7:18 PM
To: Fauci, Anthony (NIH/NIAID) [E] <[redacted]>
Cc: Grigsby, Garrett (HHS/OS/OGA) <[redacted]>
Subject: Spoke with Soumya re: evolutionary origin of nCoV

Dr. Fauci,

Soumya called today to share that they plan to raise the evolutionary origin of 2019-nCoV during the "Animal and environmental research to understand role of animals and inform outbreak control" section of the WHO "*2019 novel Coronavirus: Global research and innovation forum: towards a research roadmap*" 11-12 Feb 2020 in GVA.

If I heard her correctly she said that Jeremy Farrar is drafting a paper to frame the discussion in that session. She said that the goal of the discussion is to surface consensus opinions on what is known and what gaps in research or knowledge exist in order for WHO to put forth a research agenda to address the gaps.

She asked if I could help her organize a call the week after the conference, among major research donors that could fund researchers to address those gaps identified in the conference. Specifically she named NIH, BMGF, Wellcome, Chinese Academy of Sciences, and welcomed suggestions for others. She hopes to identify funds that can rapidly be accessed by the research community to address these gaps.

Beyond sharing this conversation with you, may I ask if you see any negatives to us (specifically a member of my team) assisting her to set up this donor call? I am sensitive to agencies not having WHO prioritizes forced on them, and I don't want that to happen. Assisting WHO may also give us insights as the discussions develop.

I welcome your advice please. Much thanks,

Larry

Message

From: Collins, Francis (NIH/OD) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=410E1CA313F44CED9938E50D2FF0B6C2-COLLINSF]
Sent: 5/31/2020 7:37:54 PM
To: Tabak, Lawrence (NIH/OD) [E] [redacted]; Wolinetz, Carrie (NIH/OD) [E] [redacted]; Burklow, John (NIH/OD) [E] [redacted]; Myles, Renate (NIH/OD) [E] [redacted]
Subject: CONFIDENTIAL document
Attachments: Yunnan Mineshaft SARS.docx

Hi all,

I just received from Eric Lander a confidential copy of the attached draft article. I've shared with Tony. Apparently this will be submitted somewhere in the next week or so.

The main author is apparently Rowan Jacobsen, who is currently a Knight Journalism Fellow at MIT. Here's a recent article from him: https://www.motherjones.com/politics/2020/05/the-non-paranoid-persons-guide-to-viruses-escaping-from-labs/

The information in the attachment is pretty intriguing, but there's a lot here that could be explosive.

Francis

Does a Yunnan Mineshaft Hold a Key to SARS-CoV-2's Origins?

In April 2012, six miners who were clearing bat guano from a mineshaft in Mojiang, Yunnan Province came down with a mysterious illness whose symptoms sound all too familiar: Fever, cough, shortness of breath, pneumonia, severe respiratory distress, ground-glass opacity in the lungs, frothy sputum, blood clots, dangerously low blood-oxygen saturation. The miners reported that the mineshaft was full of bats and noxious from the piles of guano.

The progress of the disease in the miners also fits with what we have seen from Covid-19. The two miners who were in their early 30s recovered fairly easily. The other four, three of whom were in their 40s and one who was 63, all went into critical care in the hospital at Kunming Medical University. The 63-year-old, who had pre-existing conditions, died twelve days after entering the hospital. Two of the other miners died after grueling stays in the hospital of 48 and 109 days, respectively. The only patient to recover and leave critical care (after 107 days) improved after being treated with Heparin and Warfarin, two anticoagulant medications that also have shown promise for treating severe cases of Covid-19.

But in some other ways the disease was not exactly like Covid-19. For example, it doesn't seem to have been nearly as infectious. The miners all spent many days in the mineshaft shoveling bat guano; they would have all inhaled a monstrous dose of any pathogens lurking within. But as far as we can tell, the miners didn't infect any of their family members. This matches the pattern of a zoonotic pathogen that had not yet adapted itself for effective human-to-human transmission.

The Kunming doctors were concerned enough by this mystery disease to consult with Zhong Nanshan, a towering figure known as "China's Anthony Fauci" who managed China's response to the first SARS outbreak and has been front-and-center on SARS-CoV-2. Zhong was clear in his recommendations: Test the patients for SARS, and examine the bats in that mineshaft.

Shi Zhengli's team at the Wuhan Institute of Virology (WIV) was called in. Ever since the first SARS appeared in 2002–03, Shi and her colleagues had been searching the caves of southern China for bat-borne coronaviruses with the potential to infect human beings. They were part of an international program run by EcoHealth Alliance, a U.S. organization that funded efforts around the world to sample nature for pathogens with pandemic potential. EcoHealth Alliance's grant application to the NIH, a primary funder of the work, was for "genomic characterization and isolation of novel CoVs" in order to develop predictive models for emergence and treatment.

The WIV team tested the miners' blood and detected antibodies indicating the presence of a virus. Unfortunately, we don't know which virus, because this information has not been published. In fact, virtually no information about the deaths of these miners has ever been released. Until recently, the only available reference was a 2014 [HYPERLINK "https://wwwnc.cdc.gov/eid/article/20/6/13-1022_article"] and an accompanying article in Science titled [HYPERLINK "https://www.sciencemag.org/news/2014/03/new-killer-virus-china"] that chronicled a different group of researchers from the Institute of Pathogen Biology, Beijing, who visited the cave in December 2012 but didn't find any likely culprits. That piece provided few details about the miners' illnesses or treatment.

The only reason we know the details of the tragic story of these 6 miners is because an obscure 60-page master's thesis by a student at Kunming Medical University was recently discovered online on the China National Knowledge Infrastructure, a database of academic publications and theses. The thesis describes in excruciating detail the conditions and step-by-step treatment of the miners, and it leaves no doubt about its conclusion: "Based on the above cases and related literature, the analysis of these six cases of severe pneumonia caused by an unknown virus may be considered as follows: Caused by SARS-like-CoV from the Chinese horseshoe bat or other bats." (Because the thesis sheds light on treatments for SARS-like illnesses, we have sent a translation of it to the NIH and NIAID. A copy can be read **here** [TK].)

We do know that Shi Zhengli's team visited the mineshaft and sampled the bats, because they published a paper about it a few years later in 2016. Beginning in August of 2012, when some of the miners were still fighting for their lives, and continuing over the next year, Shi's group made four trips to the mineshaft and took fecal swabs from 276 bats. Then they did a kind of shortcut genetic sequencing of the samples (to save time and money) that only sequenced a short section of a gene called RdRp that is particularly useful for comparing with other known coronaviruses and determining where the new ones fit in the family tree. They identified several known coronaviruses in the bats, as well as a few new ones. All of the known viruses and all but one of the new ones were from lineages not thought to cause any trouble in people. But the RdRp sequence of one new virus, which they named RaBtCov/4991, placed it within the deadly SARS lineage, though it wasn't quite like anything they had seen before.

This should have been a big deal: A unique SARS-related coronavirus, found in a cave where three miners had just died with SARS-like symptoms after shoveling bat guano for days. And now it looked like they might have caught a killer in the act.

But here's where things get weird. When the WIV team published its paper about the mineshaft in 2016, they published in an obscure journal and they barely mentioned virus RaBtCov/4991 – choosing instead to focus the paper on the coexistence of CoVs in bats. RaBtCov/4991 wasn't even one of the handful of viruses they chose for more extensive sequencing, which were all chosen to examine co-infection of bats by multiple CoVs.

Strangest of all, the paper neglected to mention the miners. There was no explanation of why that site was chosen for sampling. It was just "an abandoned mineshaft." The only clue in Shi's paper was that this was the same Mojiang, Yunnan mineshaft that the Beijing team had investigated. No one reading the paper would have had any clue that people had died from Sars-like symptoms brought on by a mysterious pathogen from the mineshaft, or that RaBtCov/4991 would have been a prime suspect as a Sars-like CoV isolated from bats in this particular mineshaft. As far as the world knew, RaBtCov/4991 was just a random Sars-like CoV sample sitting in a freezer at the WIV, with a snippet of code on GenBank, the online database where researchers upload the genetic sequences mentioned in their papers.

In the years that followed, Shi Zhengli and the WIV continued to visit caves and collect samples and publish important papers that described the isolation, culture, reverse genetics, and testing of infectivity of SARS-like viruses across different host cell lines. They collected dozens of SARS-like coronaviruses, including some with the ability to infect human cells in the lab, as they proved through experimentation. They kept warning the world that bat-borne coronaviruses could be the source of the next pandemic. But they never mentioned the miners who died in 2012 or virus 4991 from the cave where they had mysteriously fallen ill.

Then, in 2020, SARS-CoV-2 exploded across Wuhan, and then the world. As soon as its genome was sequenced, other scientists compared it to everything in the GenBank database,

looking for close matches, to try to figure out what it was and where it had come from. Bingo! A piece of a gene on GenBank was 98.5% identical. It was a virus called RaBtCov/4991.

Almost simultaneously, Shi Zhengli published her own paper. The bulk of the paper focused on characterizing the novel coronavirus (2019-nCoV, as she called it) but halfway through it mentioned a match to a previously discovered sample: "We then found that a short region of RNA-dependent RNA polymerase (RdRp) from a bat coronavirus (BatCoV RaTG13)—which was previously detected in *Rhinolophus affinis* from Yunnan province—showed high sequence identity to 2019-nCoV."

According to the paper, they then sequenced the entire genome of RaTG13, which was 96.2% identical to the new virus, making it the only close relative known to exist. Surely, this was a time to tell the research community about the dead miners. Yet, not only are the miners not mentioned in the paper, there's also no mention that RaTG13 is the same virus as RaBtCov/4991, no mention that it had been in the WIV since 2013, no mention where exactly it had been found, or what experiments had been performed in the past seven years to characterize this intriguing Sars-like virus. Shi didn't even cite her own 2016 paper on the mineshaft. This is all unusual, by the protocols of science and the mandate of the EcoHealth Alliance. For whatever reason, Shi neglected to reveal the important link between RaTG13 and the mineshaft from whence it had come. RaTG13 was also disconnected from its original name RaBtCov/4991 – making the trail to the source of this virus more circuitous.

As the only close relative to Sars-CoV-2, RaTG13 immediately became essential to studying it. It also helped to "naturalize" Sars-CoV-2 by proving that coronaviruses similar to Sars-CoV-2 existed in nature and could potentially cross into humans. But others eventually made the connections to the mineshaft and started asking questions online.

Not long after that, Shi did her first and only interview with the Western press, in the *Scientific American.* By then, she was the subject of many rumors in China and in the West. In the article, Shi establishes that Sars-CoV-2 was never in her lab, and she finally mentioned the miners, but not in connection with RaTG13. The miner story was an anecdote of her team's bat sampling expeditions: "'The mine shaft stunk like hell,' says Shi, who, like her colleagues, went in wearing a protective mask and clothing. 'Bat guano, covered in fungus, littered the cave.' Although the fungus turned out to be the pathogen that had sickened the miners, she says it would have been only a matter of time before they caught the coronaviruses if the mine had not been promptly shut."

This is the first and only mention of a fungus as the killer pathogen, and it's unclear where this information came from. There's no mention of it in the 2014 *Science* article, which was clearly under the impression that a virus was responsible. The only mention of fungi in the master's thesis is as possible secondary infections in the miners' lungs, which is a common symptom in Covid-19 and other diseases that debilitate immune function. It seems out of place in the middle of the *Scientific American* article, and even stranger because RaTG13 comes up a few paragraphs later and isn't connected to Shi's mineshaft story.

Around the same time that Shi was telling her story to *Scientific American*, Peter Daszak—the president and founder of EcoHealth Alliance, who worked closely with Shi Zhengli and was a coauthor on many of her papers—was defending the discovery of RaTG13 in *Wired*: "At the time, we were looking for Sars-related viruses, and this one was 20 per cent different. We thought it's interesting, but not high-risk. So we didn't do anything about it and put it in the freezer."

Daszak's rationale for not investigating a novel Sars-like virus because it is too different is puzzling to say the least. Given that RaTG13 was the only Sars-like virus found in a cave where miners had died from Sars-like indications, it seems strange that a competent scientist would have neglected to sequence the virus. Instead, the team picked eight other viruses, not from the Sars family, for more extensive partial sequencing, all of which were in the low-risk category.

In fact, closer consideration of Daszak's statement reveals that something is amiss. The original SARS-CoV and RaTG13 are 20% different (18%, actually) only if you compare their *entire genomes*. But according to Daszak and Shi, they didn't fully sequence RaTG13 until 2020. If you compare the RdRp genes of SARS and RaTG13 (aka RaBtCov/4991), which supposedly was all they sequenced in 2013, they are less than 12% different at the nucleotide level and less than 6% different at the amino acid level—close enough to have begged further scrutiny. The only plausible scenario that would have justified sticking RaTG13 in a freezer and forgetting about it is if another virus was found in that mineshaft that was even more likely to have killed the miners, but we have no reports of such a virus being found.

Even if we take Daszak at his word, it doesn't speak well of EcoHealth Alliance's decade-long project to identify viruses before they spill over from the wild—to "find them before they find us," as Shi Zhengli put it in the *Scientific American* article. At best, they found the kissing cousin of the future pathogen they'd always been warning us about, with compelling reasons to believe that it could be a killer, and chose not to follow up. This was their opportunity to preempt a pandemic, and they blew it. Even before Covid-19, [HYPERLINK "https://www.nature.com/articles/d41586-018-05373-w?utm_source=twt_nnc&utm_medium=social&utm_campaign=naturenews&sf191350257=1"] had questioned the validity of this approach. We should be even more skeptical now.

In recent days, more than 110 nations have called for [HYPERLINK "https://www.businessinsider.com/120-nations-support-un-investigating-coronavirus-origin-china-angry-2020-5"] into the origins of Covid-19. We support such an inquiry, and we believe that it should include a closer look into the origins of RaTG13 as well. While it would be wrong to draw any conclusions from the small amount of evidence currently available, it seems clear that learning more about this earlier cluster of SARS-like illnesses could yield essential information for understanding Covid-19. It might even save lives. To that end, we hope that the Wuhan Institute of Virology will furnish original samples of RaTG13 to other researchers, and we hope that the eventual investigation will include a return visit to the abandoned mineshaft in Yunnan, which seems likely to hold valuable clues.

Message

From: Peter Daszak [redacted]
Sent: 1/27/2020 10:48:48 PM
To: Morens, David (NIH/NIAID) [E] [redacted]
CC: Stemmy, Erik (NIH/NIAID) [E] [redacted]; Alison Andre[redacted]]
Subject: More on Wuhan novel coronavirus - NIAID's role in bat-origin CoVs
Attachments: Wuhan with connections 21st-28th Jan.jpg

Importance: High

Great to hear back, and of course this is all confidential. Erik – hope you don't mind this communication, and please share with your Head of Dept if you like
Re. the likely final size of this outbreak – here are the key metrics I'm looking at:

1. Mortality rate – Currently around 2-3%, which is not bad compared with the 7+% of SARS
2. Secondary outbreaks: So far, no evidence that international travelers have seeded de novo transmission within destination countries. In the richer countries, USA, Canada, Europe, Japan, Australia, I expect that Port Authority surveillance will catch most with symptoms and follow up will mop up secondary cases for the few that get through. My concern is for SE Asian and African countries that our Flight Risk Tracker predicted arrivals earlier in the outbreak (see figure attached) – https://flirt.eha.io (funded by DHS and DoD DTRA).
3. Transparency from China: Good rapid response, open sharing of information (albeit that this was once they'd all got their initial high-impact papers accepted). They're working with WHO, and WHO is holding regular meetings on sharing samples/reagents/viruses (organized via WHO R&D Blueprint group that I'm part of), as well as PHEIC meetings.
4. Travel ban: This is a significant difference to SARS, and although the virus had already traveled, the lockdown of Wuhan and many other places/sites during the New Year festivities is a remarkable move that has to have had a big impact on reducing spread.

So, for those reasons I'm cautiously optimistic that this will end up with a max of around 15-20,000 total cases identified (most mild), only a couple of examples of secondary transmission, and a lower mortality rate once all the cases are accounted for (1-2%). There'll still be a temporary shock to the global economy, and this is already similar to SARS (10% hit on airline stocks etc), but that's prob due to massive increase in travel from China to most other destinations since SARS, and to increase in social media and hype. Should settle down once we're over the peak of the epidemic curve.
Cheers,
Peter

Peter Daszak
President
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From: Morens, David (NIH/NIAID) [E] [redacted]
Sent: Monday, January 27, 2020 4:54 PM
To: Peter Daszak
Cc: Stemmy, Erik (NIH/NIAID) [E]; Alison Andre
Subject: RE: Wuhan novel coronavirus - NIAID's role in bat-origin CoVs

Great info, thanks. Tony doesn't maintain awareness of these things and doesn't know unless program officers tell him, which they rarely do, since they are across town and may not see him more than once a year, or less....

In reflecting on this, and in part from your work, many people have been saying since the beginning of MERS that these coronaviruses are just going to keep on emerging, and for reasons your whole group have been highlighting for years, the human animal interface, etc.....
Assuming this current thing turns out well, this has to be a serious wake up call that we have to do much more
I WILL pass this on to Tony. He is overwhelmed with press calls and pressure from the Dept of HHS. I have never seen him so frazzled. Saturday night he sent me a one line email. "I am brain dead". (Not for attribution or repeating!).
Interested in your feeling about where this is going. The experts buzzing around us are all over the map, between doomsday and not that big a deal, with everything in between.

David

David M. Morens, M.D.
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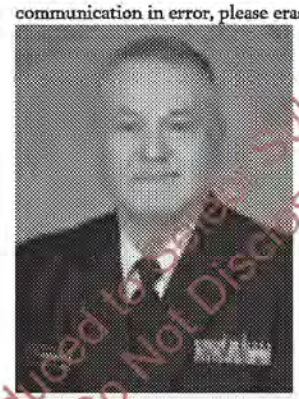
☎ 301 496 2263 (assistants: Kimberly Barasch; Whitney Robinson)
301 496 4409
[redacted]



From: Peter Daszak <[redacted]>
Sent: Monday, January 27, 2020 1:36 PM
To: Morens, David (NIH/NIAID) [E] <[redacted]>
Cc: Stemmy, Erik (NIH/NIAID) [E] <[redacted]>; Alison Andre <[redacted]>
Subject: Wuhan novel coronavirus - NIAID's role in bat-origin CoVs
Importance: High

Hi David – Happy to have a phone call re. the Wuhan CoV, but just wanted to mentioned a few things for your information and hopefully to pass on to Tony Fauci for when he's being interviewed re. the new CoV:
NIAID has been funding coronavirus work in China for the past 5 years through an R01 to me (1R01AI110964: "Understanding the Risk of Bat Coronavirus Emergence"). That's now been renewed, with a specific focus that we identify cohorts of people highly exposed to bats in China, and work out if they're getting sick from CoVs. Erik Stemmy is the Program Officer (cc'd here). Collaborators include Wuhan Institute of Virology (currently working on the nCoV), and Ralph Baric. The results of our work to date include:

- Sampled 10,074 bats and ~2,000 other mammals at 47 sites across S. China
- Discovered 172 novel β-CoVs (52 novel SARSr-CoVs), >350 novel α-CoVs
- Discovered closest relative to Wuhan nCoV (92% homology)
- Discovered Swine Acute Diarrheal Syndrome Virus (SADS-CoV) killing >25,000 pigs in Guangdong Province (Published in Nature)
- Found SARS-related CoVs that can bind to human cells (Published in Nature), and that cause SARS-like disease in humanized mouse models.
- Found that clinical signs of bat SARSr-CoVs in mice were not prevented with a vaccine candidate against SARS-CoV, and were not treatable with most monoclonal therapies being developed.
- Found serological evidence that 3% of people living at the wildlife-human interface in rural China are being exposed to these bat SARS-related coronaviruses

Also – FYI, prior to the R01, we worked under an R01 with Eun-Chung Park as Program Officer on viral discovery in bats, where originally identified SARS-CoV as having a likely origin in bats (published in Science)
As I mentioned, I'm now part of a group that's meeting by phone weekly with CEIRS to discuss the nCoV and Erik's part of that.
Cheers,
Peter

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From: Morens, David (NIH/NIAID) [E] [redacted]
Sent: Thursday, January 9, 2020 1:36 PM
To: Peter Daszak; Ian Lipkin [redacted]; Jon Epstein
Subject: RE: Wuhan virus

Thanks, the excitement never ends, right?

David M. Morens, M.D.
CAPT, United States Public Health Service
Senior Advisor to the Director
Office of the Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health

Building 31, Room 7A-03
31 Center Drive, MSC 2520
Bethesda, MD 20892-2520

☎ 301 496 2263 (assistants: Kimberly Barasch; Whitney Robinson)
301 496 4409
[redacted]

From: Peter Daszak [redacted]
Sent: Thursday, January 9, 2020 12:57 PM
To: Morens, David (NIH/NIAID) [E] [redacted]; Ian Lipkin [redacted]; Jon Epstein [redacted]
Subject: RE: Wuhan virus
Importance: High

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I've been talking with reporters today and happy to fill you in on any further information...
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From: Morens, David (NIH/NIAID) [E] [redacted]
Sent: Thursday, January 9, 2020 12:50 PM
To: W. Ian Lipkin [redacted]; Peter Daszak; Jon Epstein
Subject: Wuhan virus

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☎ 301 496 2263 (assistants: Kimberly Barasch; Whitney Robinson)
301 496 4409
[redacted]

Message

From: Peter Daszak [redacted]
Sent: 1/27/2020 6:36:16 PM
To: Morens, David (NIH/NIAID) [E] [redacted]
CC: Stemmy, Erik (NIH/NIAID) [E] [redacted] Alison Andre [redacted]
Subject: Wuhan novel coronavirus - NIAID's role in bat-origin CoVs

Importance: High

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To: Morens, David (NIH/NIAID) [E] [redacted] Ian Lipkin [redacted]
[redacted] Jon Epstein [redacted]
Subject: RE: Wuhan virus
Importance: High

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Subject: Wuhan virus

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☎ 301 496 2263 (assistants: Kimberly Barasch; Whitney Robinson)
301 496 4409
[redacted]

Message

From: Handley, Gray (NIH/NIAID) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=1CEB55D4B673477391C9DA8A3EB3C75C-HANDLEYGR]
Sent: 3/31/2021 1:11:58 PM
To: Embry, Alan (NIH/NIAID) [E] [redacted] Auchincloss, Hugh (NIH/NIAID) [E] [redacted]
CC: [redacted] [redacted]; Breen, Joseph (NIH/NIAID) [E] [redacted]; Dominique, Joyelle (NIH/NIAID) [E] [redacted]; Bernabe, Gayle (NIH/NIAID) [E] [redacted]
Subject: FW: Geneva: Joint WHO-China SARS-CoV-2 Origins Report Released; WHO Urges Subsequent Studies
Attachments: 20210328- COVID 19 Origins Full report.pdf

Alan: The NIAID COVID community may be interested in this formal notification of the origins report from WHO. Interesting politics and diplomacy underway around this and the cable from US Mission Geneva well captures all that.

Hugh: Tony may need to know the essence of this because he is very likely to be asked his opinion. This cable includes the stated USG position and includes support for that position from many key countries.

Gray

UNCLASSIFIED
SBU

Action Office: ESA, EXEC, RMA, PSA, AID, FAS
Info Office: PAS, LA

MRN: 21 GENEVA 324
Date/DTG: Mar 30, 2021 / 302100Z MAR 21
From: USMISSION GENEVA
Action: WASHDC, SECSTATE *ROUTINE*
E.O.: 13526
TAGS: ECON, SHLH, PREL, KNCV, WHO, UN, FDA, HHS, CDC, NIH, CN
Captions: SENSITIVE
Subject: Geneva: Joint WHO-China SARS-CoV-2 Origins Report Released; WHO Urges Subsequent Studies

1. (SBU) Key Points:

- WHO released to Member Sates an embargoed copy of the joint WHO-China report (attached) on the origins of SARS-CoV-2 on March 28 followed by a Member State Briefing on March 30. The report and annexes are found here.

- WHO Director-General Tedros Adhanom Ghebreyesus (DG Tedros) characterized the report at the March 30 briefing as a first step that raises more questions, urged additional investigations, called for greater access to biological samples, and criticized the report's assessment of the laboratory leak hypothesis as "not extensive enough."

- WHO international team lead, Dr. Peter Ben Embarek, pointed to evidence of symptomatic COVID-19 cases in Wuhan starting on December 8 and additional serology and epidemiology studies could offer insight into possible earlier community transmission. Embarek also noted frozen animal products entering the Wuhan market from surrounding provinces could have led to SARS-CoV-2 spread, but more research was needed. Embarek was unable to provide a timeline on any subsequent Phase 2 studies.

- Chinese team lead, Professor Liang Wannian, noted the group's science-based approach, stating the report is the Chinese contribution to the global origins search and subsequent investigations should not focus only on China given the possibility the origin could be in other regions/countries.

- The Chinese PR lauded the group's "transparent and science-based approach" and expressed hope the report would lead to similar research in other regions. China rejected claims it had not shared data with experts. Responding to the EU and US statements, China expressed concern some countries planned to issue joint statements, stating such preemptive efforts to politicize the report would impede future investigations.

- On March 29, experts from like-minded countries informally shared initial impressions of the report noting inconsistencies in the data, conclusions in the report not backed by evidence, and the information in the report was already well-known in published data so it offered little new information or insights. Experts also found the report's inclusion of the cold-chain theory and dismissal of the lab-leak theory lacked a basis in evidence.

DG Tedros: "As far as WHO is concerned, all hypotheses are still on the table."

2. (SBU) DG Tedros opened the March 30 session thanking the team for its work and reiterating the importance of the Mission. Following interventions from the international and Chinese team leads, DG Tedros then noted the report raises more questions that must be addressed through further studies. He noted the report indicates there was likely unrecognized transmission of SARS-CoV-2 in December 2019 and possibly earlier. He also noted the report offered no answers regarding how SARS-CoV-2 entered the Wuhan Seafood Market. He called on the team to have full access to biological samples from at least September 2019 to trace evidence of earlier outbreaks in Wuhan. He noted the team's frustration at the lack of access to raw data, stating "I expect better cooperation on access to data for future investigations." On the laboratory hypothesis, DG Tedros said the report's assessment of the laboratory was "not extensive enough" and needed further research including assessment by additional specialists which WHO is "ready to deploy." DG Tedros stated, "as far as WHO is concerned, all hypotheses remain on the table."

WHO and Chinese Scientific Leads Summarize Report Findings

3. (SBU) WHO's Dr. Peter Ben Embarek summarized the report's recommendations focusing on the need for additional studies in Wuhan and neighboring provinces. He highlighted the team's epidemiological surveys into influenza like illnesses (ILI), acute respiratory illness (ARI), pneumonia, and other disease data showed no uptick to suggest an outbreak earlier than December 2019. Nevertheless, the genetic sequences for early cases in Wuhan demonstrate genetic differences suggesting SARS-CoV-2 was circulating in clusters or chains of transmission outside of the Wuhan market, possibly earlier than December 2019 and possibly in regions other than Wuhan. He noted further serosurveys from blood banks with samples from Sep 2019-Dec 2019 could help trace early COVID-19 cases around Wuhan. On a possible animal source, Embarek noted China had tested tens of thousands of samples from dozens of animal species around Wuhan- all negative. He also explained the possibility the virus could have been imported into the Wuhan market, which served as a transmission hub but not necessarily the source of the virus, via cold-chain frozen products from surrounding provinces. He stated some of the Wuhan Seafood Market source farms overlap with bat populations which could be the reservoir host for the virus, but more research was needed including sampling/interviews with farms and farmers. On the cold-chain theory in particular, he stated more research was also needed on how the SARS-CoV-2 virus could be transported and transmitted to humans. The experts presented many recommendations for additional research, including serosurveys, genetic studies, additional review of notified cases, and studies of bats and farmed wildlife.

4. (SBU) China's Professor Liang Wannian expressed pride for the final report, and the team's transparent, science and evidence-based approach. He noted the report is the Chinese contribution to the global origins search and subsequent investigations shouldn't focus only on China given the possibility the origin could be in other regions/countries. Responding later to criticisms about the lack of data sharing, Wannian stated Chinese researchers shared all the data they had access to, but ongoing research was needed to identify additional data.

China Defends Its Cooperation; EU, US, Canada, and UK Raise Concerns

5. (SBU) Chinese PR Ambassador Chen Xu summarized China's collaboration with the international team on the joint mission per the Terms of Reference agreed in July 2020. He characterized China's efforts as "sparing no effort" to fight against the pandemic for all mankind with "a philosophy of a community of health for all." Xu stated the experts had all relevant data and materials, visited all relevant institutions, and held extensive exchanges with many people in Wuhan. The team worked to build a "science-based consensus" and, he continued, the international experts spoke publicly and positively about China's efforts to fully share information and data during the study. Xu noted WHO had also praised China's efforts to fully share information and data. Xu expressed hope the report would encourage similar research in other countries to identify the source of the pandemic. Xu said China would continue cooperating with WHO in a transparent and open manner.

6. (SBU) The European Union delivered its joint statement, later published on its website, which regrets the late start, delayed deployment of experts, and limited availability of data. The EU noted the joint report is an important first step, with subsequent studies needed including timely access to all relevant locations as well as human, animal, and environmental data. The EU requested WHO present a clear timeline for follow-up work. The United States delivered a statement noting the team's lack of independence resulted in an

incomplete picture, and urged momentum for expert-driven Phase 2 studies. The UK expressed similar concerns and asked how its experts could feed back questions and comments to the international team, while requesting a timeline for Phase 2 studies. Canada expressed initial concerns the conclusions in the report did not align with the data presented and asked how Phase 2 studies would be prioritized. Vanuatu also took the floor to urge progress on the investigations but to ensure resources going to the investigation would not detract from delivering COVID-19 vaccines to small countries.

7. (SBU) Following questions, Embarek noted there is no timeline for Phase 2 studies yet but the team would work to develop those studies as quickly as possible. He explained some studies could happen quickly and outside of China, while others would take more complex planning and resources to develop, such as to test additional farm and animal samples. He noted one priority next phase study would be on farms near bat population in provinces supplying Wuhan markets. He described the report as "clearly just a first step" and agreed with the "clear appetite from all" to move as quickly as possible.

8. (SBU) At the end of the session, China's Chen Xu spoke again responding to criticisms about the lack of transparency and limited access to data. Xu stating China shared all relevant raw data with the experts, but due to Chinese privacy laws some data could not be copied or brought out of China. On the lab hypothesis, Xu stated the scientists held extensive interviews with lab officials and the report offers a very conclusive finding that the "lab-leak" theory is extremely unlikely. Xu also expressed surprise countries would issue joint statements stating such preemptive politicization of the report would be harmful to ongoing work.

March 29: Like-Minded Experts Describe Concerns about the Report; DG Tedros Private Reservations

9. (SBU) On March 29, experts from Canada, Japan, Korea, UK, Australia, Germany, the Netherlands, and US officials from HHS, FDA, CDC, NIH, and State informally shared initial impressions of the report. Experts expressed questions about the lack of any evidentiary standard used to evaluate the four hypotheses, noting the lack of evidence in the report to support the cold-chain transmission theory. Experts raised concerns the graphs showing ILI and ARI data from 2016 onwards as flat lines seemed suspicious, with the 2017-2018 seasonal flu epidemic around the world, including China, not captured in the data in the report. Another expert noted the lack of any explanation of why the report characterizes the laboratory incident hypothesis as unlikely. Another expert noted the conclusions in the report did not relate to the data presented in the report, suggesting there was not a scientific process to reach the report's conclusions. There were also doubts about the evidence for a cold-chain transmission leading to human infection. Others noted the clear data limitations, expressing concern nearly all the data presented in the report was already publicly available in other publications. On the positive side, experts agreed the report provided some additional leads to pursue and all expressed support for additional investigations to continue expediently.

10. (SBU) Contacts at WHO indicate DG Tedros had hoped the report would include both perspectives from the Chinese and international teams where they disagreed. DG Tedros reportedly argued such an approach would demonstrate more independence and possibly create more credibility for the report. Contacts indicate there were differences between the two teams, but the scientists opted for a consensus report around which they all could be united. WHO leadership is also reportedly concerned strong negative reactions to the report could hinder further access to investigations in China.

11. (SBU) **Comment**: The limited content of the report, China's efforts to use the report to point to an origin outside China, and the disconnect between the international and Chinese experts in characterizing the report was disappointing but not unexpected. What was more surprising was DG Tedros taking an affirmative stand to criticize some of the report's conclusions and a veiled criticism of China's failure to provide scientists with access to data. DG Tedros has been loath to criticize China publicly throughout the process, despite ongoing delays and obfuscations from the Chinese Communist Party. The Chinese Ambassador's response to criticisms was as much focused at DG Tedros as it was the United States and European Union. After the Member State briefing, the United States issued a joint statement with Australia, Canada, Czechia, Denmark, Estonia, Israel, Japan, Latvia, Lithuania, Norway, the Republic of Korea, Slovenia, and the United Kingdom. The U.S. and EU coalition building through the joint statements may be exerting pressure (or providing

political space) for DG Tedros to speak out more objectively than he has been willing to over the past year. **End Comment.**

Signature:	CASSAYRE
Drafted By:	GENEVA [redacted] (Geneva)
Cleared By:	HHS/NIH [redacted] (Geneva) POL: [redacted] (Geneva) USAID: [redacted] (Geneva) [redacted] HHS/OGA: [redacted] (Geneva) POL-ECON [redacted] (Geneva)
Approved By:	EXEC: [redacted] (Geneva)
Released By:	GENEVA [redacted] (Geneva)
Info:	NATIONAL SECURITY COUNCIL WASHINGTON DC *ROUTINE*; DEPT OF HHS WASHINGTON DC *ROUTINE*; ATLANTA GA, CDC *ROUTINE*; IO COLLECTIVE *ROUTINE*; ENVIRONMENT SCIENCE AND TECHNOLOGY COLLECTIVE *ROUTINE*
XMT:	CARACAS, AMEMBASSY; ST PETERSBURG, AMCONSUL
Attachments:	20210328- COVID 19 Origins Full report.pdf
Action Post:	NONE
Dissemination Rule:	RMA, ESA, EXEC, PSA, AID, FAS

From: Collins, Francis (NIH/OD) [E]
To: Fauci, Anthony (NIH/NIAID) [E]
Cc: Tabak, Lawrence (NIH/OD) [E]; Lane, Cliff (NIH/NIAID) [E]; Burklow, John (NIH/OD) [E]
Subject: conspiracy gains momentum
Date: Thursday, April 16, 2020 5:01:56 PM

Wondering if there is something NIH can do to help put down this very destructive conspiracy, with what seems to be growing momentum:

https://www.mediaite.com/tv/foxs-bret-baier-sources-increasingly-confident-coronavirus-outbreak-started-in-wuhan-lab/

I hoped the Nature Medicine article on the genomic sequence of SARS-CoV-2 would settle this. But probably that didn't get much visibility.

Anything more we can do? Ask the National Academy to weigh in?

Francis

From: Fauci, Anthony (NIH/NIAID) [E]
To: Collins, Francis (NIH/OD) [E]
Subject: RE: conspiracy gains momentum
Date: Thursday, April 16, 2020 10:45:00 PM

Francis:

I would not do anything about this right now. It is a shiny object that will go away in time.

Best,

Tony

From: Collins, Francis (NIH/OD) [E] [redacted]
Sent: Thursday, April 16, 2020 5:02 PM
To: Fauci, Anthony (NIH/NIAID) [E] [redacted]
Cc: Tabak, Lawrence (NIH/OD) [E] [redacted]; Lane, Cliff (NIH/NIAID) [E] [redacted] Burklow, John (NIH/OD) [E] [redacted]>
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Sent: 6/25/2021 6:36:12 PM
To: Morens, David (NIH/NIAID) [E] [redacted] Folkers, Greg (NIH/NIAID) [E] [redacted]
Subject: Re: David ---- FW: WSJ: The Science Suggests a Wuhan Lab Leak

Hi David and Greg,

I agree with the article by Amu Maxman, and with what Kristian Andersen has said – the two "CGG" codons for Arg in the polybasic spike furin cleavage site is not evidence of engineering.

1. Furin cleavage sites have evolved multiple times independently in betacoronaviruses (eg, MERS, HKU1), as they have in H5 and H7 chicken adapted influenza A and in avian Newcastle disease viruses.
2. Codon usage and codon optimization varies by host species. CGG is one of six codons for Arg. It is common in humans, so a virus adapted to replicate in human cells would be fine with finding common tRNAs with the anticodon for this codon. In betacoronaviruses, it is less common (~5% of Arg codons) but still used. Remember that the protein in which the Arg is encoded is the same sequence regardless of which Arg codon is chosen. The hold up is not protein functionality but speed of translation at the ribosome where a rare codon can hold up the translation longer than a common codon for that species. Perhaps structural stability or speed of translation is not a problem here in humans. This codon would not be favored in E coli so it would not be good if you wanted to clone genes and produce protein in bacterial systems as an example.
3. There is no reason to state that this could not have evolved naturally during its adaptation to humans for biologic reasons that are not yet clear. It is not a marker of virulence per se in beta CoVs. MERS has a furin cleavage site and is pathogenic in humans but HKU1 is a cold virus with it and is not pathogenic. It would be unlikely to be thought of as an 'obvious virulence factor' that could be engineered in for some nefarious purpose.

Thanks,

Jeff

From: "Morens, David (NIH/NIAID) [E]" [redacted]
Date: Friday, June 25, 2021 at 11:57 AM
To: "Folkers, Greg (NIH/NIAID) [E]" [redacted]
Cc: NIAID OD AM [redacted] "Taubenberger, Jeffrey (NIH/NIAID) [E]" [redacted]
Subject: Re: David ---- FW: WSJ: The Science Suggests a Wuhan Lab Leak

Well, the best argument is that with many amino acids in a protein, coded by many codons, "rare" things happen all the time, and since CGG is uncommon, but at the same time IS found in coronaviruses, two CGGs is even more uncommon. But it is not something a crazy virologist would thing to insert because.... why would you? I am going to copy Jeff T on this bc he knows way more than me. d

Sent from my iPhone
David M Morens
OD, NIAID, NIH

On Jun 25, 2021, at 11:25, Folkers, Greg (NIH/NIAID) [E] <[redacted]> wrote:

David,

The WSJ editorial below argues that the presence of CGG-CGG is evidence that SARS-CoV-2 is the result of g#in-of-function research. What do you and the virologists in your orbit make of this? What is the best argument that this is probably not the case?

In the case of the gain-of-function supercharge, other sequences could have been spliced into this same site. Instead of a CGG-CGG (known as "double CGG") that tells the protein factory to make two arginine amino acids in a row, you'll obtain equal lethality by splicing any one of 35 of the other two-word combinations for double arginine. If the insertion takes place naturally, say through recombination, then one of those 35 other sequences is far more likely to appear; CGG is rarely used in the class of coronaviruses that can recombine with CoV-2.

In fact, in the entire class of coronaviruses that includes CoV-2, the CGG-CGG combination has never been found naturally. That means the common method of viruses picking up new skills, called recombination, cannot operate here. A virus simply cannot pick up a sequence from another virus if that sequence isn't present in any other virus.

Although the double CGG is suppressed naturally, the opposite is true in laboratory work. The insertion sequence of choice is the double CGG. That's because it is readily available and convenient, and scientists have a great deal of experience inserting it. An additional advantage of the double CGG sequence compared with the other 35 possible choices: It creates a useful beacon that permits the scientists to track the insertion in the laboratory.

Now the damning fact. It was this exact sequence that appears in CoV-2. Proponents of zoonotic origin must explain why the novel coronavirus, when it mutated or recombined, happened to pick its least favorite combination, the double CGG. Why did it replicate the choice the lab's gain-of-function researchers would have made?

Yes, it could have happened randomly, through mutations. But do you believe that? At the minimum, this fact—that the coronavirus, with all its random possibilities, took the rare and unnatural combination used by human researchers—implies that the leading theory for the origin of the coronavirus must be laboratory escape.

When the lab's Shi Zhengli and colleagues published a paper in February 2020 with the virus's partial genome, they omitted any mention of the special sequence that supercharges the virus or the rare double CGG section. Yet the fingerprint is easily identified in the data that accompanied the paper. Was it omitted in the hope that nobody would notice this evidence of the gain-of-function origin?

But in a matter of weeks virologists Bruno Coutard and colleagues published their discovery of the sequence in CoV-2 and its novel supercharged site. Double CGG is there; you only have to look. They comment in their paper that the protein that held it "may provide a gain-of-function" capability to the virus, "for efficient spreading" to humans.

The Science Suggests a Wuhan Lab Leak

The Covid-19 pathogen has a genetic footprint that has never been observed in a natural coronavirus.

By Steven Quay and Richard Muller
Dr. Quay is founder of Atossa Therapeutics and author of "Stay Safe: A Physician's Guide to Survive Coronavirus." Mr. Muller is an emeritus professor of physics at the University of California Berkeley and a former senior scientist at the Lawrence Berkeley National Laboratory.

June 6, 2021 11:59 am ET

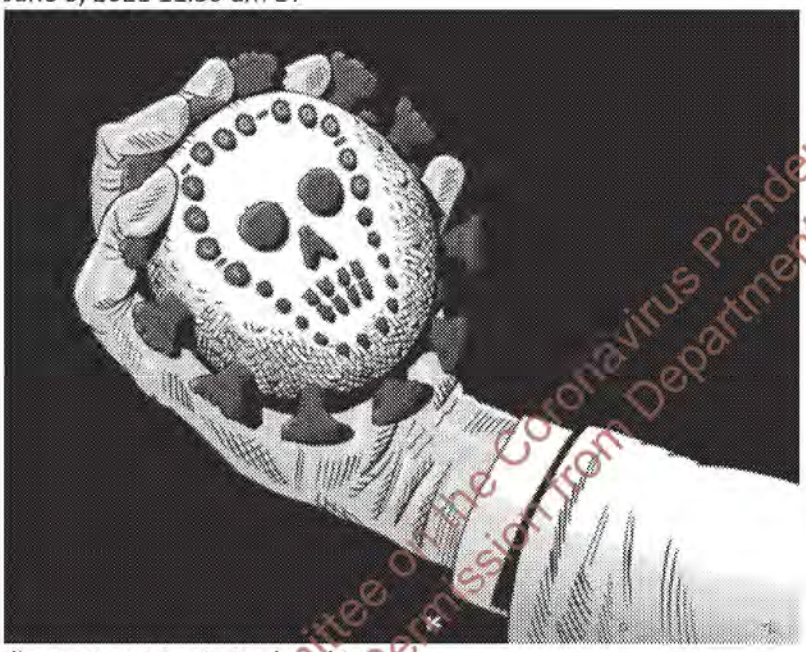

Illustration: Martin Kozlowski
This article is in your queue.

The possibility that the pandemic began with an escape from the Wuhan Institute of Virology is attracting fresh attention. President Biden has asked the national intelligence community to redouble efforts to investigate.

Much of the public discussion has focused on circumstantial evidence: mysterious illnesses in late 2019; the lab's work intentionally supercharging viruses to increase lethality (known as "gain of function" research). The Chinese Communist Party has been reluctant to release relevant information. Reports based on U.S. intelligence have suggested the lab collaborated on projects with the Chinese military.

But the most compelling reason to favor the lab leak hypothesis is firmly based in science. In particular, consider the genetic fingerprint of CoV-2, the novel coronavirus responsible for the disease Covid-19.

In gain-of-function research, a microbiologist can increase the lethality of a coronavirus enormously by splicing a special sequence into its genome at a prime location. Doing this leaves no trace of manipulation. But it alters the virus spike protein, rendering it easier for the virus to inject genetic

material into the victim cell. Since 1992 there have been at least 11 separate experiments adding a special sequence to the same location. The end result has always been supercharged viruses.

A genome is a blueprint for the factory of a cell to make proteins. The language is made up of three-letter "words," 64 in total, that represent the 20 different amino acids. For example, there are six different words for the amino acid arginine, the one that is often used in supercharging viruses. Every cell has a different preference for which word it likes to use most.

In the case of the gain-of-function supercharge, other sequences could have been spliced into this same site. Instead of a CGG-CGG (known as "double CGG") that tells the protein factory to make two arginine amino acids in a row, you'll obtain equal lethality by splicing any one of 35 of the other two-word combinations for double arginine. If the insertion takes place naturally, say through recombination, then one of those 35 other sequences is far more likely to appear; CGG is rarely used in the class of coronaviruses that can recombine with CoV-2.

In fact, in the entire class of coronaviruses that includes CoV-2, the CGG-CGG combination has never been found naturally. That means the common method of viruses picking up new skills, called recombination, cannot operate here. A virus simply cannot pick up a sequence from another virus if that sequence isn't present in any other virus.

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Now the damning fact. It was this exact sequence that appears in CoV-2. Proponents of zoonotic origin must explain why the novel coronavirus, when it mutated or recombined, happened to pick its least favorite combination, the double CGG. Why did it replicate the choice the lab's gain-of-function researchers would have made?

Yes, it could have happened randomly, through mutations. But do you believe that? At the minimum, this fact—that the coronavirus, with all its random possibilities, took the rare and unnatural combination used by human researchers—implies that the leading theory for the origin of the coronavirus must be laboratory escape.

When the lab's Shi Zhengli and colleagues published a paper in February 2020 with the virus's partial genome, they omitted any mention of the special sequence that supercharges the virus or the rare double CGG section. Yet the fingerprint is easily identified in the data that accompanied the paper. Was it omitted in the hope that nobody would notice this evidence of the gain-of-function origin?

But in a matter of weeks virologists Bruno Coutard and colleagues published their discovery of the sequence in CoV-2 and its novel supercharged site. Double CGG is there; you only have to look. They comment in their paper that the protein that held it "may provide a gain-of-function" capability to the virus, "for efficient spreading" to humans.

There is additional scientific evidence that points to CoV-2's gain-of-function origin. The most compelling is the dramatic differences in the genetic diversity of CoV-2, compared with the coronaviruses responsible for SARS and MERS.

Both of those were confirmed to have a natural origin; the viruses evolved rapidly as they spread through the human population, until the most contagious forms dominated. Covid-19 didn't work that way. It appeared in humans already adapted into an extremely contagious version. No serious viral "improvement" took place until a minor variation occurred many months later in England.

Such early optimization is unprecedented, and it suggests a long period of adaptation that predated its public spread. Science knows of only one way that could be achieved: simulated natural evolution, growing the virus on human cells until the optimum is achieved. That is precisely what is done in gain-of-function research. Mice that are genetically modified to have the same coronavirus receptor as humans, called "humanized mice," are repeatedly exposed to the virus to encourage adaptation.

The presence of the double CGG sequence is strong evidence of gene splicing, and the absence of diversity in the public outbreak suggests gain-of-function acceleration. The scientific evidence points to the conclusion that the virus was developed in a laboratory.

Dr. Quay is founder of Atossa Therapeutics and author of "Stay Safe: A Physician's Guide to Survive Coronavirus." Mr. Muller is an emeritus professor of physics at the University of California Berkeley and a former senior scientist at the Lawrence Berkeley National Laboratory.

Message

From: Memoli, Matthew (NIH/NIAID) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4D3AF4D9F3E54FBC80DDD844C16691CC-MEMOLIM]
Sent: 4/14/2020 7:51:30 PM
To: Xiao, Yongli (NIH/NIAID) [E] [redacted] Taubenberger, Jeffery (NIH/NIAID) [E] [redacted] Kash, John (NIH/NIAID) [E] [redacted] Qi, Li (NIH/NIAID) [E] [redacted] Gygli, Sebastian (NIH/NIAID) [F] [redacted] Morens, David (NIH/NIAID) [E] [redacted]
Subject: Re: WaPo: State Department cables warned of safety issues at Wuhan lab studying bat coronaviruses

I have been saying this since the beginning. Something is fishy about this.

--
Matthew J. Memoli, M.D., M.S.
Director, LID Clinical Studies Unit
Laboratory of Infectious Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health
MSC 3203 33 North Dr
Bethesda, MD 20892-3203
UNITED STATES
Email: [redacted]
Phone: 301-443-5971
Pager: 1-800-NIH-BEEP 10225

==========

From: Yongli Xiao [redacted]
Date: Tuesday, April 14, 2020 at 3:50 PM
To: Jeffery Taubenberger [redacted] John Kash [redacted] "Memoli, Matthew (NIH/NIAID) [E]" [redacted] "Qi, Li (NIH/NIAID) [E]" [redacted] "Gygli, Sebastian (NIH/NIAID) [F]" [redacted] David Morens [redacted]
Subject: Re: WaPo: State Department cables warned of safety issues at Wuhan lab studying bat coronaviruses

Wow!

From: "Taubenberger, Jeffery (NIH/NIAID) [E]" [redacted]
Date: Tuesday, April 14, 2020 at 3:08 PM
To: "Kash, John (NIH/NIAID) [E]" [redacted] "Memoli, Matthew (NIH/NIAID) [E]" [redacted] "Qi, Li (NIH/NIAID) [E]" [redacted] "Xiao, Yongli (NIH/NIAID) [E]" [redacted] "Gygli, Sebastian (NIH/NIAID) [F]" [redacted] "Morens, David (NIH/NIAID) [E]" [redacted]
Subject: FW: WaPo: State Department cables warned of safety issues at Wuhan lab studying bat coronaviruses

From: "Vandalen, Kaci (NIH/NIAID) [E]" [redacted]
Date: Tuesday, April 14, 2020 at 3:06 PM
To: NIAID HCTF <[redacted]>
Subject: FW: WaPo: State Department cables warned of safety issues at Wuhan lab studying bat coronaviruses

Good afternoon,
Marshall asked that I distribute this to the HCTF. I hope everyone is staying safe and sane!

Kaci VanDalen | *Health Specialist (BioRisk)*
National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
Surety & Preparedness Coordination Branch
5601 Fishers Lane RM 1G568, Rockville, MD 20852
C: [redacted] E: [redacted]

Remote Work Address
[redacted]

From: Bloom, Marshall (NIH/NIAID) [E] [redacted]
Sent: Tuesday, April 14, 2020 8:47 AM
To: Vandalen, Kaci (NIH/NIAID) [E] [redacted]
Subject: FW: WaPo: State Department cables warned of safety issues at Wuhan lab studying bat coronaviruses

Kaci,

Please send to the HCTF. Thanks!
Marshall

State Department cables warned of safety issues at Wuhan lab studying bat coronaviruses

A woman wearing a protective suit at a hospital in Wuhan, China. (Aly Song/Reuters)

By
Josh Rogin
Columnist
April 14, 2020 at 6:00 a.m. EDT

Two years before the novel coronavirus pandemic upended the world, U.S. Embassy officials visited a Chinese research facility in the city of Wuhan several times and sent two official warnings back to Washington about inadequate safety at the lab, which was conducting risky studies on coronaviruses from bats. The cables have fueled discussions inside the U.S. government about whether this or another Wuhan lab was the source of the virus — even though conclusive proof has yet to emerge.

In January 2018, the U.S. Embassy in Beijing took the unusual step of repeatedly sending U.S. science diplomats to the Wuhan Institute of Virology (WIV), which had in 2015 become China's first laboratory to achieve the highest level of international bioresearch safety (known as BSL-4). WIV issued a news release in English about the last of these visits, which occurred on March 27, 2018. The U.S. delegation was led by Jamison Fouss, the consul general in Wuhan, and Rick Switzer, the embassy's counselor of environment, science, technology and health. Last week, WIV erased that statement from its website, though it remains archived on the Internet.

What the U.S. officials learned during their visits concerned them so much that they dispatched two diplomatic cables categorized as Sensitive But Unclassified back to Washington. The cables warned about safety and management weaknesses at the WIV lab and proposed more attention and help. The first cable, which I obtained, also warns that the lab's work on bat coronaviruses and their potential human transmission represented a risk of a new SARS-like pandemic.

"During interactions with scientists at the WIV laboratory, they noted the new lab has a serious shortage of appropriately trained technicians and investigators needed to safely operate this high-containment laboratory," states the Jan. 19, 2018, cable, which was drafted by two officials from the embassy's environment, science and health sections who met with the WIV scientists. (The State Department declined to comment on this and other details of the story.)

The Chinese researchers at WIV were receiving assistance from the Galveston National Laboratory at the University of Texas Medical Branch and other U.S. organizations, but the Chinese requested additional help. The cables argued that the United States should give the Wuhan lab further support, mainly because its research on bat coronaviruses was important but also dangerous.

As the cable noted, the U.S. visitors met with Shi Zhengli, the head of the research project, who had been publishing studies related to bat coronaviruses for many years. In November 2017, just before the U.S. officials' visit, Shi's team had published research showing that horseshoe bats they had collected from a cave in Yunnan province were very likely from the same bat population that spawned the SARS coronavirus in 2003.

"Most importantly," the cable states, "the researchers also showed that various SARS-like coronaviruses can interact with ACE2, the human receptor identified for SARS-coronavirus. This finding strongly suggests that SARS-like coronaviruses from bats can be transmitted to humans to cause SARS-like diseases. From a public health perspective, this makes the continued surveillance of SARS-like coronaviruses in bats and study of the animal-human interface critical to future emerging coronavirus outbreak prediction and prevention."

The research was designed to prevent the next SARS-like pandemic by anticipating how it might emerge. But even in 2015, other scientists questioned whether Shi's team was taking unnecessary risks. In October 2014, the U.S. government had imposed a moratorium on funding of any research that makes a virus more deadly or contagious, known as "gain-of-function" experiments.

As many have pointed out, there is no evidence that the virus now plaguing the world was engineered; scientists largely agree it came from animals. But that is not the same as saying it didn't come from the lab, which spent years testing bat coronaviruses in animals, said Xiao Qiang, a research scientist at the School of Information at the University of California at Berkeley.

"The cable tells us that there have long been concerns about the possibility of the threat to public health that came from this lab's research, if it was not being adequately conducted and protected," he said.

There are similar concerns about the nearby Wuhan Center for Disease Control and Prevention lab, which operates at biosecurity level 2, a level significantly less secure than the level-4 standard claimed by the Wuhan Insititute of Virology lab, Xiao said. That's important because the Chinese government still refuses to answer basic questions about the origin of the novel coronavirus while suppressing any attempts to examine whether either lab was involved.

Sources familiar with the cables said they were meant to sound an alarm about the grave safety concerns at the WIV lab, especially regarding its work with bat coronaviruses. The embassy officials were calling for more U.S. attention to this lab and more support for it, to help it fix its problems.

"The cable was a warning shot," one U.S. official said. "They were begging people to pay attention to what was going on."

No extra assistance to the labs was provided by the U.S. government in response to these cables. The cables began to circulate again inside the administration over the past two months as officials debated whether the lab could be the origin of the pandemic and what the implications would be for the U.S. pandemic response and relations with China.

Inside the Trump administration, many national security officials have long suspected either the WIV or the Wuhan Center for Disease Control and Prevention lab was the source of the novel coronavirus outbreak. According to the New York Times, the intelligence community has provided no evidence to confirm this. But one senior administration official told me that the cables provide one more piece of evidence to support the possibility that the pandemic is the result of a lab accident in Wuhan.

"The idea that is was just a totally natural occurrence is circumstantial. The evidence it leaked from the lab is circumstantial. Right now, the ledger on the side of it leaking from the lab is packed with bullet points and there's almost nothing on the other side," the official said.

As my colleague David Ignatius noted, the Chinese government's original story — that the virus emerged from a seafood market in Wuhan — is shaky. Research by Chinese experts published in the Lancet in January showed the first known patient, identified on Dec. 1, had no connection to the market, nor did more than one-third of the cases in the first large cluster. Also, the market didn't sell bats.

Shi and other WIV researchers have categorically denied this lab was the origin for the novel coronavirus. On Feb. 3, her team was the first to publicly report the virus known as 2019-nCoV was a bat-derived coronavirus.

The Chinese government, meanwhile, has put a total lockdown on information related to the virus origins. Beijing has yet to provide U.S. experts with samples of the novel coronavirus collected from the earliest cases. The Shanghai lab that published the novel coronavirus genome on Jan. 11 was quickly shut down by authorities for "rectification." Several of the doctors and journalists who reported on the spread early on have disappeared.

On Feb. 14, Chinese President Xi Jinping called for a new biosecurity law to be accelerated. On Wednesday, CNN reported the Chinese government has placed severe restrictions requiring approval before any research institution publishes anything on the origin of the novel coronavirus.

The origin story is not just about blame. It's crucial to understanding how the novel coronavirus pandemic started because that informs how to prevent the next one. The Chinese government must be transparent and answer the questions about the Wuhan labs because they are vital to our scientific understanding of the virus, said Xiao.

We don't know whether the novel coronavirus originated in the Wuhan lab, but the cable pointed to the danger there and increases the impetus to find out, he said.

"I don't think it's a conspiracy theory. I think it's a legitimate question that needs to be investigated and answered," he said. "To understand exactly how this originated is critical knowledge for preventing this from happening in the future."

Josh Rogin is a columnist for the Global Opinions section of The Washington Post. He writes about foreign policy and national security. Rogin is also a political analyst for CNN. He previously worked for Bloomberg View, the Daily Beast, Foreign Policy, Congressional Quarterly, Federal Computer Week and Japan's Asahi Shimbun newspaper.

Message

From: Chen, Ping (NIH/NIAID) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=E86E86EEEEF44552B2918975F5001D13-CHENPI]
Sent: 1/7/2020 2:42:43 PM
To: Stemmy, Erik (NIH/NIAID) [E] [redacted]
CC: Handley, Gray (NIH/NIAID) [E] [redacted] Bernabe, Gayle (NIH/NIAID) [E] [redacted]
Subject: RE: Wuhan Pneumonia

No replacement for now. 😊

From: Stemmy, Erik (NIH/NIAID) [E] [redacted]
Sent: Tuesday, January 7, 2020 9:41 AM
To: Chen, Ping (NIH/NIAID) [E] [redacted]
Cc: Handley, Gray (NIH/NIAID) [E] [redacted] Bernabe, Gayle (NIH/NIAID) [E] [redacted]
Subject: RE: Wuhan Pneumonia

Thanks Ping! I think I forgot that you were back in Fishers lane. Welcome back!

Thanks for the info. I will let them know that George will be here next week. Do you know if there is a replacement for you in the embassy in Beijing? If so I'd love to connect with them.

Erik

From: Chen, Ping (NIH/NIAID) [E] <[redacted]>
Sent: Tuesday, January 7, 2020 9:38 AM
To: Stemmy, Erik (NIH/NIAID) [E] <[redacted]>
Cc: Handley, Gray (NIH/NIAID) [E] <[redacted]>; Bernabe, Gayle (NIH/NIAID) [E] <[redacted]>
Subject: RE: Wuhan Pneumonia

Hi Erik,

Happy New Year!

Do you know that I am back at OGR now? My 6 years in Beijing ended three weeks ago and had to come back.

Yes, I have been following the news. Here is what I know so far, not much though. I contacted Dr. Zhengli Shi at the Wuhan Institute of Virology (she is your grantee) and she confirmed that it is viral infection. But she won't tell me the nature of the virus. She told me to be patient and wait for the public accouchement. My friend in the US embassy in Beijing told me last night that there will be a cable coming out soon on this matter. Once I have the cable I will send to you. But I don't expect it has much scientific information in it.

Speaking of George Gao, he will be at Fishers Lane attending the bunya virus conference next Monday and Tuesday. I am sure he will have the most recent information on the virus. If Barney and Vincent are at the meeting, they can talk to him directly.

Ping

From: Stemmy, Erik (NIH/NIAID) [E] [redacted]
Sent: Tuesday, January 7, 2020 7:53 AM
To: Chen, Ping (NIH/NIAID) [E] <[redacted]>
Subject: Wuhan Pneumonia

Hi Ping,
Happy New Year! I'm sure you've been following the news of the viral pneumonia outbreak in Wuhan. I was wondering if you have any information to share beyond what's already been reported in the news? And also whether you have any contacts with anyone that may have sequenced the virus, maybe someone with George Gao's group? I've been working to put together what we know so far and have been reaching out to my investigators as well. Barney Graham and Vincent Munster were particularly interested in the sequenced virus.

Thanks for your help!
Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, Room 8E18
Bethesda, MD 20892-9825
Phone: (240)-627-3380
Email: [redacted]

Getting ready to publish? Share the good news with your program officer asap! NIAID may be able to help publicize your article. And, remember to list your NIAID grant or contract number in the publication.
****

Message

From: Myles, Renate (NIH/OD) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7D317F5626934585B3692A1823C1B522-MYLESR]
Sent: 6/18/2021 2:28:44 PM
To: Burklow, John (NIH/OD) [E] [redacted] Collins, Francis (NIH/OD) [E] [redacted]
Subject: RE: USA Today: 'I remember it very well': Dr. Fauci describes a secret 2020 meeting to talk about COVID origins

Agree and I know one is in the works.

From: Burklow, John (NIH/OD) [E] [redacted]
Sent: Friday, June 18, 2021 10:01 AM
To: Collins, Francis (NIH/OD) [E] [redacted]
Cc: Myles, Renate (NIH/OD) [E] [redacted]
Subject: Re: USA Today: 'I remember it very well': Dr. Fauci describes a secret 2020 meeting to talk about COVID origins

I think yes. To correct the record.

Sent from my iPhone

On Jun 18, 2021, at 9:54 AM, Collins, Francis (NIH/OD) [E] [redacted] wrote:

Hi Renate and John,

Tony just called. He is furious that Alison Young is insinuating in this USA Today article that the February 1, 2020 call led to a secretive effort to squash discussion of the lab leak possibility. That's just wrong – it was the opposite.

At least USA Today labeled this as "opinion" – but Tony thinks we ought to consider a brief letter to set the record straight. Your view?

Francis

From: Fauci, Anthony (NIH/NIAID) [E] [redacted]
Sent: Friday, June 18, 2021 9:38 AM
To: Collins, Francis (NIH/OD) [E] [redacted]
Subject: FW: USA Today: 'I remember it very well': Dr. Fauci describes a secret 2020 meeting to talk about COVID origins

Let us discuss.

Anthony S. Fauci, MD
Director
National Institute of Allergy and Infectious Diseases
Building 31, Room 7A-03
31 Center Drive, MSC 2520
National Institutes of Health
Bethesda, MD 20892-2520
Phone: [redacted]

FAX: [redacted]
E-mail: [redacted]

From: Folkers, Greg (NIH/NIAID) [E] [redacted]
Sent: Thursday, June 17, 2021 11:09 PM
Subject: USA Today: 'I remember it very well': Dr. Fauci describes a secret 2020 meeting to talk about COVID origins

OPINION

'I remember it very well': Dr. Fauci describes a secret 2020 meeting to talk about COVID origins

A 2020 call appears to have played a key role in shaping views of scientists who contributed to shutting down talk of whether a lab leak caused COVID.

Alison Young
Opinion contributor

In the early days of the growing coronavirus outbreak that would soon become a pandemic, an elite group of international scientists gathered on a conference call to discuss a shocking possibility: The virus looked like it might have been engineered in a laboratory.

"I remember it very well," Dr. Anthony Fauci, the top infectious disease expert at the National Institutes of Health, said in an interview with me on Wednesday. "We decided on the call the situation really needed to be looked into carefully."

The teleconference on Feb. 1, 2020, appears to have played a pivotal role in shaping the early views of several key scientists whose published papers and public statements contributed to the shutting down of legitimate discussion about whether a laboratory in Wuhan, China, might have ignited the COVID-19 pandemic.

As a reporter who has spent a decade revealing hundreds of serious safety breaches at U.S. biological research labs, it has always seemed obvious to investigate whether the Wuhan Institute of Virology, a major coronavirus research center, possibly played a role given that the initial outbreak happened in the same city.

Yet for more than a year, those who publicly raised such questions were too often deemed a crackpot conspiracy theorist or a simpleton who just didn't understand science.

It has only been in recent weeks that a growing list of high-profile scientists, intelligence officials and politicians – including President Joe Biden – have publicly acknowledged the plausibility of a lab accident and pushed for rigorous investigation.

Could an accident have caused COVID-19?: Why the Wuhan lab-leak theory shouldn't be dismissed

Perhaps that's because the early concerns among key scientists – like the conference call on Feb. 1, 2020 – were kept private until now. That call likely would have remained secret if not for documents released under the Freedom of Information Act.

A secret, high-stakes conference call

That teleconference was urgent enough it was scheduled on a Saturday afternoon.

Just two days earlier, the World Health Organization had raised the alert level on the novel coronavirus, declaring the growing outbreak a public health emergency of international concern. At the time, most Americans were still going about life as usual, blissfully unaware of what was to come, even though federal health officials had recently identified a man who had traveled from Wuhan to Washington state as the first case in this country.

<image001.jpg>

Precious little was known back then about the virus, which was assumed to have emerged in the usual way by an infected animal, or a series of animals, infecting a person. The suggestion that it might have hallmarks of genetic engineering had enormous implications, if that turned out to be true.

The group of scientists invited to the call had agreed in advance that the information they discussed would be kept in total confidence and not shared until they had agreed on next steps, emails at the time show. They were among thousands of pages of Fauci's emails on a wide range of topics that BuzzFeed News posted online recently after obtaining them through the federal Freedom of Information Act lawsuit.

Public vs. private: Compare what Dr. Fauci said in his emails to what he said publicly

A day before the teleconference, Kristian Andersen, an expert in infectious disease genomics at the prestigious Scripps Research Translational Institute in California, had told Fauci first by phone and again later by email that the genetic structure of the virus looked like it might have been engineered in a lab.

"The unusual features of the virus make up a really small part of the genome (<0.1%) so one has to look really closely at all the sequences to see that some of the features (potentially) look engineered," Andersen said in an email to Fauci on Jan. 31, 2020. Andersen added that he and University of Sydney virologist and evolutionary biologist Edward Holmes, plus a handful of other top scientists with whom Fauci was on a first-name basis, "all find the genome inconsistent with expectations from evolutionary theory."

<image002.jpg>

More work needed to be done, "so those opinions could still change," Andersen said in the email exchange.

Andersen did not respond to repeated interview requests since last week. Late Thursday, a spokesperson said Andersen was traveling and unavailable.

Discussion of Andersen's concerns had begun earlier on that Friday, Jan. 31, 2020, Fauci told me, when he had conferenced Andersen into a three-way call with Jeremy Farrar, director the Wellcome Trust, an influential and wealthy foundation based in London that funds global health research.

It was during that first call, Fauci said, that Andersen mentioned he had spoken with Holmes and that "at first glance," the genome of the virus looked unusual.

"I suggested we bring together a multidisciplinary team," Fauci said, adding that he wanted it to be an international group with wide expertise to ensure as many opinions as possible.

"We agreed to convene by phone the next day," Fauci told me, adding that he notified senior leaders at the NIH's parent agency, the Department of Health and Human Services, of the meeting. Then he called his boss, NIH Director Francis Collins, and brought him into the discussion.

<image003.jpg>

Those on the call that Saturday, Fauci said, included Collins, Farrar and Andersen, plus several other international experts on emerging infectious diseases and virology.

Emails show the agenda for the one-hour meeting was short: Farrar was responsible for kicking off the meeting with: "Introduction, focus and desired outcomes." Andersen came next, charged with providing: "Summary." Holmes spoke third: "Comments." Then the floor was opened for Q&A.

But details of what was said in the meeting, including extensive notes taken by one participant and further thoughts shared by others, were blacked out by the NIH before the emails were made public.

"It was a very productive back-and-forth conversation where some on the call felt it could possibly be an engineered virus," Fauci said in our interview. Others, he said, felt the evidence was "heavily weighted" toward the virus emerging from an animal host.

Fauci said his role in helping to organize the meeting shows he has always been open to the possibility of a lab leak or an engineered virus. "I always had an open mind," he said, "even though I felt then, and still do, the most likely origin was in an animal host."

At the end of the call that winter Saturday in 2020, Fauci said, it was decided that Farrar would "give a heads up" to WHO Director-General Tedros Adhanom Ghebreyesus "and determine what further needed to be done." Fauci said he doesn't know whether Farrar reached Tedros.

<image004.jpg>

Farrar was unavailable for an interview, a spokesperson said. Holmes and Tedros did not respond to requests for comment.

Meanwhile, Fauci said, Andersen was planning to devote considerable time in the ensuing two or three weeks taking a closer look at the genetic sequences.

A change in position in three days

Yet just three days after that Feb. 1 meeting, Andersen's position on the virus' potential origin changed dramatically. He had gone from having concerns about possible genetic engineering to telling another group of scientists "the data conclusively show" the virus wasn't engineered, and calling suggestions of engineering "fringe" and "crackpot" theories.

Andersen gave this feedback in a Feb. 4, 2020, email to several scientists who were helping craft a letter about the new virus for the National Academies of Sciences, Engineering, and Medicine to send to the White House Office of Science and Technology Policy. The email was obtained by the nonprofit group U.S. Right to Know through a public records request last year.

"Reading through the letter I think it's great," Andersen wrote to the group, "but I do wonder if we need to be more firm on the question of engineering. The main crackpot theories going around at the moment relate to this virus being somehow engineered with intent and that is demonstrably not the case. Engineering can mean many things and could be done for either basic research or nefarious reasons, but the data conclusively show that neither was done..."

He added: "If one of the main purposes of this document is to counter those fringe theories, I think it's very important that we do so strongly and in plain language ('consistent with' [natural evolution] is a favorite of mine when talking to scientists, but not when talking to the public – especially conspiracy theorists)."

<image005.jpg>

The National Academies' letter didn't end up incorporating these pushback suggestions. Instead, the letter focused on the need for more research, saying: "The experts informed us that additional genomic sequence data from geographically- and temporally-diverse viral samples are needed to determine the origin and evolution of the virus. Samples collected as early as possible in the outbreak in Wuhan and samples from wildlife would be particularly valuable."

Within a few weeks Andersen and a team of highly respected scientists, including Holmes, published their analysis of the SARS-CoV-2 virus, first on a pre-print site, then as a letter in the journal Nature Medicine on March 17, 2020.

The letter, titled "The proximal origin of SARS-CoV-2," has been hugely influential and is among the key reasons that any kind of lab-related hypothesis – involving either a natural or man-made virus – was dismissed by so many for so long.

"Our analyses clearly show that SARS-CoV-2 is not a laboratory construct or a purposefully manipulated virus," the letter said, before detailing the group's findings. The letter concludes by saying that since notable features of the virus are observed in related coronaviruses in nature, "we do not believe that any type of laboratory-based scenario is plausible."

Demand accountability: Trump and raging pandemic helped China dodge COVID accountability.

Farrar, who along with Fauci helped organize the Feb. 1, 2020, meeting discussing Andersen's initial concerns, considers the analysis in that letter to be the "most important research on the genomic epidemiology of the origins of this virus to date," his spokesperson said in an email to me.

It remains unclear what new evidence came to light in those three days in early February 2020 to change Andersen's opinion. He wouldn't talk with me about that. On Twitter – a platform where he was prolific – he had only addressed how his view of the virus changed over a period of weeks, from his Jan. 31, 2020, email with Fauci to the publication of his "proximal origin" letter.

"What the email shows, is a clear example of the scientific process," Andersen tweeted earlier this month when his emails with Fauci first became public. "As I have said many times, we seriously

considered a lab leak a possibility. However, significant new data, extensive analyses, and many discussions led to the conclusions in our paper."

Soon after, he deleted his entire Twitter account, which he often used to share his firm view that the SARS-CoV-2 virus emerged from nature and not from a lab.

Andersen has since said that some of the analyses were completed in days.

Scientists who have long urged investigations of all plausible origins of the virus – including the potential for a lab accident with a natural virus, point to the certainty of the statements in Andersen's paper as one of the key reasons the lab-leak hypothesis was dismissed as a conspiracy theory. To journalists and many scientists, the prestige of the writers and the certainty of their words made it seem the science was settled.

Lab leak?: Biden tells intelligence agencies to step up probe of COVID-19's origins

<image006.jpg>

And it didn't help that the questions about a lab leak had become conflated with the notion of a deliberately created bioweapon and that were also early on tied to President Donald Trump's China-bashing rhetoric.

"A small group of scientists, and a larger group of science journalists, established and enforced the false narrative that scientific evidence supported natural spillover, and (also) the false narrative that this was the scientific consensus," said Richard Ebright, a molecular biologist and biosafety expert at Rutgers University in New Jersey.

There were other views out there, they just weren't given much coverage as being credible.

"The February 1 telecon," Ebright said, "appears to have played an important – probably crucial – role in establishing and enforcing that false narrative."

Lingering questions about a lab leak

There remain some legitimate scientific debate about whether genetic manipulation of the virus can be completely ruled out, in part because not all genetic engineering methods leave tell-tale markers and also because the virus' genome does have some unusual features.

While regretting using the term "smoking gun" in a recent high-profile interview, Nobel Prize-winning virologist David Baltimore remains concerned that a feature of the virus, called a "furin cleavage site," could point to engineering.

"I believe that the question of whether the sequence was put in naturally or by molecular manipulation is very hard to determine but I wouldn't rule out either origin," he told the Los Angeles Times.

But lab accidents with a fully natural virus – one that might have been collected, stored or studied at the Wuhan Institute of Virology and infected a worker – are also the focus of calls for investigation. The institute's top coronavirus researcher Shi Zhengli and representatives of the Chinese government have repeatedly said the lab never had any such virus and had nothing to do with starting the pandemic. They have expressed outrage and frustration at what they see as baseless and politically motivated questions.

The real issue with the lab leak theory?: The US isn't spying on China like it used to

<image007.jpg>

Fauci told me that he thinks it is important to dig deeper on a U.S. intelligence report to determine whether, in fact, three researchers at the Wuhan Institute of Virology became so ill in November 2019 that they sought hospital care. That timing is just before the first known cases of COVID-19 appeared. Shi has said that there were no sick workers.

"My question is how credible is that intelligence? ... If it really is credible, we need to see the medical records," Fauci said. "We really need to call upon the Chinese government, in a diplomatic way, to allow scientific experts to take a look at what has gone on there."

Alison Young is an investigative reporter in Washington, D.C. She is also the Curtis B. Hurley Chair in Public Affairs Reporting at the Missouri School of Journalism. During 2009-19, she was a reporter and member of USA TODAY's national investigative team. Follow her on Twitter: @alisonannyoung

<image008.png>
<image008.png>
<image009.gif>

Message

From: Collins, Francis (NIH/OD) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=410E1CA313F44CED9938E50D2FF0B6C2-COLLINSF]
Sent: 3/19/2021 1:08:54 AM
To: Roberts, Rich [redacted]
CC: Tabak, Lawrence (NIH/OD) [E] [redacted]
Subject: RE: EcoHealth Alliance

Hi Rich,

Thanks for writing again. I wish I could provide you and your colleagues with a more direct response, but NIH is not in a position to discuss publicly internal deliberations on grants or on administrative or compliance matters related to grants.

Regards, Francis

From: Roberts, Rich [redacted]
Sent: Wednesday, March 17, 2021 8:51 AM
To: Collins, Francis (NIH/OD) [E] [redacted]
Cc: Tabak, Lawrence (NIH/OD) [E] [redacted]
Subject: EcoHealth Alliance

Dear Francis:

You may remember the letter that was sent last year protesting the treatment of Dr. Peter Daszak and the EcoHealth Alliance. We laureates would like to bring this matter to your attention once again. With the current change in Administration it seems to us that this matter needs to be re-opened and dealt with promptly to ensure that the grant is reinstated as soon as can be managed.

Rich

Sir Richard J. Roberts Ph.D. F.R.S.
1993 Nobel Laureate in Physiology or Medicine
Chief Scientific Officer
New England Biolabs
240 County Road
Ipswich, MA 01938-2723 USA

Tel: [redacted]
Fax:
email: [redacted]

Executive Assistant: Karen Otto
Tel: [redacted]
Fax:
email: [redacted]

----------original letter----------

The 81 signatories of this letter, American Nobel Laureates in Physiology or Medicine, Chemistry, and Physics, are gravely concerned about the recent cancellation of a grant from the National Institutes of Health (NIH) to Dr. Peter Daszak at the EcoHealth Alliance in New York. We believe that this action sets a dangerous precedent by interfering in the conduct of science and jeopardizes public trust in the process of awarding federal funds for research.

For many years, Dr. Daszak and his colleagues have been conducting highly regarded, NIH-supported research on coronaviruses and other infectious agents, focusing on the transmission of these viruses from animal hosts to human beings. Their work depends on productive collaborations with scientists in other countries, including scientists in Wuhan, China, where the current pandemic caused by a novel coronavirus arose. Now is precisely the time when we need to support this kind of research if we aim to control the pandemic and prevent subsequent ones.

As has now been widely reported, the grant to the EcoHealth Alliance was abruptly terminated by NIH on April 24, 2020, just a few days after President Trump responded to a question from a reporter who erroneously claimed that the grant awarded millions of dollars to investigators in Wuhan. Despite the misrepresentation of Dr. Daszak's grant, despite the high relevance of the studies to the current pandemic, and despite the very high priority score that his application for renewal had received during peer review, the NIH informed Dr. Daszak and his colleagues that the grant was being terminated because "NIH does not believe that the current project outcomes align with the program goals and agency priorities." Such explanations are preposterous under the circumstances.

We are scientists who have devoted our careers to research, both in medical and related scientific disciplines that bear on the overall health and well-being of society, as well as fundamental scientific research, much of it supported by NIH and other federal agencies. We take pride in our nation's widely admired system for allocating funds based on expert review and public health needs. The abrupt revoking of the award to Dr. Daszak contravenes these basic tenets and deprives the nation and the world of highly regarded science that could help control one of the greatest health crises in modern history and those that may arise in the future.

We ask that you act urgently to conduct and release a thorough review of the actions that led to the decision to terminate the grant, and that, following this review, you take appropriate steps to rectify the injustices that may have been committed in revoking it.

Peter Agre Chemistry 2003
Sidney Altman Chemistry 1989
Frances H. Arnold Chemistry 2018
Paul Berg Chemistry 1980
Thomas R. Cech Chemistry 1989
Martin Chalfie Chemistry 2008
Elias James Corey Chemistry 1990
Robert F. Curl Jr. Chemistry 1996
Johann Deisenhofer Chemistry 1988
Joachim Frank Chemistry 2017
Walter Gilbert Chemistry 1980
Dudley R. Herschbach Chemistry 1986

Roald Hoffmann Chemistry 1981
Brian K. Kobilka Chemistry 2012
Roger D. Kornberg Chemistry 2006
Robert J. Lefkowitz Chemistry 2012
Michael Levitt Chemistry 2013
Roderick MacKinnon Chemistry 2003
William E. Moerner Chemistry 2014
Mario J. Molina Chemistry 1995
Richard R. Schrock Chemistry 2005
George P. Smith Chemistry 2018
James P. Allison Medicine 2018
Richard Axel Medicine 2004
David Baltimore Medicine 1975
J. Michael Bishop Medicine 1989
Elizabeth H. Blackburn Medicine 2009
Michael S. Brown Medicine 1985
Linda B. Buck Medicine 2004
William C. Campbell Medicine 2015
Mario R. Capecchi Medicine 2007
Andrew Z. Fire Medicine 2006
Edmond H. Fischer Medicine 1992
Joseph L. Goldstein Medicine 1985
Carol W. Greider Medicine 2009
Roger Guillemin Medicine 1977
Leland H. Hartwell Medicine 2001
H. Robert Horvitz Medicine 2002
Louis J. Ignarro Medicine 1998
William G. Kaelin Jr. Medicine 2019
Eric R. Kandel Medicine 2000
Craig C. Mello Medicine 2006
Ferid Murad Medicine 1998
Sir Richard J. Roberts Medicine 1993
Michael Rosbash Medicine 2017
James E. Rothman Medicine 2013
Randy W. Schekman Medicine 2013
Gregg L. Semenza Medicine 2019
Phillip A. Sharp Medicine 1993
Hamilton O. Smith Medicine 1978
Thomas C. Sudhof Medicine 2013
Jack W. Szostak Medicine 2009
Susumu Tonegawa Medicine 1987
Harold E. Varmus Medicine 1989
Eric F. Wieschaus Medicine 1995
Torsten N. Wiesel Medicine 1981
Michael W. Young Medicine 2017
Barry Clark Barish Physics 2017
Steven Chu Physics 1997
Jerome I. Friedman Physics 1990
Sheldon Glashow Physics 1979
David J. Gross Physics 2004
Wolfgang Ketterle Physics 2001
Anthony J. Leggett Physics 2003
John C. Mather Physics 2006

Douglas D. Osheroff Physics 1996
James Peebles Physics 2019
Saul Perlmutter Physics 2011
William D. Phillips Physics 1997
H. David Politzer Physics 2004
Adam G. Riess Physics 2011
George F. Smoot Physics 2006
Horst L. Stormer Physics 1998
Joseph H. Taylor Jr. Physics 1993
Kip Stephen Thorne Physics 2017
Daniel C. Tsui Physics 1998
Steve Weinberg Physics 1979
Rainer Weiss Physics 2017
Carl E. Wieman Physics 2001
Frank Wilczek Physics 2004
Robert Woodrow Wilson Physics 1978

Message

From: Tabak, Lawrence (NIH/OD) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=02E22836B5FF4E9988E3770CFC7EE770-TABAKL]
Sent: 8/20/2020 1:40:14 AM
To: Collins, Francis (NIH/OD) [E] [redacted]
BCC: Tabak, Lawrence (NIH/OD) [E] [redacted]
Subject: Re: Science: NIH imposes 'outrageous' conditions on resuming coronavirus grant targeted by Trump

No surprise there...

From: Francis Collins [redacted]
Date: Wednesday, August 19, 2020 at 9:32 PM
To: "Tabak, Lawrence (NIH/OD) [E]" [redacted]
Subject: FW: Science: NIH imposes 'outrageous' conditions on resuming coronavirus grant targeted by Trump

Jeremy joins the ranks of righteous protest.

From: Fine, Amanda (NIH/OD) [E] [redacted]
Sent: Wednesday, August 19, 2020 9:07 PM
To: Collins, Francis (NIH/OD) [E] [redacted]; NIH Director's Executive Committee [redacted]
Cc: Burklow, John (NIH/OD) [E] [redacted]; OCPLPressTeam [redacted]
Subject: Science: NIH imposes 'outrageous' conditions on resuming coronavirus grant targeted by Trump

NIH imposes 'outrageous' conditions on resuming coronavirus grant targeted by Trump

By Meredith Wadman
Aug. 19, 2020 , 10:55 AM

The National Institutes of Health is requiring a small nonprofit research organization to take unusual—and perhaps impossible—steps to end a controversial suspension of an NIH grant related to bat coronavirus research in China. NIH's conditions for reinstating the funding to the EcoHealth Alliance are "outrageous," former NIH Director Harold Varmus **told *The Wall Street Journal* (*WSJ*) in an article published today** that first reported the agency's demands.

The controversy began in April, after President Donald Trump complained about NIH's grant to the EcoHealth Alliance because it involved researchers at China's Wuhan Institute of Virology (WIV). Conservative commentators, Trump, and Trump administration officials have asserted, without evidence, that the novel coronavirus that causes COVID-19 escaped from WIV. Shortly after Trump's complaint, **NIH abruptly canceled the grant**, stating that its goal of studying bat coronavirus spillovers into humans did not "align with … agency priorities." NIH's move drew extensive criticism from the scientific community.

Last month, NIH Deputy Director for Extramural Research Michael Lauer sent the EcoHealth Alliance a letter stating the agency was reinstating the grant, but also instantly suspending it again pending the completion of certain actions. (*Science*Insider has now independently reviewed a copy of the 8 July letter.) Among the conditions included:

- The EcoHealth Alliance must provide a sample of the pandemic coronavirus that WIV used **to determine its genetic sequence**.
- The group must arrange for an outside inspection of WIV and its records "with specific attention to addressing the question of whether WIV staff had SARS-CoV-2 in their possession prior to December 2019," Lauer wrote.
- The nonprofit must explain purported restrictions at WIV including "diminished cell-phone traffic in October 2019, and the evidence that there may have been roadblocks surrounding the facility from October 14-19, 2019."
- The nonprofit must "provide the NIH with WIV's responses to the 2018 Department of State cables regarding safety concerns."

NIH declined interview requests for Lauer and agency Director Francis Collins, saying in a statement: "NIH does not discuss internal deliberations on specific grants."

The EcoHealth Alliance said **in a statement** that "NIH's letter cynically reinstates and instantly suspends the EcoHealth Alliance's funding, then attempts to impose impossible and irrelevant conditions that will effectively block us from continuing this critical work."

Varmus, one of 77 Nobel laureates who **wrote to current NIH Director** Francis Collins in May demanding that he review the grant's initial cancellation, told *WSJ* that NIH's list of conditions for reinstating the funding "is outrageous, especially when a grant has already been carefully evaluated by peer review and addresses one of the most important problems in the world right now—how viruses from animals spill over to human beings."

Peter Daszak, the EcoHealth Alliance's president, called out Collins in an interview with *Science*Insider today, saying: "It undermines biomedical science to give in to politics. I think that's a failure. And I think that Dr. Collins fell at the first hurdle. When challenged by the White House to cancel this grant he just gave in."

Jeremy Berg, who directed NIH's National Institute of General Medical Sciences from 2003 to 2011, notes that Collins is a political appointee who serves at the president's pleasure. (Berg was also editor-in-chief of the *Science* family of journals until 2019.) He says: "The question for anybody in [such] a leadership position is: 'Is there a line that you are not willing to cross? And that you think it would be more appropriate to stand on principle and resign rather than to give in?' In my view, that line has been crossed with this."

With reporting by Kai Kupferschmidt.

***Update, 19 August, 5:10 p.m.:** This story has been updated to include additional material from NIH's 8 July letter to the EcoHealth Alliance, a statement from NIH, and comments from Jeremy Berg and Peter Daszak.*

Jeremy Farrar

When:	Sat Feb 01 19:00:00 2020 +00:00
Until:	Sat Feb 01 20:00:00 2020 +00:00
Organisers	"Fauci, Anthony (NIH/NIAID) [E]" <"/o=exchangelabs/ou=exchange administrative group (fydibohf23spdlt)/cn=recipients/cn=df38103d75134f658ae2d356f0396b94-afauci">
Required Attendees:	"Fauci, Anthony (NIH/NIAID) [E]" [redacted]

Francis S. Collins, M.D., Ph.D., Director
Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director
National Institutes of Health
Briefing for Secretary Becerra

Origin of SARS-CoV-2

July 6, 2021

Importance of Studying Coronaviruses

- SARS-CoV-2 is the third coronavirus to emerge in the 21st century
- In addition to SARS-CoV and MERS-CoV, evidence suggests the four endemic coronaviruses spilled over from animal reservoirs
- The cost of the COVID-19 pandemic exemplifies the need to understand the potential risks of coronaviruses and to be prepared if they emerge in the human population
  - Lives lost: >600K in U.S. and >3.9M worldwide
  - Economic loss as of Oct 2020: 16 trillion dollars in U.S. alone[1]

Cutler DM, Summers LH. JAMA. 2020

Early Timeline of SARS-CoV-2

- China confirmed that there were dozens of cases of unexplained pneumonia in Wuhan on Dec. 31, 2019
- Huanan Seafood Market initially suspected as epicenter of the epidemic; reminiscent of SARS epidemic in 2002-2004
- Market closed on Jan 1, 2020 for disinfection
- Subsequent investigations found that many early cases were associated with other markets or had no association to a market
- Limited investigations did not identify a zoonotic source of SARS-CoV-2

EcoHealth Alliance Grant

- Sought to understand how animal coronaviruses evolve naturally in the environment to become transmissible to humans
- Research included:
  - Studying viral diversity in bat reservoirs
  - Surveying people with high exposure to wildlife for evidence of bat coronavirus infection
  - Characterizing viruses to predict which potentially pose a threat to human health

EcoHealth Alliance Grant

- To support its work, EcoHealth made sub-awards to the Wuhan Institute of Virology (WIV) and other institutions based in China, where coronaviruses have emerged in the past and are prevalent
- <u>The grant did not propose research to enhance a coronavirus to be more transmissible or virulent</u>
- The terms of the grant were thoroughly reviewed by NIH staff, and detailed documentation shows that this grant did not meet the standards of gain of function research that would require high level oversight

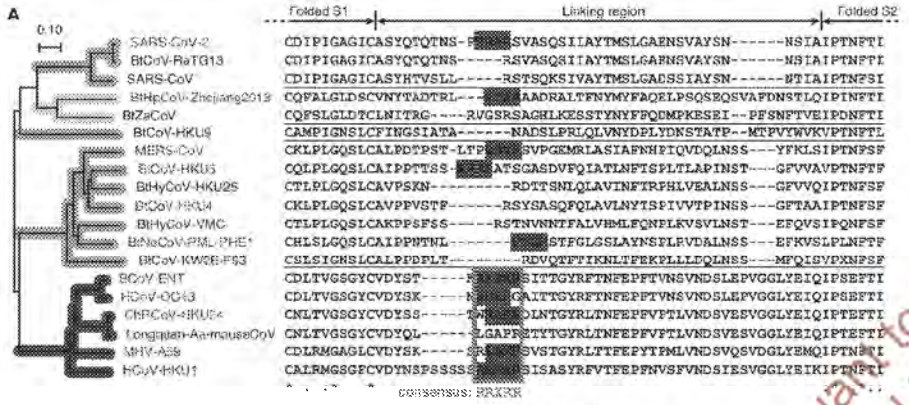
Viruses Studied Have Only A Distant Relationship to SARS-CoV-2

- A current narrative is that the experiments done in the EcoHealth grant are "gain-of-function" and thus could have led to SARS-CoV-2
- The research in this grant was carefully reviewed and determined not to be subject to the gain-of-function funding pause or P3CO framework
- Importantly, the viruses studied in the EcoHealth grant are very distant relatives and could not have led to SARS-CoV-2
- The closest bat virus reported by WIV (RaTG13) differs by >1100 nucleotides, representing decades of evolutionary divergence from SARS-CoV-2; other viruses studied in this grant are much more distant

Presence of A Furin Cleavage Site Is Not *A Priori* Evidence of Bioengineering

- SARS-CoV-2 requires cleavage of the spike glycoprotein to mediate membrane fusion
- SARS-CoV-2 has a furin cleavage site caused by a 12-nucleotide insertion not present in its closest relatives
- Some claim this is evidence of bioengineering
- Furin cleavage sites are common in other coronaviruses, and the lineage of viruses that led to SARS-CoV-2 is poorly sampled

Furin Cleavage Sites Are Common in Betacoronavirus Spike Proteins



Furin cleavage sites present in MERS-CoV, endemic human coronaviruses HCoV-HKU1 and HCoV-OC43, and other coronaviruses

Wu and Zhao, Stem Cell Res. 2020

Double CGG Sequence Is Also Not *A Priori* Evidence of Bioengineering

- Some contend that the presence of double CGG CGG arginine codons (in furin site) is exceedingly rare and thus evidence of bioengineering
- Despite being rare, CGG arginine codons are found in all coronaviruses
- Feline coronavirus furin cleavage site contains: CGG CGA
- Double CGG sequence found in at least 2 other coronaviruses
- Again, the NIH did not approve research to manipulate a coronavirus to increase its virulence or transmissibility

Precedent for Zoonotic Origin

- Many viruses have emerged from animals to cause epidemics/pandemics, including influenza, Ebola, Zika, West Nile virus, SARS and other coronaviruses
- SARS-CoV spilled over into humans in large cities in the Guangdong province of China in 2002-3
- Both SARS-CoV events were associated with live animal markets and involved species that were present in Wuhan markets in 2019[1]
- Serological surveys found ~3% positivity rates in residents living close to bat caves in the Yunnan province suggesting regular exposure to SARS-CoV related viruses[2]

[1]Xiao et al. Sci Rep. 2021
[2]Wang et al. Virologica Sinica. 2018

Bloom Paper on "deleted" sequence

- Identified 13 partial SARS-CoV-2 genomes from Wuhan, China from early epidemic
- Sequences had been deposited in NIH database and then removed at request of investigator – but were available in an online publication
- Findings consistent with prior studies:
  - Huanan Seafood Market unlikely the original source of pandemic
  - The virus was likely circulating in humans for weeks prior to the December outbreak in Wuhan
- No obvious implications for or against lab leak theory
- The great difference in sequences between bat virus and SARS-CoV-2 means researchers cannot use a few mutations (~3) to look back in time to see the "roots" of the family tree of SARS-CoV-2.

Conclusions And Next Steps

- Based on the mutation rate of SARS-CoV-2, virus was likely circulating in humans for weeks prior to the December outbreak in Wuhan
- Historic precedent and epidemiologic links to animal markets suggest SARS-CoV-2 evolved through natural transmission from animals to humans, but it will be important to confirm the origin of the pandemic to inform strategies needed to prevent future outbreaks
- Cannot rule out the possibility that SARS-CoV-2 or its proximal progenitor was under secret study at WIV and was accidentally released – but there is no compelling evidence to support this.
- The key to resolving the origin of SARS-CoV-2 is further investigation of early cases, animal reservoirs, and WIV records
- NIH fully supports the expert-driven investigations by the U.S. Intelligence community and the World Health Organization into the origin of the COVID-19 pandemic

Message

From: Lauer, Michael (NIH/OD) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=90FE9CAE30C64CFBB67ABD568E882796-LAUERM]
Sent: 11/10/2021 5:00:54 PM
To: Tabak, Lawrence (NIH/OD) [E] [redacted]
CC: Lauer, Michael (NIH/OD) [E] [redacted]
Subject: Re: Editorial running tomorrow
Attachments: 1112Editorial_Thorp_D[1].pdf

Flag: Follow Up

Thanks Larry. He's remarkably clueless. I wonder why he didn't contact us to at least talk on background.

Mike

From: "Tabak, Lawrence (NIH/OD) [E]" [redacted]
Date: Wednesday, November 10, 2021 at 11:58 AM
To: "Lauer, Michael (NIH/OD) [E]" [redacted]
Subject: FW: Editorial running tomorrow

fyi

From: Francis Collins [redacted]
Date: Wednesday, November 10, 2021 at 11:39 AM
To: "Myles, Renate (NIH/OD) [E]" [redacted] "Burklow, John (NIH/OD) [E]" [redacted] "Tabak, Lawrence (NIH/OD) [E]" [redacted] Anthony Fauci [redacted]
Subject: FW: Editorial running tomorrow

You won't love this. I certainly didn't.

FC

From: Holden Thorp [redacted]
Sent: Wednesday, November 10, 2021 11:27 AM
To: Collins, Francis (NIH/OD) [E] [redacted]
Subject: Editorial running tomorrow

Francis – this is running tomorrow, FYI. I hope you think it's a fair assessment of where things stand on EcoHealth. Hang in there.
Holden

Holden Thorp
Editor-in-Chief, Science Family of Journals
1200 New York Ave NW
Washington, DC 20005
Cell: [redacted]
[redacted]g

EDITORIAL

Self-inflicted wounds

H. Holden Thorp
Editor-in-Chief, *Science* journals.
[redacted]
@hholdenthorp

It has been a rough couple of weeks for scientific public relations regarding COVID-19. Missteps by researchers and funding agencies around the origins of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have provided fodder for conspiracy theorists, and caveats about the children's vaccine have provided more ammo for anti-vaxxers. None of these miscues say anything substantive about the science and the conclusion that the virus is almost certainly of zoonotic origin and that the vaccine is safe for children. But clumsy behavior is more eye-catching than the details of research, especially when scientists are so often held to unrealistic standards, expected to be both experts in their fields and skilled communicators.

The latest round of foibles on the origin of SARS-CoV-2 began with the release of an unfunded grant proposal that was submitted in 2018 to the US Defense Advanced Research Projects Agency by the nonprofit EcoHealth Alliance. The proposal featured EcoHealth's president, Peter Daszak, as the principal investigator, and several coronavirus researchers from the University of North Carolina (UNC) at Chapel Hill, the Wuhan Institute of Virology, and Duke-National University of Singapore Medical School. It described experiments to introduce proteolytic cleavage sites into SARS-like coronaviruses. Such a site in SARS-CoV-2 (cleaved by furin) enables the virus to efficiently infect human cells. How the furin cleavage site wound up in the virus is a focus of debate over the origins of the pandemic. Never mind that the experiments, which hardly posed a threat, were not conducted and were proposed by UNC scientists. The researchers failed to get ahead of the story. They should have known that the proposal would arouse interest, especially because the collaborators included scientists at the Wuhan Institute of Virology and US scientists. When the rejected proposal was "leaked," it looked like the scientists were hiding something. This misstep has nothing to do with SARS-CoV-2's origin, but it nevertheless looked suspicious.

Another misstep occurred when the US National Institutes of Health (NIH) sent a letter to Congress chastising EcoHealth for failing to promptly report an "unexpected result" where a bat coronavirus became more infectious than anticipated in laboratory mice. Nothing about this experiment suggests that the new virus could have become SARS-CoV-2, but the assertion that EcoHealth was late in submitting a report that it knew would be explosive again struck detractors as suspicious. EcoHealth stumbled yet again when earlier this fall a spokesman incorrectly said that the organization had not modified a different coronavirus (one that causes Middle East respiratory syndrome) and then walked back the statement, needlessly provoking suspicion among antiscience forces. Matters were not helped when NIH Director Francis Collins appeared on CNN and struggled to answer questions without seeming to contradict himself. He blamed EcoHealth for not complying with the grant but also said that the experiments didn't meet the standard of problematic gain-of-function research and that NIH didn't fail in monitoring. Collins's performance is understandable: There are details here that are hard to explain in a cable news hit.

> **"...by seeming to contradict themselves, scientists look like they can't get their stories straight..."**

Miscues like these are not limited to SARS-CoV-2 origins. Last week, when the Vaccines and Related Biological Products Advisory Committee met to advise the US Food and Drug Administration on the Pfizer vaccine for children ages 5 to 11, one member abstained and issued a statement implying that the vaccine was inadequately tested and marginally effective—another scrap to be exploited by anti-vaxxers. Once again, by seeming to contradict themselves, scientists look like they can't get their stories straight and are hiding facts.

These events raise questions about the responsibilities of scientists. These miscues could be honest mistakes or simply people disagreeing. Should scientists be expected to be perfect at communicating and coordinating messages? Scientists have consistently put forward a picture of themselves as highly objective automatons governed solely by their data, when in reality, science is a messy, human process subject to all features of human frailty. Scientists are expected to balance this reality with the fact that their every word and action, when it comes to the pandemic, is under intense scrutiny.

It may seem unfair that scientists are being held to such a high standard. But that is where we find ourselves right now. So, let's strive to be much more thoughtful, because ineptness can cut deep and damaging wounds.

–H. Holden Thorp

PHOTO: CAMERON DAVIDSON

10.1126/science.abn1244

Message

From: Marston, Hilary (NIH/NIAID) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=AB30660917B942FFBA9AE95D631116F3-MARSTONHD]
Sent: 1/28/2020 12:03:47 AM
To: Folkers, Greg (NIH/NIAID) [E] [redacted] Fauci, Anthony (NIH/NIAID) [E] [redacted]
CC: Morens, David (NIH/NIAID) [E] [redacted] Doepel, Laurie (NIH/NIAID) [E] [redacted]
Eisinger, Robert (NIH/NIAID) [E] [redacted] Lerner, Andrea (NIH/NIAID) [E] [redacted]
Subject: RE: some background on our support of the EcoHealth group

Ralph and Peter are two of the main grantees that we are drawing on for this start up work. Thanks for sharing the summary David!

From: Folkers, Greg (NIH/NIAID) [E] [redacted]
Sent: Monday, January 27, 2020 6:09 PM
To: Fauci, Anthony (NIH/NIAID) [E] [redacted]
Cc: Morens, David (NIH/NIAID) [E] [redacted] Doepel, Laurie (NIH/NIAID) [E] [redacted]
Eisinger, Robert (NIH/NIAID) [E] [redacted] Folkers, Greg (NIH/NIAID) [E] [redacted]
Lerner, Andrea (NIH/NIAID) [E] [redacted] Marston, Hilary (NIH/NIAID) [E] [redacted]
Subject: some background on our support of the EcoHealth group

Thanks david
"In short, we have on our team (I.e., these folks we fund, Peter, Ralph, Ian, etc.) probably the world's experts in these non-human coronaviruses."

From: Morens, David (NIH/NIAID) [E] [redacted]
Sent: Monday, January 27, 2020 5:04 PM
To: Folkers, Greg (NIH/NIAID) [E] [redacted]
Subject:

Hi Greg,

some background on our support of the EcoHealth group (Peter Daszak et al), which has for years been among the biggest players in coronavirus work, also in collaboration with Ralph Baric, Ian Lipkin and others. I have been getting some of this info from Peter, and Tony may wish to be aware if he isn't already.

NIAID has been funding Peter's group for coronavirus work in China for the past 5 years through R01 1R01AI110964: "Understanding the Risk of Bat Coronavirus Emergence". That's now been renewed, with a specific focus to identify cohorts of people highly exposed to bats in China, and work out if they're getting sick from CoVs. Erik Stemmy is the Program Officer. Collaborators include Wuhan Institute of Virology (currently working on the nCoV), and Ralph Baric. The results of the work to date include:

- Sampled 10,074 bats and ~2,000 other mammals at 47 sites across S. China
- Discovered 172 novel β-CoVs (52 novel SARSr-CoVs), >350 novel α-CoVs
- Discovered closest relative to Wuhan nCoV (92% homology)
- Discovered Swine Acute Diarrheal Syndrome Virus (SADS-CoV) killing >25,000 pigs in Guangdong Province (Published in *Nature*)
- Found SARS-related CoVs that can bind to human cells (Published in *Nature*), and that cause SARS-like disease in humanized mouse models.

- Found that clinical signs of bat SARSr-CoVs in mice were not prevented with a vaccine candidate against SARS-CoV, and were not treatable with most monoclonal therapies being developed
- Found serological evidence that 3% of people living at the wildlife-human interface in rural China are being exposed to these bat SARS-related coronaviruses

Also – prior to the above R01, Peter's folks worked under an R01 with Eun-Chung Park as Program Officer on viral discovery in bats, and originally identified SARS-CoV as having a likely origin in bats (published in *Science*)

In short, we have on our team (I.e., these folks we fund, Peter, Ralph, Ian, etc.) probably the world's experts in these non-human coronaviruses.

I think this outbreak, however it plays out, is a wake up call that we need to do more. It's happened 3 times in 17 years, and it will happen again. If we dodge this bullet, we might not be as lucky next time.

David

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☎ [redacted] (assistants: Kimberly Barasch, Whitney Robinson)
[redacted]
[redacted]

Message

From: Tabak, Lawrence (NIH/OD) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=02E22836B5FF4E9988E3770CFC7EE770-TABAKL]
Sent: 4/15/2020 2:58:57 PM
To: Collins, Francis (NIH/OD) [E] [redacted] Fauci, Anthony (NIH/NIAID) [E] [redacted]
CC: Erbelding, Emily (NIH/NIAID) [E] [redacted] Fenton, Matthew (NIH/NIAID) [E] [redacted] Marston, Hilary (NIH/NIAID) [E] [redacted] Lauer, Michael (NIH/OD) [E] [redacted] Schwetz, Tara (NIH/OD) [E] [redacted] Wolinetz, Carrie (NIH/OD) [E] [redacted]
Subject: HEADS UP: Wuhan lab research

Importance: High

Francis, Tony -

The **WH has strongly embraced concerns** raised by Congressman Gaetz who is publicly criticizing HHS/NIH for funding the Wuhan laboratory's bat research. Here's this quote from another article: "I'm disgusted to learn that for years the US government has been funding dangerous and cruel animal experiments at the Wuhan Institute, which may have contributed to the global spread of coronavirus, and research at other labs in China that have virtually no oversight from US authorities."

This is a large multi- country study with Wuhan being one site. The principal investigator, Peter Daszak, is based in NY at Ecohealth Alliance, Inc

Project Number:	2R01AI110964-06	**Contact PI / Project Leader:**	DASZAK, PETER
Title:	UNDERSTANDING THE RISK OF BAT CORONAVIRUS EMERGENCE	**Awardee Organization:**	ECOHEALTH ALLIANCE, INC.

https://projectreporter.nih.gov/project_info_description.cfm?aid=9819304&icde=49588715&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

The 3.7M dollar figure is the total over 6 years to all sites which include (several in) China, Thailand, Cambodia, Laos, Vietnam, Malaysia, Indonesia, and Myanmar. We estimate that approximately 826,300 has been spent at this site since the inception of the grant. Yearly costs appear to be about 80K/year. It is in year 6 of a total of 10 year.

More by phone.
Larry

Message

From: Fauci, Anthony (NIH/NIAID) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=DF38103D75134F658AE2D356F0396B94-AFAUCI]
Sent: 2/1/2020 2:00:36 PM
To: Collins, Francis (NIH/OD) [E] [redacted]
Subject: FW: IMPORTANT
Attachments: Baric, Shi et al - Nature medicine - SARS Gain of function.pdf

Flag: Follow up

From: Fauci, Anthony (NIH/NIAID) [E]
Sent: Saturday, February 1, 2020 8:19 AM
To: Tabak, Lawrence (NIH/OD) [E] [redacted]
Subject: FW: IMPORTANT

Here it is

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SARS-like cluster of circulating bat coronavirus pose threat for human emergence

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Abstract

The emergence of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome (MERS)-CoV underscores the threat of cross-species transmission events leading to outbreaks in humans. In this study, we examine the disease potential for SARS-like CoVs currently circulating in Chinese horseshoe bat populations. Utilizing the SARS-CoV infectious clone, we generated and characterized a chimeric virus expressing the spike of bat coronavirus SHC014 in a mouse adapted SARS-CoV backbone. The results indicate that group 2b viruses encoding the SHC014 spike in a wild type backbone can efficiently utilize multiple ACE2 receptor orthologs, replicate efficiently in primary human airway cells, and achieve *in vitro* titers equivalent to epidemic strains of SARS-CoV. Additionally, *in vivo* experiments demonstrate replication of the chimeric virus in mouse lung with notable pathogenesis. Evaluation of available SARS-based immune-therapeutic and prophylactic modalities revealed poor efficacy; both monoclonal antibody and vaccine approaches failed to neutralize and protect from CoVs utilizing the novel spike protein. Importantly, based on these findings, we synthetically rederived an

Corresponding Authors: Ralph S. Baric [redacted] Vineet D. Menachery [redacted]

Author Contributions

VDM designed, coordinated, performed experiment, completed analysis, and wrote the manuscript. BLY designed infectious clone and recovered chimeric viruses. SA completed neutralization assays. LEG helped perform mouse experiments, TS and JAP completed mouse experiments and plaque assays. XG performed pseudotyping experiments. KD generated structural figures and predictions. ED generated phylogenetic analysis. RLG completed RNA analysis. SHR provided primary human airway epithelial cultures. AL and WM provided critical monoclonal antibody reagents. ZLS provided SHC014 spike sequences and plasmids. RSB designed experiments and wrote manuscript.

The authors declare no competing financial interest.

infectious full length SHC014 recombinant virus and demonstrate robust viral replication both *in vitro* and *in vivo*. Together, the work highlights a continued risk of SARS-CoV reemergence from viruses currently circulating in bat populations.

Introduction

Emergence of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) heralded a new era in the cross-species transmission of severe respiratory illness[1,2]. Since then, several strains, including influenza A H5N1, H1N1, H7N9, and Middle East Respiratory Syndrome (MERS) CoV have emerged from animal populations causing considerable disease and mortality[3]. While public health measures silenced the SARS-CoV outbreak[2], recent metagenomics studies have identified sequences of closely related SARS-like viruses circulating in Chinese bat populations that may pose a future threat[4,5]. However, sequence data alone provides minimal insights to identify and prepare for future pre-pandemic viruses. Therefore, to examine emergence potential of circulating CoVs, we built a chimeric virus that encodes a novel, zoonotic spike protein in the context of a viable CoV backbone. This approach characterized the threat posed by SHC014-CoV spike in primary human airway cells, *in vivo*, as well as the efficacy of available immune therapeutics. Together, the strategy translates metagenomics data to help predict and prepare for future emergent viruses.

Results

SHC014 and WIV1 sequences represent the closest relatives to the epidemic SARS-CoV strains (Fig. 1 a,b), but maintain important differences in the 14 residues that bind human ACE2, including the five critical for host range: Y442, L472, N479, T487, and Y491[6]. In WIV1, three of these residues vary from SARS-CoV Urbani, but were not expected to alter binding (Supplementary Fig. 1a, b, Supplementary Table 1). This fact is confirmed by both pseudotyping experiments (Supplementary Fig. 1d) and *in vitro* replication of WIV1-CoV[5]. In contrast, seven of the 14 ACE2 interaction residues in SHC014 are different than SARS-CoV, including all five critical residues (Supplementary Fig. 1c, Supplementary Table 1). These changes, coupled with failure of pseudotyping (Supplementary Fig. 1d), suggested that SHC014 spike is unable to bind human ACE2. However, similar changes had been reported to convey ACE2 binding in related SARS-CoV strains[6,7] and thus suggested functional testing was required for verification. Therefore, we synthesized the SHC014 spike in the context of the replication competent, mouse-adapted SARS-CoV backbone (SHC014-MA15) (Supplementary Fig. 2a). Despite predictions from both structure-based modeling and pseudotyping experiments, SHC014-MA15 was viable and replicated to high titers in Vero cells (Supplementary Fig. 2b). Similar to SARS, SHC014-MA15 also required a functional ACE2 molecule for entry, but uses human, civet, and bat orthologs (Supplementary Fig. 2c, d). To test the ability of SHC014 spike to mediate infection of the human airway, we examined 2B4 Calu-3 cells, a human epithelial airway cell line[8], and found robust SHC014-MA15 replication comparable to SARS-CoV Urbani (Fig. 1c). To extend these findings, primary human airway epithelial cultures (HAEs) were infected and indicated robust replication of both viruses (Fig. 1d). Together, the data confirm the ability

of SHC014 spike to infect human airway cells and underscore the threat of cross-species transmission.

We next evaluated *in vivo* infection of 10-week old BALB/c mice with 10^4 plaque-forming units (PFU) of either SARS-MA15 or SHC014-MA15 (Fig. 1e–h). Animals infected with SARS-MA15 experienced rapid weight loss and lethality by four days post infection (DPI); in contrast, SHC014-MA15 produced substantial weight loss (10%), but no lethality (Fig. 1e). Examination of viral replication revealed nearly equivalent titers from lungs of mice infected with SARS-MA15 and SHC014-MA15 (Fig. 1f). While SARS-CoV MA15 produced robust staining in both the terminal bronchioles and the lung parenchyma 2 DPI (Fig. 1g), SHC014-MA15 had a deficit in airway antigen staining (Fig. 1h). In contrast, no equivalent deficit was observed in the parenchyma or overall histology scoring, suggesting differential infection following SHC014-MA15 (Supplementary Table 2). Shifting to more susceptible aged animals, SARS-MA15 infected animals rapidly lost weight and succumb to infection (Supplementary Fig. 3 a, b); SHC014-MA15 induced robust and sustained weight loss, but had minimal lethality. Histology and antigen staining trends observed in young mice were conserved in the older animals (Supplementary Table 3). We excluded use of an alterative receptor based on $Ace2^{-/-}$ mice infection, which did not produce weight loss or antigen staining following SHC014-MA15 infection (Supplementary Fig. 4a, b; Supplementary Table 2). Together, the data indicate that viruses utilizing SHC014 spike are capable of inducing considerable disease in mice in the context of a virulent CoV backbone.

Given the efficacy of Ebola monoclonal antibody therapies like ZMApp[9], we next sought to determine the efficacy of SARS-CoV monoclonal antibodies against SHC014-MA15. Four broadly neutralizing human monoclonal antibodies had been previously reported and are likely reagents for immunotherapy[10–12]. Examining percent inhibition, wild-type SARS-CoV Urbani was strongly neutralized by all four antibodies at relatively low antibody concentrations (Fig. 2a–d). In contrast, neutralization varied for SHC014-MA15. Fm6, an antibody generated by phage display and escape mutants[10,11], achieved only background levels of inhibition of SHC014-MA15 (Fig. 2a). Similarly, antibodies 230.15 and 227.14, derived from memory B cells of SARS-CoV infected patients[12], also failed to block SHC014-MA15 (Fig. 2b, c). For all three antibodies, differences between SARS and SHC014 spikes corresponded to direct or adjacent residue changes found in escape mutants (fm6 - N479R; 230.15 - L443V; 227.14- K390). Finally, monoclonal antibody 109.8 was able to achieve 50% neutralization of SHC014-MA15, but only at very high concentrations (Fig. 2d). Together, the results demonstrate that despite the development of broadly neutralizing antibodies against SARS-CoV, these reagents may only have marginal efficacy against emergent SARS-like CoV strains like SHC014.

To evaluate existing vaccines against SHC014-MA15, aged mice were vaccinated with double-inactivated whole SARS-CoV (DIV). Previously, DIV had shown neutralization and protection from homologous virus challenge[13], but vaccine failure and augmented immune pathology in aged animals indicated a possibility for harm due to vaccination[14]. In this study, DIV provided no protection from SHC014-MA15 in regards to weight loss or viral titer (Supplementary Fig. 5a, b). Consistent with previous reports[14], serum from DIV-vaccinated aged mice also failed to neutralize SHC014-MA15 (Supplementary Fig. 5c).

Perhaps most importantly, DIV vaccination resulted in robust immune pathology (Supplementary Table 4) and eosinophilia (Supplementary Fig. 5d–f). Together, these results confirm DIV vaccine failure and illustrated augmented disease for the aged vaccinated group.

In contrast to DIV, SHC014-MA15 challenge as a vaccine showed promise, but with important caveats. Utilizing a high dose, we infected young mice with SHC014-MA15 and followed over 28-days; the mice were subsequently challenged with SARS-MA15 (Supplementary Fig. 6a). Prior high-dose infection with SHC014-MA15 conferred protection against lethal SARS-MA15 challenge, but only minimal SARS-CoV neutralization response from SHC014-MA15 antisera (Supplementary Fig. 6b, 1/200) implying diminished protection over time. Similar results were observed in aged BALB/C mice in terms of weight loss and viral replication (Supplementary Fig. 6c, d). However, this infection dose induced > 10% weight loss and lethality in some aged animals (Fig. 1 and Supplementary Fig. 3). Using low-dose infection, SHC014-MA15 failed to protect aged animals from lethal SARS-CoV challenge (Supplementary Fig. 6e, f). Together, the data suggest that SHC014-MA15 challenge can confer cross-protection against SARS-CoV through conserved epitopes, but requires a dose that induces pathogenesis.

Having established SHC014 spike as a potential threat, we next synthesized a full-length SHC014-CoV infectious clone based on the approach used for SARS-CoV (Fig. 3a)[15]. Replication in Vero cells revealed no deficit for SHC014-CoV relative to SARS-CoV (Fig. 3b); however, SHC014-CoV was significantly ($p < 0.01$) attenuated in primary human airway epithelial cultures at both 24 and 48 hours post infection (Fig. 3c). *In vivo* infection demonstrated no significant weight loss, but defined reduced viral replication for full length SHC014-CoV infection compared to SARS-CoV Urbani (Fig. 3d, e). Together, the results establish the viability of full length SHC014-CoV, but suggest further adaptation is required to be equivalent to epidemic SARS-CoV replication in human respiratory cells and in mice.

During the SARS-CoV epidemic, links were quickly established between palm civets and coronavirus strains detected in humans[2]. Building upon this finding, the common emergence paradigm argued that epidemic SARS-CoV originated as a bat virus, jumped to civets, and incorporated changes within the RBD to improve binding to civet *Ace2*[16]. Subsequent exposure to humans in live markets permitted infection with the civet strain, which, in turn, adapted to become the epidemic strain (Fig. 4a). However, phylogenetic analysis suggested that early human SARS strains appear more closely related to bat than civet strains[16]. Therefore, a second paradigm argued that direct bat-human transmission initiated SARS-CoV emergence, with palm civets serving as a secondary host and reservoir for continued infection (Fig. 4b,[17]). For both paradigms, spike adaptation in a secondary host is seen as a necessity, with most mutations expected within the RBD and facilitating improved infection. Both theories imply that pools of bat CoVs are limited and host range mutations are both random and rare, reducing the likelihood of future emergence events in humans.

While not invalidating the other emergence routes, the current study argues for a third paradigm in which circulating bat CoV pools maintain "poised" spike proteins capable of infecting humans without mutation or adaptation (Fig. 4c). Illustrated with SHC014 spike in

the SARS-CoV backbone, robust infection occurs in both human airway cultures and *in vivo* without RBD adaptation. Coupled with previous identification of pathogenic CoV backbones[1,18], the results suggest that the starting materials required for SARS-like emergent strains are currently circulating in animal reservoirs. Importantly, while full-length SHC014-CoV likely requires additional backbone adaption to mediate human disease, the documented high frequency recombination events in CoV families underscores the possibility of future emergence and the need for further preparation.

To date, genomics screens of animal populations have primarily been used to identify novel viruses in outbreak settings[19]. The approach in this manuscript extends these datasets to examine questions of emergence and therapeutic efficacy. For the SHC014 spike, we define a threat due to replication in primary human airway cultures, the best available model for human disease. In addition, pathogenesis in mice indicates a capacity to cause disease in mammalian models without RBD adaptation. Notably, differential tropism in the lung and attenuation of full-length SHC014-CoV in HAE cultures suggest factors beyond ACE2 binding may contribute to emergence including spike processivity, receptor bio-availability, or antagonism of the host immune responses. However, further testing in non-human primates is required to translate these finding into pathogenic potential in humans. Importantly, the failure of available therapeutics defines a critical need for further study and treatment development. With this knowledge, surveillance programs, diagnostic reagents, and effective treatments can be produced to protect from emergence of group 2b specific CoVs like SHC014 as well as other CoV branches that maintain similar heterogeneous pools.

While offering preparation against future emerging viruses, this approach must be considered in the context of the US government-mandated pause on gain of function (GOF) studies[20]. Based on previous models of emergence (Fig. 4a, b), the creation of chimeric viruses like SHC014-MA15 was not expected to increase pathogenicity. However, while SHC014-MA15 is attenuated relative to parental mouse adapted, equivalent studies examining the wild-type Urbani spike within the MA15 backbone produced no weight loss and replication attenuation[21]. As such, relative to the Urbani Spike-MA15 CoV, SHC014-MA15 constitutes a gain in pathogenesis (Fig. 1). Based on these findings, review panels may deem similar studies too risky to pursue as increased pathogenicity in mammalian models cannot be excluded. Coupled with restrictions on mouse adapted strains and monoclonal antibodies generated against escape mutants, research into CoV emergence and therapeutic efficacy may be severely limited moving forward. Together, these data and restrictions represent a crossroads of GOF research concerns; the potential to prepare and mitigate future outbreaks must be weighed against the risk of creating more dangerous pathogens. In developing policies moving forward, it is important to consider the value of the data generated by these studies and if they warrant further study or the inherent risks involved.

Overall, our approach has used metagenomics data to identify a threat posed by circulating bat SARS-like CoV SHC014. With the ability to replicate in human airway cultures, produce *in vivo* pathogenesis, and escape current therapeutics, SHC014 chimeric viruses illustrate the need for both surveillance and improved therapeutics against circulating SARS-

like viruses. The approach also unlocks metagenomics data to predict viral emergence with possible applications for preparing to treat future emerging virus infections.

Online Methods

Viruses, Cells, In Vitro Infection, and Plaque Assays. Wild-type SARS-CoV (Urbani), mouse adapted SARS-CoV (MA15) and chimeric SARS-like CoVs were cultured on Vero E6 cells, grown in DMEM (Gibco, CA) and 5% Fetal Clone Serum (Hyclone, South Logan, UT) along with anti/anti (Gibco, Carlsbad, CA). DBT cells expressing ACE2 orthologs have been previously described for both human and civet; bat ACE2 sequence based on *Rhinolophus leschenaulti* and established as described previously[22]. Pseudotyping experiments were based on HIV-based pseudovirus prepared as previously described[23] and examined on HeLa cells expressing ACE2 orthologs grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum (Gibco) as previously described[24]. Growth curves in Vero, DBT, Calu-3 2B4, and primary human airway epithelial cells were performed as previously described[22, 25]. Vero E6 cells were originally obtained from USAMRIID; Calu3 cells were originally provided by Dr. CT Tseng, Universtiy of Texas Medical Branch; none of the cell line working stocks have not been recently authenticated or tested for mycoplasma, although the original seed stocks used to create the working stocks are free from contamination. HIuman lungs for HAE cultures were procured under University of North Carolina at Chapel Hill Institutional Review Board-approved protocols and represent highly differentiated human airway epithelium containing ciliated and non-ciliated epithelial cells as well as goblet cells. The cultures are also grown on an air-liquid interface for several weeks prior to use as previously described[26]. Briefly, cells were washed with PBS, and inoculated with virus or mock diluted in PBS for 40 minutes at 37 °C. Following inoculation, cells were washed 3 times, and fresh media added to signify time 0. Three or more biological replicates were harvested at each described time point. No blinding was used in any sample collections nor were samples randomized. All virus cultivation was performed in a BSL3 laboratory with redundant fans in Biosafety Cabinets as described previously by our group. All personnel wore Powdered Air Purifying Respirator (3M breathe easy) with Tyvek suits, aprons, booties and were double-gloved.

Sequence Clustering and Structural Modeling

The full-length genome sequences and S1 domains of spike amino acid sequences of representative CoVs were downloaded from Genbank or PATRIC, aligned with ClustalX, and phylogenetically compared by Maximum Likelihood using 100 bootstraps or with the PhyML package respectively. The tree was generated using Maximum Likelihood with the PhyML package. The scale bar represents nucleotide substitutions. Only nodes with bootstrap support above 70% are labeled. The tree shows that CoVs are divided into three distinct phylogenetic groups defined as α, β, and γ. Classical subgroup clusters are marked as 2a–2d for β CoVs and 1a and 1b for the α CoVs. Structural models were generated using Modeller (Max Planck Institute Bioinformatics Toolkit) to generate homology models for SHC014 and Rs3367 of the SARS RBD in complex with ACE2 based on crystal structure 2AJF (RCSB PBD identifier). Homology models were visualized and manipulated in MacPyMol (version 1.3).

Construction of chimeric SL-Viruses

Both wild-type and chimeric viruses were derived from either SARS-CoV Urbani or corresponding mouse adapted (MA15) infectious clone as previously described[27]. Plasmids containing spike sequences for SHC014 were extracted by restriction digest and ligated into the E and F plasmid of the MA15 infectious clone. The clone was designed and purchased from Bio Basic as six contiguous cDNAs using published sequences flanked by unique class II restriction endonuclease sites (BglI). Thereafter, plasmids containing wild-type, chimeric SARS-CoV and SHC014-CoV genome fragments were amplified, excised, ligated, and purified. In vitro transcription reactions were then preformed to synthesize full-length genomic RNA, which was transfected into Vero E6 cells as previously described[28]. The media from transfected cells were harvested and served as seed stocks for subsequent experiments. Chimeric and full length viruses were confirmed by sequence analysis prior to use in these studies. Synthetic construction of chimeric mutant and full length SHC014-CoV were approved by the University of North Carolina Institutional Biosafety Committee and the Dual Use Research of Concern committee.

Ethics Statement

This study was carried out in accordance with the recommendations for care and use of animals by the Office of Laboratory Animal Welfare (OLAW), National Institutes of Health. The Institutional Animal Care and Use Committee (IACUC) of The University of North Carolina at Chapel Hill (UNC, Permit Number A-3410-01) approved the animal study protocol (IACUC #13-033) followed in this manuscript.

Mice & In Vivo Infection

Female 10 week and 12 month old Balb/cAnNHsD mice were ordered from the Harlan Labs. Mouse infections occurred as previously described[29]. Briefly, animals were brought into a biosafety lab level 3 and allowed to acclimate for 1 week prior to infection. For infection and live-attenuated virus vaccination, mice were anesthetized with a mixture of ketamine and xylazine and infected intranasally when challenged with 50 μl of phosphate-buffered saline (PBS) or diluted virus with three to four mice per time point, per infection group per dose as described in the figure legends. For individual mice, notations for infection including failure to inhale entire dose, bubbling of inoculum from nose, or infection through the mouth may lead to exclusion of mouse data at discretion of the researcher; post-infection, no other pre-established exclusion/inclusion criteria are defined. No blinding was used in any animal experiments and animals were not randomized. For vaccination, young and aged mice were vaccinated by footpad injection with a 20 μl volume of either 0.2 μg of double-inactivated SARS-CoV vaccine with alum or mock PBS; mice were then boosted with the same regimen 22 days later, and challenged 21 days thereafter. For all groups, as per protocol, animals were monitored daily for clinical signs of disease (hunching, ruffled fur, reduced activity) for the duration of the experiment. Weight loss was monitored daily for the first 7 days after which, weight monitoring continued until the animals recovered to their initial starting weight or displayed three continuous days of weight gain. All mice losing greater than 20% of their starting body weight were ground fed and further monitored multiple times per day as long as they were under the 20% cutoff.

Mice losing greater than 30% of their starting body weight were immediately sacrificed as per protocol. Any mouse deemed to be moribund or unlikely to recover were also humanly sacrificed at the discretion of the researcher. Euthanasia was preformed via isoflurane overdose and confirmation of death by cervical dislocation. All mouse studies were performed at the University of North Carolina (Animal Welfare Assurance #A3410-01) using protocols approved by the UNC Institutional Animal Care and Use Committee (IACUC).

Histological Analysis

The left lung was removed and submerged in 10% buffered formalin (Fisher) without inflation for 1 week. Tissues were embedded in paraffin, and 5 μm sections were prepared by the UNC Lineberger Comprehensive Cancer Center histopathology core facility. To determine the extent of antigen staining, sections were stained for viral antigen using a commercially available polyclonal SARS-CoV anti-nucleocapsid antibody (Imgenex) and scored in a blinded manner by for staining of the airway and parenchyma as previously described[29]. Images were captured using an Olympus BX41 microscope with an Olympus DP71 camera.

Virus Neutralization Assays

Plaque reduction neutralization titer assays were performed with previously characterized antibodies against SARS-CoV as previously described[30–32]. Briefly, nAbs or serum were serially diluted 2-fold and incubated with 100 PFU of the different icSARS-CoV strains for 1 h at 37°C. The virus and antibodies were then added to a 6-well plate with 5×10^5 Vero E6 cells/well with $N \geq 2$. After a 1-h incubation at 37°C, cells were overlaid with 3 ml of 0.8% agarose in media. Plates were incubated for two days at 37° C and then stained with neutral red for 3 hours, and plaques were counted. The percentage of plaque reduction was calculated as [1 − (no. of plaques with antibody/no. of plaques without antibody)] × 100.

Statistical Analysis

All experiments were conducted contrasting two experimental groups (either two viruses, or vaccinated and unvaccinated cohorts). Therefore, significant differences in viral titer and histology scoring were determined by a two-tailed student's t test at individual time points. Data was normally distributed in each group being compared and had similar variance.

Biosafety and biosecurity

Reported studies were initiated after the University of North Carolina Institutional Biosafety Committee approved the experimental protocol: Project Title: Generating infectious clones of Bat SARS-like CoVs; Lab Safety Plan ID: 20145741; Schedule G ID: 12279. These studies were initiated prior to the U.S. Government Deliberative Process Research Funding Pause on Selected Gain of Function Research Involving Influenza, MERS, and SARS Viruses (http://www.phe.gov/s3/dualuse/Documents/gain-of-function.pdf), and the current manuscript has been reviewed by the funding agency, the National Institutes of Health (NIH). Continuation of these studies have been requested and approved by NIH.

SARS-CoV is a select agent

All work for these studies was performed with approved standard operating procedures (SOPs) and safety conditions for SARS-CoV, MERs-CoV and other related CoVs. Our institutional CoV BSL3 facilities have been designed to conform to the safety requirements recommended in Biosafety in Microbiological and Biomedical Laboratories (BMBL), the U.S. Department of Health and Human Services, the Public Health Service, the Centers for Disease Control (CDC) and the NIH. Laboratory safety plans have been submitted, and the facility has been approved for use by the UNC Department of Environmental Health and Safety (EHS) and the CDC. Electronic card access is required for entry into the facility. All workers have been trained by EHS to safely use powered air purifying respirators (PAPRs), and appropriate work habits in a BSL3 facility and active medical surveillance plans are in place. Our CoV BSL3 facilities contain redundant fans, emergency power to fans, and biological safety cabinets and freezers and can accommodate SealSafe mouse racks. Materials classified as BSL3 agents will consist of SARS-CoV, bat CoV precursor strains, MERS-CoV, and mutants derived from these pathogens. Within the BSL3 facilities, experimentation with infectious virus will be performed in a certified Class II Biosafety Cabinet (BSC). All staff wear scrubs, PAPRs, tyvek suits and aprons, and shoe covers, and hands are double-gloved. BSL3 users are subject to a medical surveillance plan monitored by the University Employee Occupational Health Clinic (UEOHC), which includes a yearly physical, annual influenza vaccination, and mandatory reporting of any symptoms associated with CoV infection during periods when working in the BSL3. All BSL3 users are trained in exposure management and reporting protocols, are prepared to self-quarantine, and have been trained for safe delivery to a local infectious disease management department in an emergency situation. All potential exposure events are reported and investigated by EHS and UEOHC, with reports filed to both the CDC and the NIH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research in this manuscript was supported by grants from the National Institute of Allergy & Infectious Disease and the National Institute of Aging of the National Institutes of Health (NIH) under awards U19AI109761 (RSB), U19AI107810 (RSB), AI1085524 (WM), F32AI102561 (VDM), K99AG049092 (VDM); and National Natural Science Foundation of China Award 81290341 (ZLS) and 31470260 (XYG). Human airway epithelial cultures were supported by the National Institute of Diabetes and Digestive and Kidney Disease under award NIH DK065988 (SHR). The authors also recognize MT Ferris, Dept. of Genetics, University of North Carolina for review of statistical approaches and CT Tseng, Dept. of Microbiology and Immunology, University of Texas Medical Branch for provision of Calu3 cells. Experiments with the full length and chimeric SHC014 recombinant viruses were initiated and performed prior to the gain of function research funding pause and have since been reviewed and approved for continued study by NIH. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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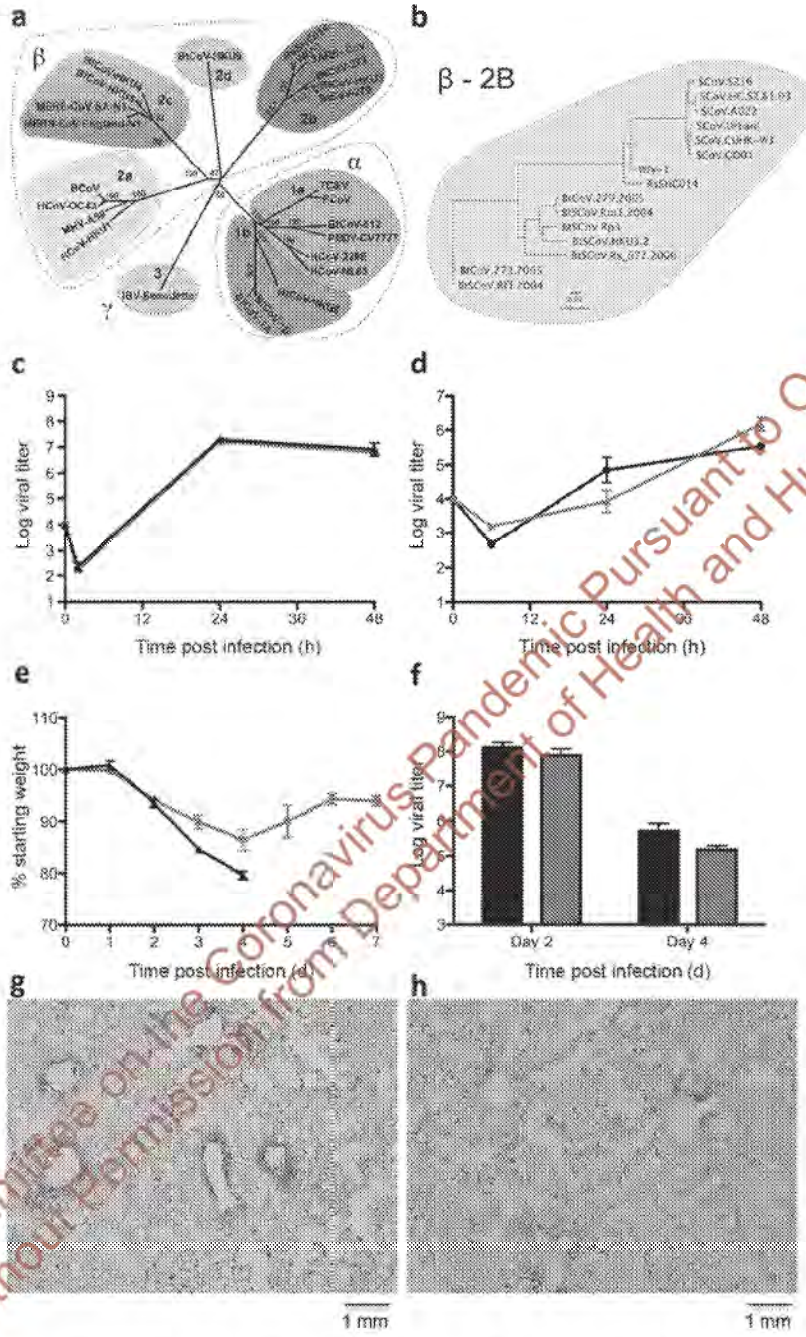

Figure 1. SARS-like viruses replicate in human airway cells and produce *in vivo* pathogenesis

(**a**) The full-length genome sequences of representative CoVs were aligned and phylogenetically mapped as described in the methods. The scale bar represents nucleotide substitutions, with only bootstrap support above 70% labeled. The tree shows CoVs divided into three distinct phylogenetic groups, defined as α,β, and γ. Classical subgroup clusters are marked as 2a–2d for the β CoVs and 1a and 1b for the α CoVs. (**b**) The S1 domains of the spike amino acid sequences of representative β CoVs of the 2b group, including SARSCoV. were aligned and phylogenetically mapped. The scale bar represents amino acid

substitutions. (**c**–**d**) Viral replication of SARS-CoV Urbani (black) and SHC014-MA15 (green) following infection of (**c**) Calu-3 2B4 cells or (**d**) well-differentiated, primary air-liquid interface human airway epithelial cell cultures at an MOI of 0.01. Samples were collected at individual time point with biological replicates (n =3) for both Calu3 experiments and HAE. (**e**–**h**) *In vivo* infection of 10-week-old BALB/c mice infected with 1×10^4 PFU of mouse adapted SARS-CoV MA15 (black) or SHC014-MA15 (green) via the *i.n.* route showing (**e**) weight loss (n =9 for MA15 n =16 for SHC014-MA15) and (**f**) viral replication in the lung (n =3 for MA15, n =4 for SHC014-MA15), and representative anti-SARS-CoV N antigen straining for (**g**) SARS-CoV MA15 and (**h**) SHC014-MA15. For each graphical figure, center value representative of group mean and error bars defined by SEM.

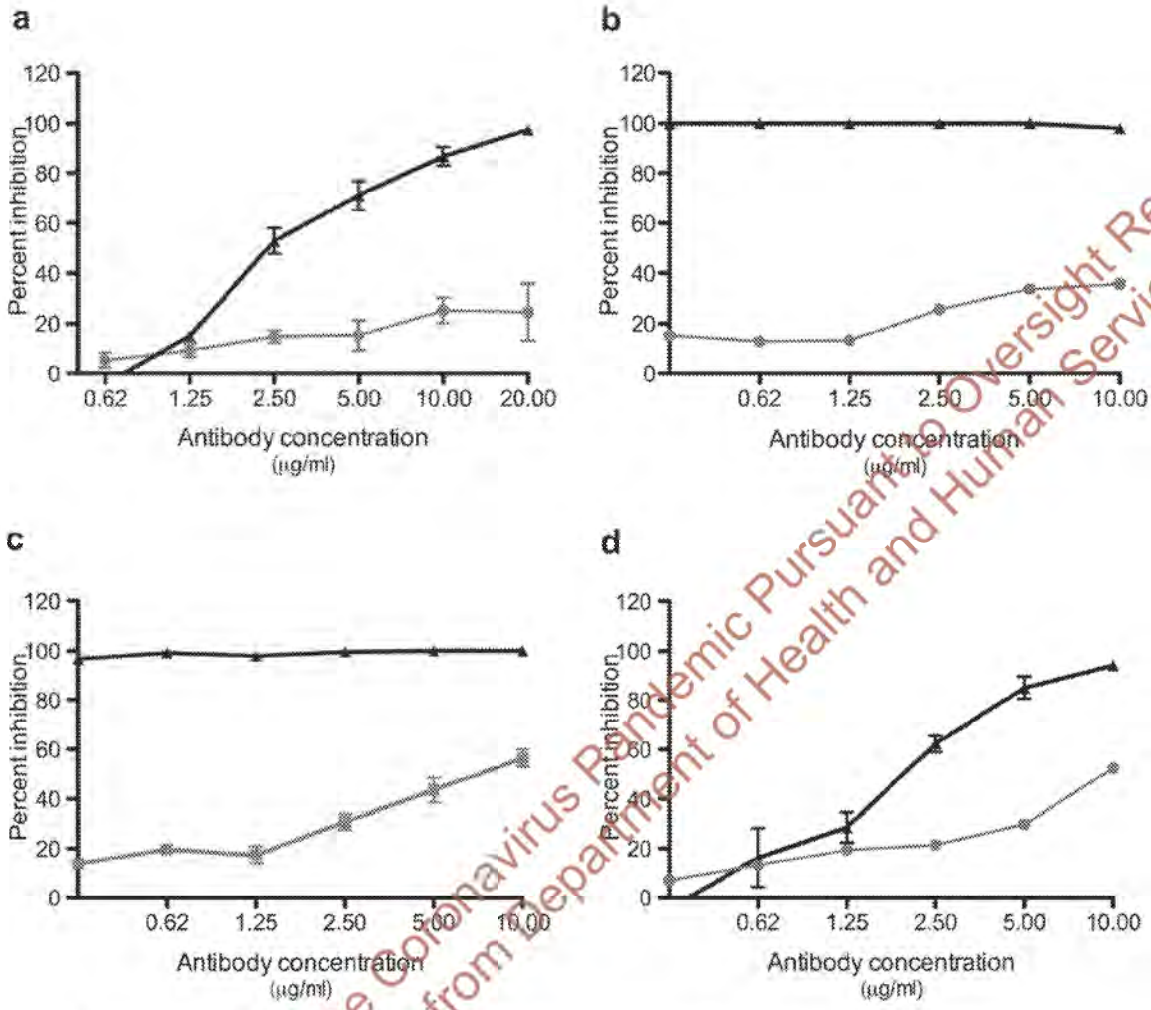

Figure 2. SARS-CoV monoclonal antibodies have marginal efficacy against SARS-like CoVs

Neutralization efficacy was evaluated using percent neutralization assays against SAR-CoV Urbani (black) or SHC014-MA15 with a panel of monoclonal antibodies: (**a**) fm6 ($n = 3$ for Urbani, $n = 5$ for SHC014-MA15)[10,11], (**b**) 230.15 ($n = 3$ for Urbani, $n = 2$ for SHC014-MA15), (**c**) 227.15 ($n = 3$ for Urbani, $n = 5$ for SHC014-MA15) and (**d**) 109.8 ($n = 3$ for Urbani, $n = 2$ for SHC014-MA15)[12], were all originally generated against epidemic SARS-CoV. Each data point representative of multiple center value represents group mean and error bars defined by SEM.

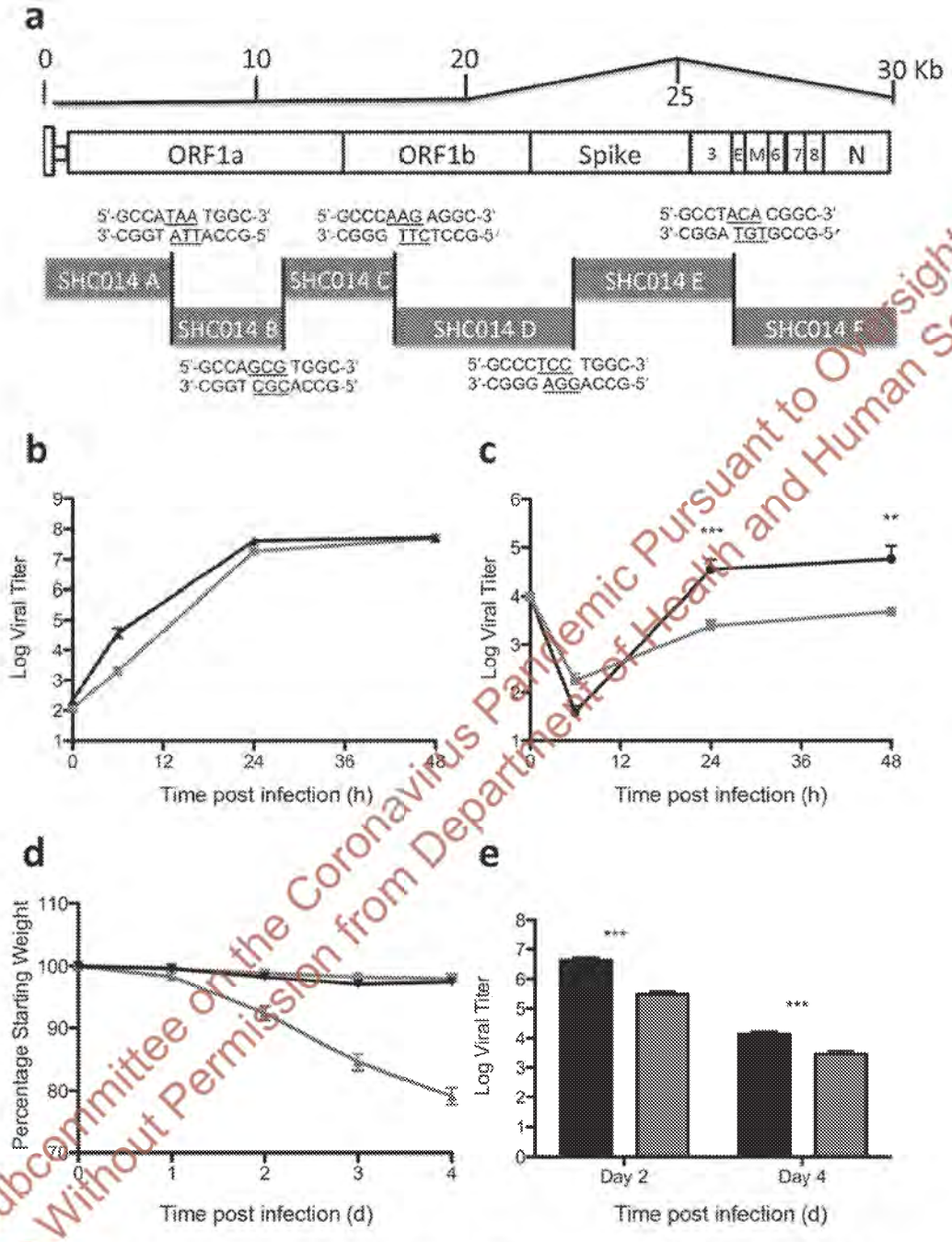

Figure 3. Full-length SHC014-CoV replicates in human airways, but lacks epidemic SARS virulence

(**a**) SHC014-CoV molecular clone was synthesized as six contiguous cDNAs designated A – F flanked by unique BglI sites that allowed for directed assembly of full-length cDNA. (**b–c**) Viral replication of SARS-CoV Urbani (black) and SHC014-CoV (green) following infection of (**b**) Vero cells or (**c**) well differentiated, primary air liquid interface human airway epithelial cell cultures at an MOI of 0.01. Samples were collected at individual time point with biological replicates ($n = 3$) for each group and representative of 1 experiment for

both Vero and HAE. (**d–e**) *In vivo* infection of 10-week-old BALB/c mice infected with 1×10^5 PFU of SARS-CoV Urbani (black), SARS-CoV MA15 (gray), or SHC014-CoV (green) via the *i.n.* route showing (**d**) weight loss ($n = 3$ for MA15, $n = 7$ for SHC014-CoV, $n = 6$ for SARS-Urbani) and (**e**) viral replication ($n = 3$ for SARS-Urbani and SHC014-CoV) in the lung. Each data point representative of multiple center value represents group mean and error bars defined by SEM. *P-values* based on 2-tailed Student's T-test of individual time points and are marked as indicated: **<0.01 ***<0.001.

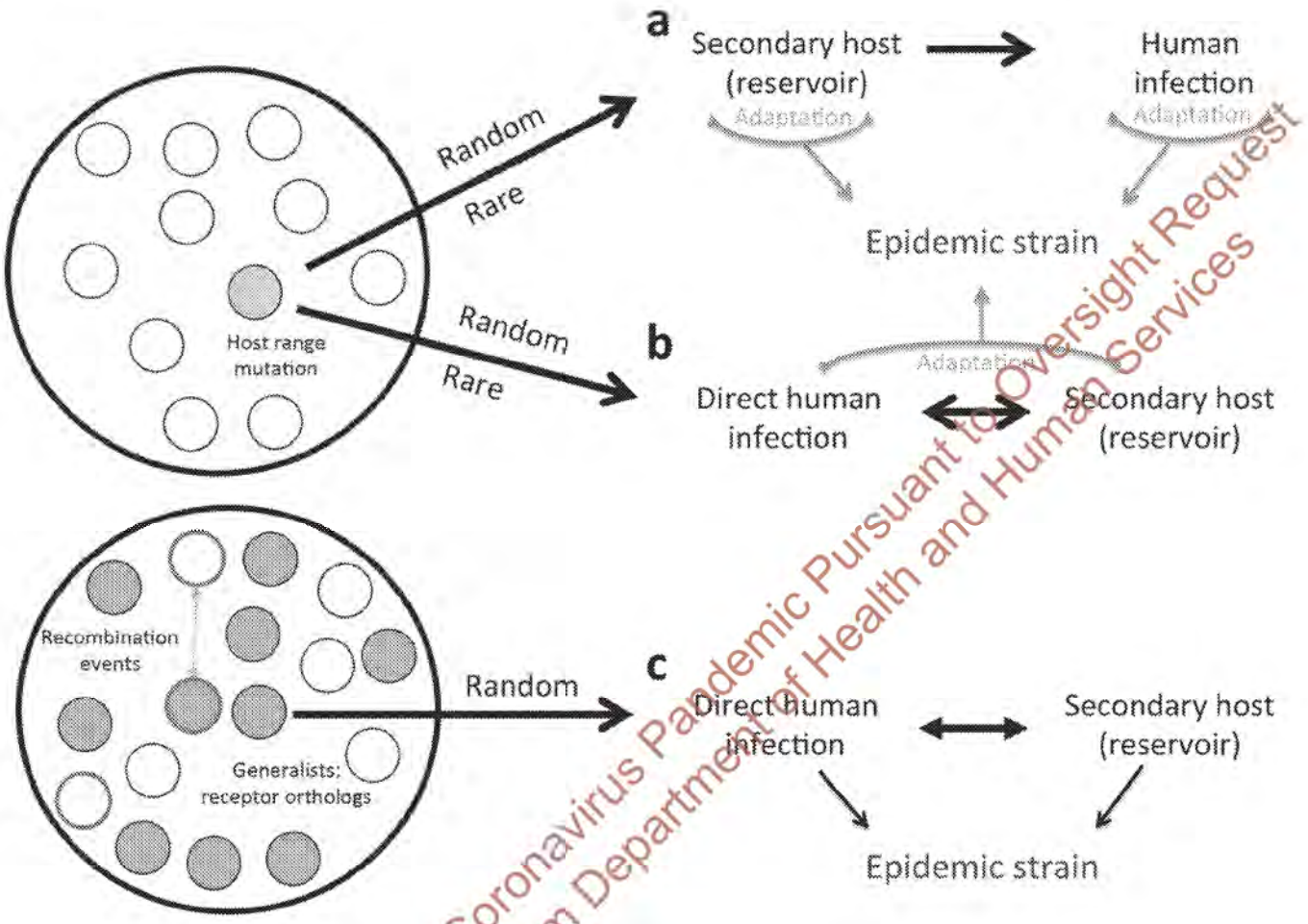

Figure 4. Emergence paradigms for coronaviruses

Coronavirus strains are maintained in quasi-species pools circulating in bat populations. (**a**–**b**) Traditional SARS-CoV emergence theories posit that host range mutants (red-filled circle) represent random and rare occurrences that permit infection of alternative hosts. (**a**) The secondary host paradigm argues that a non-human host is infected by a bat progenitor virus and, through adaptation, facilitates transmission to humans; subsequent replication in humans leads to the epidemic virus. (**b**) The direct paradigm suggests that transmission occurs between bats and humans without an intermediate host required; selection then occurs in the human population with closely related viruses replicating in a secondary host, permitting continued viral persistence and adaptation in both. (**c**) The data from chimeric SARS-like viruses argue that the quasi-species pools maintain multiple viruses capable of infecting human cells without the need for mutations (red-filled circles). While adaptations in secondary or human hosts may be required for epidemic emergence, if combined with virulent CoV backbones (green outlines), epidemic disease may be the result in humans. Existing data supports elements of all three paradigms.

RPPR related activities for R01AI110964-05 and other actions performed

The user was never locked out of the system:

1. eRA logs show that there was activity by PI and SO from the organization.
2. PI has a proven history of familiarity with and usage of eRA Commons, having initiated and routed 7 RPPRs during years 2015, 2016, 2017, 2018, 2019, 2021.
3. PI Initiated the Interim RPPR through the link provided on **07/24/2019** but he did not route it to the SO.
4. The day before the I-RRPR was routed by the PI to the SO (**07/26/2021**), the PI linked his account to Login.gov.
5. Then on **07/27/2021** he unsuccessfully attempted to change his eRA Commons password, and the password was locked.
6. He continues accessing eRA using Login.gov

Details:

Interim RPPR for Year 5

- R01AI110964-05 went into the systematic Closeout Process at the end of the project period.
- 06/04/2019 first email regarding documents needed for closeout was sent to the PI, the SO and the Closeout email identified by the organization in their Commons Institutional Profile.
- 07/19/2019 grant was removed from closeout and the Interim RPPR link became available systematically to both the PI and all SOs of the organization.
- **07/24/2019** - PI Initiated the Interim RPPR through the link provided.
- 05/26/2020 - PI accessed this Interim RPPR to upload a document and to enter data.
- **07/27/2021** - PI routed this Interim RPPR to SO.
- 08/02/2021 - SO uploaded documents for this Interim RPPR.
- 08/03/2021 - SO submitted this Interim RPPR to NIH.

From 7/19/2019 to 8/3/2021 the Interim RPPR link was available to access in both the PI and SOs Commons Status. Both the PI and SO accessed other applications and grants via their Commons Status, including but not limited to Just-In-Time actions and Application viewing.

During the timeframe after PI initiated the Interim RPPR through routing to the SO (07/24/2019 - 07/27/2021), the PI successfully logged into and was active in eRA systems (Commons, Commons Status, Assist) a total of 72 days. Each of those times accessing Commons was an opportunity to route the RPPR so it could be submitted to NIH.

- 12 more days in 2019 (07/25/2019, 08/05/2019, 08/16/2019, 09/10/2019, 10/02/2019, 11/08/2019, 11/18/2019, 11/21/2019, 11/22/2019, 12/03/2019, 12/05/2019, 12/06/2019)
- 38 days in 2020 (01/24/2020, 01/28/2020, 01/29/2020, 01/30/2020, 02/20/2020, 02/21/2020, 05/08/2020, 05/15/2020, 05/25/2020, 05/26/2020, 06/01/2020, 06/02/2020, 06/09/2020, 06/11/2020, 07/03/2020, 07/07/2020, 07/11/2020, 07/15/2020, 07/28/2020, 08/07/2020, 08/10/2020, 08/13/2020, 08/20/2020, 09/16/2020, 09/17/2020, 09/23/2020, 09/28/2020, 09/30/2020, 10/05/2020, 11/06/2020, 11/11/2020, 11/16/2020, 11/27/2020, 11/19/2020, 12/01/2020, 12/14/2020, 12/19/2020, 12/21/2020)
- 22 days in 2021 (03/10/2021, 03/15/2021, 03/22/2021, 03/23/2021, 03/24/2021, 03/25/2021, 03/29/2021, 03/30/2021, 03/31/2021, 04/08/2021, 04/09/2021, 04/25/2021, 05/19/2021, 05/21/2021, 05/24/2021, 06/08/2021, 06/09/2021, 06/10/2021, 06/11/2021, 06/15/2021, 07/26/2021, 07/27/2021)

PI Account details regarding "locked account"

- 07/26/2021 PI mapped their Commons account to Login.gov.
- 07/27/2021 PI was logged in with their Commons account to route the Interim RPPR to the SO and entered invalid credentials 5 times to lock their Commons password. However, before the password was locked, the PI had

already successfully logged in, was using multiple browser windows (logs show same IP and browser) and was able to continue working in another active browser window.

- 07/28/2021 - PI logged into Commons using Login.gov and logs show continued activity through present day.

"Regenerated" Annual RPPR

- 09/16/2020 - Signing Official contacted the eRA service desk about filling out the Inclusion Enrollment data. During that call, the eRA service desk agent inadvertently regenerated the RPPR, which caused the date and list of publications to be updated.
- Grant Folder: the Annual RPPR in the eAppls section reflects the regenerated RPPR and the original RPPR is included in the eAdditions section.

Message

From: Lane, Cliff (NIH/NIAID) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2D7E368A3137473BBCE161547A82F2DE-CLANE]
Sent: 3/26/2020 2:57:00 AM
To: Kuhn, Jens (NIH/NIAID) [C] [redacted] Schmaljohn, Connie (NIH/NIAID) [E]
[redacted]
BCC: Lane, Cliff (NIH/NIAID) [E] [redacted]
Subject: Re: Navigating politics

From my perspective – more important than ever to maintain such contacts.

From: "Kuhn, Jens (NIH/NIAID) [C]" [redacted]
Date: Wednesday, March 25, 2020 at 10:40 PM
To: "Lane, Cliff (NIH/NIAID) [E]" [redacted] "Schmaljohn, Connie (NIH/NIAID) [E]" [redacted]
Subject: Navigating politics

Connie, Cliff,

Please see the email below. I know Zhiming for quite some time and also met him personally in Wuhan twice (as he invited me to the institute's annual virology conferences to speak). He used to be responsible for the BSL-4 there, although I assume that is not the case anymore (based on press reports that the military took over?). There is no request or anything attached to his email – I just want to know whether it is okay for me to reply with a friendly email? I am just treading carefully, as this is coming from the epicenter...

Thanks,
Jens

From: Yuan Zhiming [redacted]
Sent: Friday, March 20, 2020 3:06 AM
To: Kuhn, Jens (NIH/NIAID) [C] [redacted]
Subject: 回复: RE: ask for help

Dear Jens,
I sincerely hope everything goes well with you and your family!
The 2019 novel coronavirus (SARS-CoV-2) outbreak is a major challenge for global public health security. Infection with SARS-CoV-2 has been associated with serious acute respiratory distress syndrome with large number of patients' hospitalization and relatively high mortality. We had a very hard time in combating the infection in Wuhan, the epicenter of the COVID-19 in China, and now we can see the situation goes in good direction, with no reported confirmed case, no reported suspected case in last two days here.
My colleagues and I, have been working on characterization of pathogens, antiviral screen, vaccine development, animal modeling since the early January this year, and some progresses have been made. I hope our understanding of the virus and the technology could be valuable in the global fighting to the virus.
As I can see from the media, the virus is spreading in your country, and more people are infected during the last days, and the situation worries me a lot. I am confident that we could finally curb the spreading of the virus with our joint effort, and our life will return back to the normal soon. I do not know what I can do for you in the special moment and I hope you could protect you and your family.
Best regards

Zhiming

Yuan Zhiming, Ph. D.
Professor of Wuhan Institute of Virology
President of Wuhan Branch
Chinese Academy of Sciences
Wuhan 430071, China
Tel: [redacted]
Fax: [redacted]

From: Kuhn, Jens (NIH/NIAID) [C]
Date: 2016-07-20 03:13
To: 'Yuan Zhiming'
CC: Barr, Jason (NIH/OD/ORS) [E]; Jahrling, Peter (NIH/NIAID) [E]; Holbrook, Michael (NIH/NIAID) [C]
Subject: RE: ask for help

Dear Zhiming,

It is great to hear that the Wuhan BSL-4 is now under operation, even though still without pathogens! I am unfortunately not the right person to weigh in on official biosafety procedures. I copied our Assistant Director (Safety Operations) Jason Barr, our director Peter Jahrling, and our BSL-4 Supervisor Michael Holbrook. They may be able to point you in the right directions.

Can't wait to one day visit your facility!

Best,
Jens

-----Original Message-----
From: Yuan Zhiming [redacted]
Sent: Friday, July 15, 2016 3:55 AM
To: Kuhn, Jens (NIH/NIAID) [C] [redacted]
Subject: ask for help
Importance: High

Dear Jens,

I have not heared for you for a long time and I hope everythign goes well with you and your work. I was glad to have met you last year and shared the experience on laboratory

management. I am writing to you to ask your help. Our laboratory is under operation without pathogens and we are now looking for the disinfectants for decontamination of airtight suits and surface decontamination indoor decontamination. We have tried several ones do determine their antiviral efficacy and corrosion to pipeline and wastewater treatment equipment. Unfortunately, we have found a good candidates. I hope you can give us some help, to give us some suggestion for the choice of disinfectants used in P4 laboratory.

What kind of disinfectants for decontamination of airtight protective clothes?

What kind of disinfectants for surface decontamination in door?

What kind of disinfectants for air decontamination in door?

What kind of disinfectants for infectious materials indoor?

What is the approval procedure for the choice of disinfectants in laboratory?

I am sorry to disturb you and I really hope you could give us some suggestion and cooment.

Best regards and looking forward to seeing you in Wuhan.

Yuan Zhiming

Message

From: Lane, Cliff (NIH/NIAID) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2D7E368A3137473BBCE161547A82F2DE-CLANE]
Sent: 8/18/2020 8:29:59 PM
To: Lane, Cliff (NIH/NIAID) [E] [redacted]
Subject: FW: A Proposed Origin for SARS-CoV-2 and the COVID-19 Pandemic - Independent Science News | Food, Health and Agriculture Bioscience News

From: Anthony Fauci [redacted]
Date: Tuesday, August 18, 2020 at 12:41 PM
To: "Collins, Francis (NIH/OD) [E]" [redacted] "Lane, Cliff (NIH/NIAID) [E]" [redacted]
Cc: Lawrence Tabak [redacted] "Lauer, Michael (NIH/OD) [E]" [redacted] "Wolinetz, Carrie (NIH/OD) [E]" [redacted] John Burklow [redacted] "Myles, Renate (NIH/OD) [E]" [redacted] Hilary Marston [redacted]
Subject: RE: A Proposed Origin for SARS-CoV-2 and the COVID-19 Pandemic - Independent Science News | Food, Health and Agriculture Bioscience News

Francis:

The obvious critical question is whether Dr. Shi has the viral isolates from the miners in her lab and what was the provenance of those isolates. Not sure what the Andersen et al group would think of this.

Best,

Tony

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From: Collins, Francis (NIH/OD) [E] [redacted]
Sent: Tuesday, August 18, 2020 9:21 AM
To: Fauci, Anthony (NIH/NIAID) [E] [redacted] Lane, Cliff (NIH/NIAID) [E] [redacted]
Cc: Tabak, Lawrence (NIH/OD) [E] [redacted] Lauer, Michael (NIH/OD) [E] [redacted] Wolinetz, Carrie (NIH/OD) [E] [redacted] Burklow, John (NIH/OD) [E] [redacted] Myles, Renate (NIH/OD) [E] [redacted] Marston, Hilary (NIH/NIAID) [E] [redacted]

Subject: FW: A Proposed Origin for SARS-CoV-2 and the COVID-19 Pandemic - Independent Science News | Food, Health and Agriculture Bioscience News

Hi Tony and Cliff,

We knew this analysis of the origin of SARS-CoV-2 was coming, but it's taken a long time to get published, and it's published in an odd place. If it gets picked up by other media, it will add considerable fuel to the argument that there was a lab accident at WIV.

Tony, what would the viral genomic epidemiology experts that published Andersen et al. in *Nature Medicine* say about this? Would they buy the idea that evolution from RaTG13 to SARS-CoV-2 could have happened in the lungs of those miners back in 2012?

Francis

https://www.independentsciencenews.org/commentaries/a-proposed-origin-for-sars-cov-2-and-the-covid-19-pandemic/

A Proposed Origin for SARS-CoV-2 and the COVID-19 Pandemic

by Jonathan Latham

by Jonathan Latham, PhD and Allison Wilson, PhD

In all the discussions of the origin of the COVID-19 pandemic, enormous scientific attention has been paid to the molecular character of the SARS-CoV-2 virus, including its novel genome sequence in comparison with its near relatives. In stark contrast, virtually no attention has been paid to the physical provenance of those nearest genetic relatives, its presumptive ancestors, which are two viral sequences named BtCoV/4991 and RaTG13.

This neglect is surprising because their provenance is more than interesting. BtCoV/4991 and RaTG13 were collected from a mineshaft in Yunnan province, China, in 2012/2013 by researchers from the lab of Zheng-li Shi at the Wuhan Institute of Virology (WIV). Very shortly before, in the spring of 2012, six miners working in the mine had contracted a mysterious illness and three of them had died (Wu et al., 2014). The specifics of this mystery disease have been virtually forgotten; however, they are described in a Chinese Master's thesis written in 2013 by a doctor who supervised their treatment.

We arranged to have this Master's thesis translated into English. The evidence it contains has led us to reconsider everything we thought we knew about the origins of the COVID-19 pandemic. It has also led us to theorise a plausible route by which an apparently isolated disease outbreak in a mine in 2012 led to a global pandemic in 2019.

The origin of SARS-CoV-2 that we propose below is based on the case histories of these miners and their hospital treatment. This simple theory accounts for all the key features of the novel SARS-CoV-2 virus, including ones that have puzzled virologists since the outbreak began.

The theory can account for the origin of the polybasic furin cleavage site, which is a region of the viral spike protein that makes it susceptible to cleavage by the host enzyme furin and which greatly enhances viral spread in the body. This furin site is novel to SARS-CoV-2 compared to its near relatives (Coutard, et al., 2020). The theory also explains the exceptional affinity of the virus spike protein for human receptors, which has also surprised virologists (Letko et al., 2020; Piplani et al., 2020; Wrapp et al., 2020; Walls et al., 2020). The theory further explains why the virus has barely evolved since the pandemic began, which is also a deeply puzzling aspect of a virus supposedly new to humans (Zhan et al., 2020; van Dorp et al., 2020; Chaw et al., 2020). Lastly, the theory neatly explains why SARS-CoV-2 targets the lungs, which is unusual for a coronavirus (Huang et al., 2020).

We do not propose a specifically genetically engineered or biowarfare origin for the virus but the theory does propose an essential causative role in the pandemic for scientific research carried out by the laboratory of Zheng-li Shi at the WIV; thus also explaining Wuhan as the location of the epicentre.

Why has the provenance of RaTG13 and BtCoV/4991 been ignored?

The apparent origin of the COVID-19 pandemic is the city of Wuhan in Hubei province, China. Wuhan is also home to the world's leading research centre for bat coronaviruses. There are two virology labs in the city, both have either collected bat coronaviruses or researched them in the recent past. The Shi lab, which collected BtCoV/4991 and RaTG13, recently received grants to evaluate *by experiment* the potential for pandemic pathogenicity of the novel bat coronaviruses they collected from the wild.

To add to these suggestive data points, there is a long history of accidents, disease outbreaks, and even pandemics resulting from lab accidents with viruses (Furmanski, 2014; Weiss et al., 2015). For these and other reasons, summarised in our article *The Case is Building that COVID-19 Had a Lab Origin*, we (a virologist and a geneticist) and others have concluded that a lab outbreak is a credible thesis. Certainly, a lab origin has at least as much circumstantial evidence to support it as does any natural zoonotic origin theory (Piplani et al., 2020; Segreto and Deigin, 2020; Zhan et al., 2020).

The media, normally so enamoured of controversy, has largely declined even to debate the possibility of a laboratory escape. Many news sites have simply labelled it a conspiracy theory.

The principal reason for media dismissals of the lab origin possibility is a review paper in *Nature Medicine* (Andersen et al., 2020). Although by Jun 29 2020 this review had almost 700 citations it also has major scientific shortcomings. These flaws are worth understanding in their own right but they are also useful background for understanding the implications of the Master's thesis.

Andersen et al., a critique

The question of the origin of the COVID-19 pandemic is, in outline, simple. There are two incontrovertible facts. One, the disease is caused by a human viral pathogen, SARS-CoV-2, first identified in Wuhan in December 2019 and whose RNA genome sequence is known. Second, all of its nearest known relatives come from bats. Beyond any reasonable doubt SARS-CoV-2 evolved from an ancestral bat virus. The task the *Nature Medicine* authors set for themselves was to establish the relative merits of each of the various possible routes (lab vs natural) by which a bat coronavirus might have jumped to humans and in the same process have acquired an unusual furin site and a spike protein having very high affinity for the human ACE2 receptor.

When Andersen et al. outline a natural zoonotic pathway they speculate extensively about how the leap might have occurred. In particular they elaborate on a proposed residence in intermediate animals, likely pangolins. For example, "The presence in pangolins of an RBD [Receptor Binding Domain] very similar to that of SARS-CoV-2 means that we can infer that this was probably in the virus that jumped to humans. This leaves the insertion of [a] polybasic cleavage site to occur during human-to-human transmission." This viral evolution occurred in "Malayan pangolins illegally imported into Guangdong province". Even with these speculations there are major gaps in this theory. For example, why is the virus so well adapted to humans? Why Wuhan, which is 1,000 Km from Guangdong? (See map).

china province guide

The authors provide no such speculations in favour of the lab accident thesis, only speculation *against* it:

"Finally, the generation of the *predicted* O-linked glycans is also *unlikely* to have occurred due to cell-culture passage, as such features suggest the involvement of an immune system." (italics added).

[Passaging is the deliberate placing of live viruses into cells or organisms to which they are NOT adapted for the purpose of making them adapted, i.e. speeding up their evolution.]

It is also noteworthy that the Andersen authors set a higher hurdle for the lab thesis than the zoonotic thesis. In their account, the lab thesis is required to explain *all* of the evolution of SARS-CoV-2 from its presumed bat viral ancestor, whereas under their telling of the zoonotic thesis the key step of the addition of the furin site is allowed to happen in humans and is thus effectively unexplained.

A further imbalance is that key information needed to judge the merits of a lab origin theory is missing from their account. As we detailed in our previous article, in their search for SARS-like viruses with zoonotic spillover potential, researchers at the WIV have passaged live bat viruses in monkey and

human cells (Wang et al., 2019). They have also performed many recombinant experiments with diverse bat coronaviruses (Ge et al., 2013; Menachery et al., 2015; Hu et al., 2017). Such experiments have generated international concern over the possible creation of potential pandemic viruses (Lipsitch, 2018). As we showed too, the Shi lab had also won a grant to extend that work to whole live animals. They planned "virus infection experiments across a range of cell cultures from different species and humanized mice" with recombinant bat coronaviruses. Yet Andersen et al did not discuss this research at all, except to say:

"Basic research involving passage of bat SARS-CoV-like coronaviruses in cell culture and/or animal models has been ongoing for many years in biosafety level 2 laboratories across the world"

This statement is fundamentally misleading about the kind of research performed at the Shi lab.

A further important oversight by the Andersen authors concerns the history of lab outbreaks of viral pathogens. They write: "there are documented instances of laboratory escapes of SARS-CoV". This is a rather matter-of-fact allusion to the fact that since 2003 there have been six documented outbreaks of SARS from labs, not all in China, with some leading to fatalities (Furmanski, 2014).

Andersen et al might have also have noted that two major human pandemics are widely accepted to have been caused by lab outbreaks of viral pathogens, H1N1 in 1977 and Venezuelan Equine Encephalitis (summarised in Furmanski, 2014). Andersen could even have noted that literally hundreds of lab accidents with viruses have resulted in near-misses or very localised outbreaks (summarised by Lynn Klotz and Sam Husseini and also Weiss et al., 2015).

Also unmentioned were instances where a lab outbreak of an experimental or engineered virus has been plausibly theorised but remains uninvestigated. For example, the most coherent explanation for the H1N1 variant 'swine flu' pandemic of 2009/10 that resulted in a death toll estimated by some as high as 200,000 (Duggal et al., 2016; Simonsen et al. 2013), is that a vaccine was improperly inactivated by its maker (Gibbs et al., 2009). If so, H1N1 emerged from a lab not once but twice.

Given that human and livestock viral outbreaks have frequently come from laboratories and that many scientists have warned of probable lab escapes (Lipsitch and Galvani, 2014), and that the WIV itself has a questionable biosafety record, the Andersen paper is not an even-handed treatment of the possible origins of the COVID-19 virus.

Yet its text expresses some strong opinions: "Our analyses clearly show that SARS-CoV-2 is not a laboratory construct or a purposefully manipulated virus….It is improbable that SARS-CoV-2 emerged through laboratory manipulation of a related SARS-CoV-like coronavirus…..the genetic data irrefutably show that SARS-CoV-2 is not derived from any previously used backbone….the evidence shows that SARS-CoV2 is not a purposefully manipulated virus….we do not believe that any type of laboratory-based scenario is possible." (Andersen et al., 2020).

It is hard not to conclude that what their paper mostly shows is that Drs. Andersen, Rambaut, Lipkin, Holmes and Garry much prefer the natural zoonotic transfer thesis. Their rhetoric is forthright but the evidence does not support that confidence.

Indeed, since the publication of Andersen et al., important new evidence has emerged that undermines their zoonotic origin theory. On May 26th the Chinese CDC ruled out the Huanan "wet" market in Wuhan as the source of the outbreak. Additionally, new research on pangolins, the favoured intermediate mammal host, suggests they are not a natural reservoir of coronaviruses (Lee et al., 2020; Chan and Zhan, 2020). Furthermore, SARS-CoV-2 was found not to replicate in bat kidney or lung cells (*Rhinolophus sinicus*), implying that SARS-CoV-2 is not a recently-adapted spill over (Zhu et al., 2020).

The Mojiang mine and the Master's thesis

In our own search to resolve the COVID-19 origin question we chose to focus on the provenance of the coronavirus genome sequences BtCoV/4991 and RaTG13, since these are the most closely related sequences to SARS-CoV-2 (98.7% and 96.2% identical respectively). See FIG 1. (reproduced from P. Zhou et al., 2020).

Similarity of SARS-CoV-2 to RaTG13 (blue line) and other coronaviruses (red, green, pink) (Image from Zhou et al., 2020). The higher the line the more similar the virus.

For comparison, the next closest virus to SARS-CoV-2 is RmYN02 (not shown in Fig 1.) (H. Zhou et al., 2020). RmYN02 has an overall similarity to SARS-CoV-2 of 93.2%, making its evolutionary distance from SARS-CoV-2 almost twice as great.

BtCoV/4991 was first described in 2016. It is a 370 nucleotide virus fragment collected from the Mojiang mine in 2013 by the lab of Zeng-li Shi at the WIV (Ge et al., 2016). BtCoV/4991 is 100% identical in sequence to one segment of RaTG13. RaTG13 is a complete viral genome sequence (almost 30,000 nucleotides) that was only published in 2020, after the pandemic began (P. Zhou et al., 2020).

Despite the confusion created by their different names, in a letter obtained by us Zheng-li Shi confirmed to a virology database that BtCoV/4991 and RaTG13 are both from the same bat faecal sample and the same mine. They are thus sequences from the same virus. In the discussion below we will refer primarily to RaTG13 and specify BtCoV/4991 only as necessary.

These specifics are important because it is these samples and their provenance that we believe are ultimately key to unravelling the mystery of the origins of COVID-19.

The story begins in April 2012 when six workers in that same Mojiang mine fell ill from a mystery illness while removing bat faeces. Three of the six subsequently died.

In a March 2020 interview with Scientific American Zeng-li Shi dismissed the significance of these deaths, claiming the miners died of fungal infections. Indeed, no miners or deaths are mentioned in the paper published by the Shi lab documenting the collection of RaTG13 (Ge et al., 2016).

But Shi's assessment does not tally with any other contemporaneous accounts of the miners and their illness (Rahalkar and Bahulikar, 2020). As these authors have pointed out, *Science* magazine wrote up part of the incident in 2014 as A New Killer Virus in China?. *Science* was citing a different team of virologists who found a paramyxovirus in rats from the mine. These virologists told *Science* they found "no direct relationship between human infection" and their virus. This expedition was later published as the discovery of a new virus called MojV after Mojiang, the locality of the mine (Wu et al., 2014).

What this episode suggests though is that these researchers were looking for a potentially lethal virus and not a lethal fungus. Also searching the Mojiang mine for a virus at around the same time was Canping Huang, the author of a PhD thesis carried out under the supervision of George Gao, the head of the Chinese CDC.

All of this begs the question of why the Shi lab, which has no interest in fungi but a great interest in SARS-like bat coronaviruses, also searched the Mojiang mine for bat viruses on four separate occasions between August 2012 and July 2013, even though the mine is a 1,000 Km from Wuhan (Ge et al., 2016). These collecting trips began while some of the miners were still hospitalised.

Fortunately, a detailed account of the miner's diagnoses and treatments exists. It is found in a Master's thesis written in Chinese in May 2013. Its suggestive English title is "*The Analysis of 6 Patients with Severe Pneumonia Caused by Unknown viruses*".

The original English version of the abstract implicates a SARS-like coronavirus as the probable causative agent and that the mine "had a lot of bats and bats' feces".

The findings of the Master's thesis

To learn more, especially about the reasonableness of this diagnosis, we arranged to have the whole Master's thesis translated into English and are here making the translation available. To read it in full see the embedded document below (or download it here).

 Analysis of Six Patients With Unknown Viruses (PDF)</p> <p>Analysis of Six Patients With Unknown Viruses (Text)

The six ill miners were admitted to the No. 1. School of Clinical Medicine, Kunming Medical University, in short succession in late April and early May 2012. Kunming is the capital of Yunnan province and 250 Km from Mojiang.

Of the descriptions of the miners and their treatments, which include radiographs and numerous CAT scans, several features stand out:

1) From their admission to the hospital their doctors informed the "medical office" of a potential "outburst of disease" i.e. a potential epidemic outbreak. Thus, the miners were treated for infections and not as if they had inhaled noxious gases or other toxins.

2) The symptoms (on admission) of the six miners were: a) dry cough, b) sputum, c) high fevers, especially shortly before death d) difficulty breathing, e) myalgia (sore limbs). Some patients had hiccoughs and headaches. (See Table 1).

The Syndromes of the six Mojiang Mine patients

3) Clinical work established that patients 1-4 had low blood oxygen "for sure it was ARDS" (Acute Respiratory Distress Syndrome) and immune damage considered indicative of viral infection. Additionally, a tendency for thrombosis was noted in patients 2 and 4. Symptom severity and mortality were age-related (though from a sample of 6 this must be considered anecdotal).

4) Potential common and rare causes of their symptoms were tested for and mostly eliminated. For patients 3 and 4 these included tests for HIV, Cytomegalovirus, Epstein-Barr Virus (EBV), Japanese encephalitis, haemorrhagic fever, Dengue, Hepatitis B, SARS, and influenza. Of these, only patient 2 tested positive for Hepatitis and EBV.

5) Treatment of the six patients included ventilation (patients 2-4), steroids (all patients), antivirals (all except patient 5), and blood thinners (patients 2 and 4). Antibiotics and antifungal medications were administered to counter what were considered secondary (but significant) co-infections.

6) A small number of remote meetings were held with researchers at other universities. One was with Zhong Nanshan at Sun Yat-Sen University, Guangdong. Zhong is the Chinese hero of the SARS epidemic, a virologist, and arguably the most famous scientist in China.

7) Samples from the miners were later sent to the WIV in Wuhan and to Zhong Nanshan, further confirming that viral disease was strongly suspected. Some miners did test positive for coronavirus (the thesis is unclear on how many).

8) The source of infection was concluded to be *Rhinolophus sinicus*, a horseshoe bat and the ultimate conclusion of the thesis reads "the unknown virus lead to severe pneumonia could be: The SARS-like-CoV from the Chinese rufous horseshoe bat." Thus the miners had a coronavirus but it apparently was not SARS itself.

The significance of the Master's thesis

These findings of the thesis are significant in several ways.

First, in the light of the current coronavirus pandemic it is evident the miners' symptoms very closely resemble those of COVID-19 (Huang et al. 2020; Tay et al., 2020; M. Zhou et al., 2020). Anyone presenting with them today would immediately be assumed to have COVID-19. Likewise, many of the treatments given to the miners have become standard for COVID-19 (Tay et al., 2020).

Second, the remote meeting with Zhong Nanshan is significant. It implies that the illnesses of the six miners were of high concern and, second, that a SARS-like coronavirus was considered a likely cause.

Third, the abstract, the conclusions, and the general inferences to be made from the Master's thesis contradict Zheng-li Shi's assertion that the miners died from a fungal infection. Fungal infection as a potential primary cause was raised but largely discarded.

Fourth, if a SARS-like coronavirus was the source of their illness the implication is that it could *directly* infect human cells. This would be unusual for a bat coronavirus (Ge et al., 2013). People do sometimes get ill from bat faeces but the standard explanation is histoplasmosis, a fungal infection and not a virus (McKinsey and McKinsey, 2011; Pan et al., 2013).

Fifth, the sampling by the Shi lab found that bat coronaviruses were unusually abundant in the mine (Ge at al., 2016). Among their findings were two betacoronaviruses, one of which was RaTG13 (then known as BtCoV/4991). In the coronavirus world betacoronaviruses are special in that both SARS and MERS, the most deadly of all coronaviruses, are both betacoronaviruses. Thus they are considered to have special pandemic potential, as the concluding sentence of the Shi lab publication which found RaTG13 implied: "special attention should particularly be paid to these lineages of coronaviruses" (Ge at al., 2016). In fact, the Shi and other labs have for years been predicting that bat betacoronaviruses like RaTG13 would go pandemic; so to find RaTG13 where the miners fell ill was a scenario in perfect alignment with their expectations.

The Mojiang miners passaging proposal

How does the Master's thesis inform the search for a plausible origin of the pandemic?

In our previous article we briefly discussed how the pandemic might have been caused either by a virus collection accident, or through viral passaging, or through genetic engineering and a subsequent lab escape. The genetic engineering possibility deserves attention and is extensively assessed in an important preprint (Segreto and Deigin, 2020).

We do not definitively rule out these possibilities. Indeed it now seems that the Shi lab at the WIV did not forget about RaTG13 but were sequencing its genome in 2017 and 2018. However, we believe that the Master's thesis indicates a much simpler explanation.

We suggest, first, that inside the miners RaTG13 (or a very similar virus) evolved into SARS-CoV-2, an unusually pathogenic coronavirus highly adapted to humans. Second, that the Shi lab used medical samples taken from the miners and sent to them by Kunming University Hospital for their research. It was this human-adapted virus, now known as SARS-CoV-2, that escaped from the WIV in 2019.

We refer to this COVID-19 origin hypothesis as the Mojiang Miners Passage (MMP) hypothesis.

Passaging is a standard virological technique for adapting viruses to new species, tissues, or cell types. It is normally done by deliberately infecting a new host species or a new host cell type with a high dose of virus. This initial viral infection would ordinarily die out because the host's immune system vanquishes the ill-adapted virus. But, in passaging, before it does die out a sample is extracted and transferred to a new identical tissue, where viral infection restarts. Done iteratively, this technique (called "serial passaging" or just "passaging") intensively selects for viruses adapted to the new host or cell type (Herfst et al., 2012).

At first glance RaTG13 is unlikely to have evolved into SARS-CoV-2 since RaTG13 is approximately 1,200 nucleotides (3.8%) different from SARS-CoV-2. Although RaTG13 is the most closely related virus to SARS-CoV-2, this sequence difference still represents a considerable gap. In a media statement evolutionary virologist Edward Holmes has suggested this gap represents 20-50 years of evolution and others have suggested similar figures.

We agree that ordinary rates of evolution would not allow RaTG13 to evolve into SARS-CoV-2 but we also believe that conditions inside the lungs of the miners were far from ordinary. Five major factors specific to the hospitalised miners favoured a very high rate of evolution inside them.

i) When viruses infect new species they typically undergo a period of very rapid evolution because the selection pressure on the invading pathogen is high. The phenomenon of rapid evolution in new hosts is well attested among corona- and other viruses (Makino et al., 1986; Baric et al., 1997; Dudas and Rambaut 2016; Forni et al., 2017).

ii) Judging by their clinical symptoms such as the CT scans, all the miner's infections were primarily of the lungs. This localisation likely occurred initially because the miners were exerting themselves and therefore inhaling the disturbed bat guano deeply. As miners, they may already have had damaged lung tissues (patient 3 had suspected pneumoconiosis) and/or particulate matter was present that irritated the tissues and may have facilitated initial viral entry.

In contrast, standard coronavirus infections are confined to the throat and upper respiratory tract. They do not normally reach the lungs (Perlman and Netland, 2009). Lungs are far larger tissues by weight (kilos vs grammes) than the upper respiratory tract. There was therefore likely a much larger quantity of virus inside the miners than would be the case in an ordinary coronavirus infection.

Comparing a typical coronavirus respiratory tract infection with the extent of infected lungs in the miners from a purely mathematical point of view indicates the potential scale of this quantitative difference. The human aerodigestive tract is approximately 20cm in length and 5cm in circumference, i.e. approximately 100 cm^2 in surface area. The surface area of a human lung ranges from 260,000-680,000 cm^2 (Hasleton, 1972). The amount of potentially infected tissue in an average lung is therefore approximately 4500-fold greater than that available to a normal coronavirus infection. The amount of virus present in the infected miners, sufficient to hospitalise all of them and kill half of them, was thus proportionately very large.

Evolutionary change is in large part a function of the population size. The lungs of the miners, we suggest, supported a very high viral load leading to proportionately rapid viral evolution.

Furthermore, according to the Master's thesis, the immune systems of the miners were compromised and remained so even for those discharged. This weakness on the part of the miners may also have encouraged evolution of the virus.

iii) The length of infection experienced by the miners (especially patients 2, 3 and 4) far exceeded that of an ordinary coronavirus infection. From first becoming too sick to work in the mine, patient 2 survived 57 days until he died. Patient 3 survived 120 days after stopping work. Patient 4 survived 117 days and then was discharged as cured. Each had been exposed in the mine for 14 days prior to the onset of severe symptoms; thus each presumably had nascent infections for some time before calling in sick (See Table 2 of the thesis).

In contrast, in ordinary coronavirus infections the viral infection is cleared within about ten to fourteen days after being acquired (Kay et al., 2020). Thus, unlike most sufferers from coronavirus infection, the hospitalised miners had very long-term bouts of disease characterised by a continuous high load of virus. In the cases of patients 3 and 4 their illnesses lasted over 4 months.

iv) Coronaviruses are well known to recombine at very high rates: 10% of all progeny in a cell can be recombinants (Makino et al., 1986; Banner and Lai, 1991; Dudas and Rambaut, 2016). In normal virus evolution the mutation rate and the selection pressure are the main foci of attention. But in the case of a coronavirus adapting to a new host where many mutations distributed all over the genome are required to fully adapt to the new host, the recombination rate is likely to be highly influential in determining the overall speed of adaptation by the virus population (Baric et al., 1997).

Inside the miners a large tissue was simultaneously infected by a population of poorly-adapted viruses, with each therefore under pressure to adapt. Even if the starting population of virus lacked any diversity, many individual viruses would have acquired mutations independently but only recombination would have allowed these mutations to unite in the same genome. To recombine, viruses must be present in the same cell. In such a situation the particularities of lung tissues become potentially important because the existence of airways (bronchial tubes, etc.) allows partially-adapted viruses from independent viral populations to travel to distal parts of the lung (or even the other lung) and encounter other such partially-adapted viruses and populations. This movement around the lungs would likely have resulted in what amounted to a passaging effect without the need for a researcher to infect new tissues. Indeed, in the Master's thesis the observation is several times made that areas of the lungs of a specific patient would appear to heal even while other parts of the lungs would become infected.

v) There were also a number of unusual things about the bat coronaviruses in the mine. They were abnormally abundant but also there were many different kinds, often causing co-infections of the bats (Ge et al., 2016). Viral co-infections are often more infectious or more pathogenic (Latham and Wilson, 2007).

As the WIV researchers remarked about the bats in the mine:

"we observed a high rate of co-infection with two coronavirus species and interspecies infection with the same coronavirus species within or across bat families. These phenomena may be owing to the diversity and high density of bat populations in the same cave, facilitating coronavirus intra- and interspecies transmissions, which may result in recombination and acceleration of coronavirus evolution." (Ge et al., 2016).

The diversity of coronaviruses in the mine suggests that the miners were similarly exposed and that their illness may potentially have begun as co-infections.

Combining these observations, we propose that the miners' lungs offered an unprecedented opportunity for accelerated evolution of a highly bat-adapted coronavirus into a highly human-adapted coronavirus and that decades of ordinary coronavirus evolution could easily have been condensed into months. However, we acknowledge that these conditions were unique. They and their scale have no exact scientific precedent we can refer to and they would be hard to replicate in a lab; thus it is important to emphasize that our proposal is fully consistent with the underlying principles of viral evolution as understood today.

In support of the MMP theory we also know something about the samples taken from the miners. According to the Master's thesis, samples were taken from patients for "scientific research" and blood samples (at least) were sent to the WIV.

"In the later stage we worked with Dr. Zhong Nan Shan and did some sampling. The patient* tested positive for serum IgM by the WuHan Institute of Virology. It suggested the existence of virus infection" (p62 in the section "Comprehensive Analysis".)

(*The original does not specify the number of patients tested.)

The Master's thesis also states its regret that no samples for research were taken from patients 1 and 2, implying that samples were taken from all the others.

We further know that, on June 27th, 2012, the doctors performed an unexplained thymectomy on patient 4. The thymus is an immune organ that can potentially be removed without greatly harming the patient and it could have contained large quantities of virus. Beyond this the Master's thesis is unfortunately unclear on the specifics of what sampling was done, for what purpose, and where each particular sample went.

Given the interests of the Shi lab in zoonotic origins of human disease, once such a sample was sent to them, it would have been obvious and straightforward for them to investigate how a virus from bats had managed to infect these miners. Any viruses recoverable from the miners would likely have been viewed by them as a unique natural experiment in human passaging offering unprecedented and otherwise-impossible-to-obtain insights into how bat coronaviruses can adapt to humans.

The logical course of such research would be to sequence viral RNA extracted directly from unfrozen tissue or blood samples and/or to generate live infectious clones for which it would be useful (if not imperative) to amplify the virus by placing it in human cell culture. Either technique could have led to accidental infection of a lab researcher.

Our supposition as to why there was a time lag between sample collection (in 2012/2013) and the COVID-19 outbreak is that the researchers were awaiting BSL-4 lab construction and certification, which was underway in 2013 but delayed until 2018.

We propose that, when frozen samples derived from the miners were eventually opened in the Wuhan lab they were already highly adapted to humans to an extent possibly not anticipated by the researchers. One small mistake or mechanical breakdown could have led directly to the first human infection in late 2019.

Thus, one of the miners, most likely patient 3, or patient 4 (whose thymus was removed), was effectively patient zero of the COVID-19 epidemic. In this scenario, COVID-19 is not an engineered virus; but, equally, if it had not been taken to Wuhan and no further molecular research had been performed or planned for it then the virus would have died out from natural causes, rather than escaped to initiate the COVID-19 pandemic.

Evidence in favour of the MMP proposal

Our proposal is consistent with all the principal undisputed facts concerning SARS-CoV-2 and its origin. The MMP proposal has the additional benefit of reconciling many observations concerning SARS-CoV-2 that have proven difficult to reconcile with any natural zoonotic hypothesis.

For instance, using different approaches, numerous researchers have concluded that the SARS-CoV-2 spike protein has a very high affinity for the human ACE2 receptor (Walls et al., 2020; Piplani et al., 2020; Shang and Ye et al., 2020; Wrapp et al., 2020). Such exceptional affinities, ten to twenty times as great as that of the original SARS virus, do not arise at random, making it very hard to explain in any other way than for the virus to have been strongly selected in the presence of a human ACE2 receptor (Piplani et al., 2020).

In addition to this, a recent report found that the spike of RaTG13 binds the human ACE2 receptor (Shang and Ye et al., 2020). We proposed above that the virus in the mine directly infected humans lung cells. The main determinant of cell infection and species specificity of coronaviruses is initial receptor binding (Perlman and Netland, 2009). Thus RaTG13, unlike most bat coronaviruses, probably can enter and infect human cells, providing biological plausibility to the idea that the miners became infected with a coronavirus resembling RaTG13.

Moreover, the receptor binding domain (RBD) of SARS-CoV-2, which is the region of the spike that physically contacts the human ACE2 receptor, has recently been crystallised to reveal its spatial structure (Shang and Ye et al., 2020). These authors found close structural similarities between the spikes of SARS-CoV-2 and RaTG13 in how they bound the human ACE2 receptor:

"Second, as with SARS-CoV-2, bat RaTG13 RBM [a region of the RBD] contains a similar four-residue motif in the ACE2 binding ridge, *supporting the notion that SARS-CoV-2 may have evolved from RaTG13 or a RaTG13-related bat coronavirus* (Extended Data Table 3 and Extended Data Fig. 7). Third, the L486F, Y493Q and D501N residue changes from RaTG13 to SARS CoV-2 enhance ACE2 recognition and may have facilitated the bat-to-human transmission of SARS-CoV-2 (Extended Data Table 3 and Extended Data Fig. 7). A lysine-to-asparagine mutation at the 479 position in the SARS-CoV RBD (corresponding to the 493 position in the SARS-CoV-2 RBD) enabled SARS-CoV to infect humans. Fourth, Leu455 contributes favourably to ACE2 recognition, and it is conserved between RaTG13 and SARS CoV-2; its presence in the SARS CoV-2 RBM may be important for the bat-to-human transmission of SARS-CoV-2" (Shang and Ye et al., 2020). (*italics added*)

The significance of this molecular similarity is very great. Coronaviruses have evolved a diverse set of molecular solutions to solve the problem of binding ACE2 (Perlman and Netland, 2009; Forni et al., 2017). The fact that RaTG13 and SARS CoV-2 share the same solution makes RaTG13 a highly likely direct ancestor of Sars-CoV-2.

A further widely noted feature of SARS-CoV-2 is its furin site (Coutard et al., 2020). This site is absent from RaTG13 and other closely related coronaviruses. The most closely related virus with such a site is

the highly lethal MERS (which broke out in 2012). Possession of a furin site enables SARS-CoV-2 (like MERS) to infect lungs and many other body tissues (such as the gastrointestinal tract and neurons), explaining much of its lethality (Hoffman et al., 2020; Lamers et al., 2020). However, no convincing explanation for how SARS-CoV-2 acquired this site has yet been offered. Our suggestion is that it arose due to the high selection pressure which existed in the miner's lungs and which in general worked to ensure that the virus became highly adapted to the lungs. This explanation, which encompasses how SARS-CoV-2 came to target lung tissues in general, is an important aspect of our proposal.

The implication is therefore that the furin site was not acquired by recombination with another coronavirus and simply represents convergent evolution (as suggested by Andersen et al., 2020).

An intriguing alternative possibility is that SARS-CoV-2 acquired its furin site directly from the miner's lungs. Humans possess an epithelial sodium channel protein called ENaC-a whose furin cleavage site is identical over eight amino acids to SARS-CoV-2 (Anand et al., 2020). ENaC-a protein is present in the same airway epithelial and lung tissues infected by SARS-CoV-2. It is known from plants that positive-stranded RNA viruses recombine readily with host mRNAs (Greene and Allison, 1994; Greene and Allison, 1996; Lommel and Xiong, 1991; Borja et al., 2007). The same evidence base is not available for positive-stranded animal RNA viruses, (though see Gorbalenya, 1992) but if plant viruses are a guide then acquisition of its furin site via recombination with the mRNA which encodes ENaC-a by SARS-CoV-2 is a strong possibility.

A further feature of SARS-CoV-2 has been the very limited adaptive evolution of its genome since the pandemic began (Zhan et al., 2020; van Dorp et al., 2020; Starr et al., 2020). It is a well-established principle that viruses that jump species undergo accelerated evolutionary change in their new host (e.g. Baric et al., 1997). Thus, SARS and MERS (both coronaviruses) underwent rapid and readily detectable adaptation to their new human hosts (Forni et al., 2017; Dudas and Rambaut, 2016). Such an adaptation period has not been observed for SARS-CoV-2 even though it has now infected many more individuals than SARS or MERS did. This has even led to suggestions that the SARS-CoV-2 virus had a period of cryptic circulation in humans infections that predated the pandemic (Chaw et al., 2020). The sole mutation consistently observed to accumulate across multiple studies is a D614G substitution in the spike protein (e.g. Korber et al., 2020). The numerically largest analysis of SARS-CoV-2 genomes, however, found no evidence at all for adaptive evolution, even for D614G (van Dorp et al., 2020).

The general observation is therefore that Sars-CoV-2 has remained functionally unchanged or virtually so (except for inconsequential genetic changes) since the pandemic began. This is a very important observation. It implies that SARS-CoV-2 is highly adapted across its whole set of component proteins and not just at the spike (Zhan et al., 2020). That is to say, its evolutionary leap to humans was completed before the 2019 pandemic began.

It is hard to imagine an explanation for this high adaptiveness other than some kind of passaging in a human body (Zhan et al., 2020). Not even passaging in human cells could have achieved such an outcome.

Two examples illustrate this point. In a follow up to Shang and Ye et al., (2020), a similar group of Minnesota researchers identified a distinct strategy by which the spike (S) protein (which contains the receptor bind domain; RBD) of SARS-CoV-2 evades the human immune system (Shang and Wan et al., 2020). This strategy involves more effective hiding of its RBD, but it implies again that the spike and the RBD evolved in tandem and in the presence of the human immune system (i.e. in a human body and not in tissue culture).

The Andersen authors, in their critique of a possible engineered origin for SARS-CoV-2, also stress the need for passaging in whole humans:

"Finally, the generation of the predicted O-linked glycans is also unlikely to have occurred during cell-culture passage, as such features suggest the involvement of an immune system" (Andersen et al., 2020).

The final point that we would like to make is that the principal zoonotic origin thesis is the one proposed by Andersen et al. Apart from being poorly supported this thesis is very complex. It requires two species jumps, at least two recombination events between quite distantly related coronaviruses and the physical transfer of a pangolin (having a coronavirus infection) from outside China (Andersen et al., 2020). Even then it provides no logical explanation of the adaptedness of SARS-CoV-2 across its whole genome or why the virus emerged in Wuhan.

By contrast, our MMP proposal requires only the one species jump, which is documented in the Master's thesis. Although we do not rule out a possible role for mixed infections in the lungs of the miners, nor the possibility of recombination between closely related variants in those lungs, nor the potential acquisition of the furin site from a host mRNA, only mutation was needed to derive SARS-CoV-2 from RaTG13. Hence our attention earlier to the figure from P. Zhou et al., 2020 showing that RaTG13 is the most closely related virus to SARS-CoV-2 *over its entire length*. This extended similarity is perfectly consistent with a mutational origin of SARS-CoV-2 from RaTG13.

In short, the MMP theory is a plausible and parsimonious explanation of all the key features of the COVID-19 pandemic and its origin. It accounts for the propensity of SARS-CoV-2 infections to target the lungs; the apparent preadapted nature of the virus; and its transmission from bats in Yunnan to humans in Wuhan.

Further questions

The hypothesis that SARS-CoV-2 evolved in the Mojiang miner's lungs potentially resolves many scientific questions about the origin of the pandemic. But it raises others having to do with why this information has not come to light hitherto. The most obvious of these concern the actions of the Shi lab at the WIV.

Why did the Shi lab not acknowledge the miners' deaths in any paper describing samples taken from the mine (Ge et al., 2016 and P. Zhou et al., 2020)? Why in the title of the Ge at al. 2016 paper did the Shi lab call it an "abandoned" mine? When they published the sequence of RaTG13 in Feb. 2020, why did the Shi lab provide a new name (RaTG13) for BtCoV/4991 when they had by then cited BtCoV/4991 twice in publications and once in a genome sequence database and when their sequences were from the same sample and 100% identical (P. Zhou et al., 2020)? If it was just a name change, why no acknowledgement of this in their 2020 paper describing RaTG13 (Bengston, 2020)? These strange and unscientific actions have obscured the origins of the closest viral relatives of SARS-CoV-2, viruses that are suspected to have caused a COVID-like illness in 2012 and which may be key to understanding not just the origin of the COVID-19 pandemic but the future behaviour of SARS-CoV-2.

These are not the only questionable actions associated with the provenance of samples from the mine. There were five scientific publications that very early in the pandemic reported whole genome sequences for SARS-CoV-2 (Chan et al., 2020; Chen et al., 2020; Wu et al., 2020; P. Zhou et al., 2020; Zhu et al., 2020). Despite three of them having experienced viral evolutionary biologists as authors (George Gao, Zheng-li Shi and Edward Holmes) only one of these (Chen et al., 2020) succeeded in identifying the most closely related viral sequence by far: BtCoV/4991 a viral sequence in the possession of the Shi lab at the WIV that differed from SARS-CoV-2 by just 5 nucleotides.

As we noted in our earlier article, the most important of the questions surrounding the origins of SARS-CoV-2 could potentially be resolved by a simple examination of the complete lab notebooks and biosafety records of relevant researchers at the WIV. Now that a credible and testable lab escape hypothesis exists this task becomes potentially much easier. This moment thus represents an opportune one to renew that call for an independent and transparent investigation of the WIV.

In requesting an investigation we are aware that no scientific institution anywhere has made a comparable request. We believe that this failure undermines public trust in a "scientific response" to the pandemic. Instead, the scientific establishment has labeled the lab escape theory a "rumor", an "unverified theory" and a "conspiracy" when its proper name is a hypothesis. By taking this stance the scientific establishment has given the unambiguous message that scientists who take the possibility of a lab origin seriously are jeopardising their careers. Thus, while countless scientific publications on the pandemic assert in their introductions that a zoonotic origin for SARS-CoV-2 is a matter of fact or near-certainty (and Andersen et al has 860 citations as of July 14th), there is still not one published scientific paper asserting that a lab escape is even a credible hypothesis that deserves investigation.

Anyone who doubts this pressure should read the interview with Birger Sørensen in Norway's Minerva magazine in which Sørensen discusses the "reluctance" of journals to publish his assessment that the existence of a virus that is "exceptionally well adjusted to infect humans" is "suspicious" and "cannot have evolved naturally". The source of this reluctance, says Sørensen, is not rationality or scientific evidence. It results from conflicts of interest. This mirrors our experience. To find genuinely critical analysis of COVID-19 origin theories one has to go to Twitter, blog posts, and preprint servers. The malaise runs deep when even scientists start to complain that they don't trust science.

We nevertheless hope that journalists will investigate some of the conflicts of interest that are keeping scientists and institutions from properly investigating the lab escape hypothesis.

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Sent: 7/8/2021 1:46:41 PM
To: Fauci, Anthony (NIH/NIAID) [E] [redacted]
Subject: Very thorough analysis of SARS-CoV-2 origins by world class virology experts
Attachments: Holmes_SARS-CoV-2_Origins.pdf

Hi Tony,

In case you haven't seen. See attached, very worth reading in detail. Strongly favors a zoonotic origin.

Francis

The Origins of SARS-CoV-2: A Critical Review

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Since the first reports of a novel SARS-like coronavirus in December 2019 in Wuhan, China, there has been intense interest in understanding how SARS-CoV-2 emerged in the human population. Recent debate has coalesced around two competing ideas: a "laboratory escape" scenario and zoonotic emergence. Here, we critically review the current scientific evidence that may help clarify the origin of SARS-CoV-2.

Evidence supporting a zoonotic origin of SARS-CoV-2

Coronaviruses have long been known to present pandemic risks. SARS-CoV-2 is the ninth documented coronavirus that infects humans and the seventh identified in the last 20 years[1,2]. All previous human coronaviruses have zoonotic origins, as have the vast majority of human viruses. The emergence of SARS-CoV-2 bears several signatures of these prior zoonotic events. It displays clear similarities to SARS-CoV that spilled over into humans in Foshan, Guangdong province, China in November 2002, and again in Guangzhou, Guangdong province in 2003[3]. Both these SARS-CoV emergence events were associated with markets selling live animals and involved species, particularly civets and raccoon dogs[4], that were also sold live in Wuhan markets in 2019[5] and are known to be susceptible to SARS-CoV-2 infection[6]. Animal traders working in 2003, without a SARS diagnosis, were documented to have high levels of IgG to SARS-CoV (13% overall and >50% for traders specializing in civets[7]). Subsequent serological surveys found ~3% positivity rates to SARS-CoV related (SARSr-CoV) viruses in residents of Yunnan province living close to bat caves[8], demonstrating regular exposure in rural locations. The closest known relatives to both SARS-CoV and SARS-CoV-2 are viruses from bats in Yunnan, although animals from this province have been preferentially sampled. For both SARS-CoV and SARS-CoV-2, there is a considerable geographic gap between Yunnan and the location of the first human cases, highlighting the difficulty in identifying the exact pathway of virus emergence and the importance of sampling beyond Yunnan.

SARS-CoV-2 also shows similarities to the four endemic human coronaviruses: HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63. These viruses have zoonotic origins and the circumstances of their emergence are unclear. In direct parallel to SARS-CoV-2, HCoV-HKU1, which was first described in a large Chinese city (Shenzhen, Guangdong) in the winter of 2004, has an unknown animal origin, contains a furin cleavage site in its spike protein, and was originally identified in a case of human pneumonia[9].

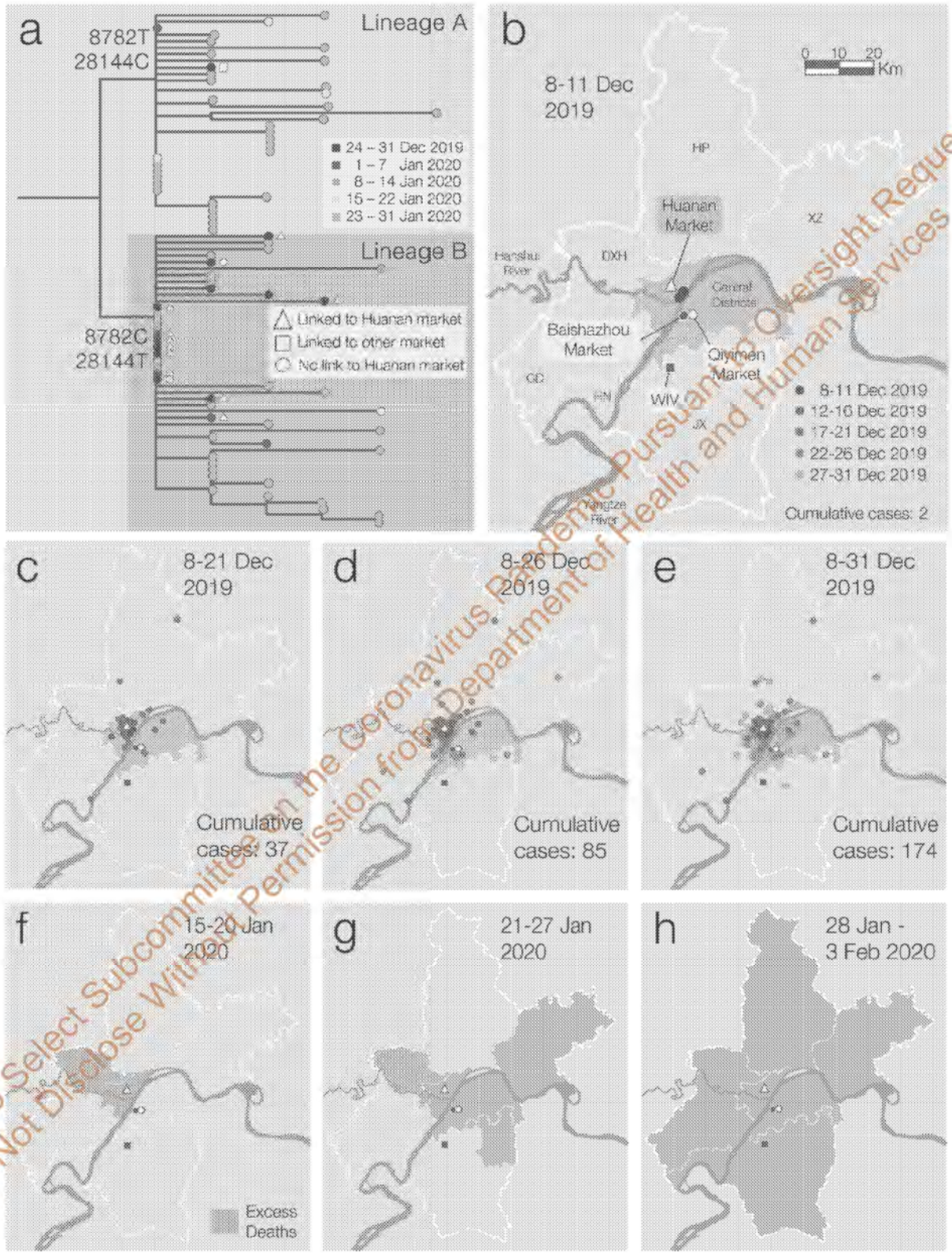

Figure 1 | Phylogenetic and epidemiological data on the early COVID-19 pandemic in Wuhan.

(**a**) Phylogenetic tree of early SARS-CoV-2 genomes sampled from Wuhan during December 2019-

January 2020. The split between lineages A and B is labelled with the coordinates and base of the two differentiating nucleotide mutations. Cases with a known association to the Huanan or other markets are denoted by symbols (reported in ref. 10). (**b**) Map of districts of Wuhan showing the location of markets, the BSL-4 campus of the Wuhan Institute of Virology (where the coronavirus work of Dr. Shi Zhengli is performed) and the earliest known cases. (**c-e**) Location of recorded COVID-19 cases in Wuhan from 8th December to 31st December 2019. Cases with a home address outside of Wuhan city are not shown. (**f-h**) Map of districts of Wuhan indicating the first record of excess deaths due to pneumonia (shaded green) from 15th January 2020. Case and excess death data were extracted and redrawn from figures provided in ref 10. For more details see **supplementary information**.

Based on epidemiological data, the Huanan market in Wuhan was an early and major epicenter of SARS-CoV-2 infection. Two of the three earliest documented COVID-19 cases were directly linked to this market selling wild animals, as were 28% of all cases reported in December 2019[10]. Overall, 55% of cases during December 2019 had an exposure to either the Huanan or other markets in Wuhan, with these cases more prevalent in the first half of that month[10]. Examination of the locations of early cases shows that most cluster around the Huanan market, located north of the Yangtze river (**Fig. 1a-e**). These districts were also the first to exhibit excess pneumonia deaths in January 2020 (**Fig. 1f-h**). There is no epidemiological link to any other locality in Wuhan, including the BSL-4 campus of the Wuhan Institute of Virology (WIV) located south of the Yangtze and the subject of considerable speculation. Although some early cases do not have a direct epidemiological link to a market[10], this is expected given high rates of asymptomatic transmission and undocumented secondary transmission events, and was similarly observed in early SARS-CoV cases in Foshan[3].

During 2019, markets in Wuhan – including the Huanan market – traded many thousands of live wild animals including high-risk species such as civets and raccoon dogs[5]. Following its closure, SARS-CoV-2 was detected in environmental samples at the Huanan market, primarily in the western section that traded in wildlife and domestic animal products, as well as in associated drainage areas[10]. While animal carcasses retrospectively tested negative for SARS-CoV-2, these were unrepresentative of the live animal species sold, and specifically did not include raccoon dogs and other animals known to be susceptible to SARS-CoV-2[5].

The earliest split in the SARS-CoV-2 phylogeny defines two lineages - denoted A and B[11] - that likely circulated contemporaneously (**Fig. 1a**). Lineage B, which became dominant globally, was observed in early cases linked to the Huanan market and environmental samples taken there, while lineage A contains a case with exposure to other markets (**Fig. 1a,b**) as well as with later cases in Wuhan and other parts of China[10]. This phylogenetic pattern is consistent with the emergence of SARS-CoV-2 involving one or more contacts with infected animals and/or traders, including multiple spill-over events, as potentially infected or susceptible animals were moved into or between Wuhan markets via shared supply chains and sold for human consumption[9]. The potential emergence of SARS-CoV-2 across multiple markets again mirrors SARS-CoV in which high levels of infection, seroprevalence and genetic diversity in animals were documented at both the Dongmen market in Shenzhen[4,12] and the Xinyuan market in Guangzhou[13,14].

Viruses closely related to SARS-CoV-2 have been documented in bats and pangolins in multiple localities in South-East Asia, including in China, Thailand, Cambodia, and Japan[15,16], with serological evidence for viral infection in pangolins for more than a decade[17]. However, a significant evolutionary gap exists between SARS-CoV-2 and the closest related animal viruses: their genetic distances of approximately 4% (~1,150 mutations) equates to decades of evolutionary divergence[18]. Widespread genomic recombination also complicates the assignment of which viruses are closest to SARS-CoV-2. Although *Rhinolophus* bat virus RaTG13 collected in Yunnan has the highest average genetic similarity to SARS-CoV-2, a history of recombination means that three other bat viruses – RmYN02, RpYN06 and PrC31 – are closer in most of the virus genome (particularly ORF1ab) and thus share a more recent common ancestor with SARS-CoV-2[15,16,19]. None of these closer viruses were collected by the WIV. This demonstrates beyond reasonable doubt that RaTG13 is not the progenitor of SARS-CoV-2, with or without laboratory manipulation or experimental mutagenesis.

Although no bat reservoir nor intermediate animal host for SARS-CoV-2 has been identified to date, initial cross-species transmission events are very likely to go undetected. Most SARS-CoV-2 index case infections are unlikely to have resulted in sustained onward transmission[20] and only a very small subset of spillover events from animals to humans result in major outbreaks. Indeed, the animal origins of many well-known human pathogens, including Ebola virus, Hepatitis C virus, poliovirus, and the coronaviruses HCoV-HKU1 and HCoV-NL63, are yet to be identified,

while it took over a decade to discover bat viruses with >95% similarity to SARS-CoV and able to use hACE-2 as a receptor[21].

Could SARS-CoV-2 have escaped from a laboratory?

There are precedents for laboratory incidents leading to isolated infections and transient transmission chains, including SARS-CoV[22]. Aside from the 1977 A/H1N1 influenza pandemic that likely originated from a large-scale vaccine challenge trial[23], there are no documented examples of human epidemics or pandemics resulting from research activity.

The emergence of SARS-CoV-2 differs markedly from documented laboratory escapes that, with the exception of Marburg virus[24], have been of readily identifiable viruses capable of human infection and associated with sustained work in high titer cultures[25–27]. No previous epidemic has been caused by the escape of a novel virus and there is no data to suggest that the WIV—or any other laboratory—were working on SARS-CoV-2, or any virus close enough to be the progenitor, prior to the COVID-19 pandemic. Viral genomic sequencing without cell culture, which was routinely performed at the WIV, represents a negligible risk as viruses are inactivated during RNA extraction[28] and no case of laboratory escape has been documented following the sequencing of viral samples.

Known laboratory outbreaks have been traced to both workplace and family contacts of index cases and to the laboratory of origin[25–27,24]. Despite extensive contact tracing of early cases during the COVID-19 pandemic, there have been no reported cases related to any laboratory staff at the WIV and all staff in the laboratory of Dr. Shi Zhengli were reported to be seronegative for SARS-CoV-2 when tested in March 2020[10]. During a period of high influenza transmission and other respiratory virus circulation[29] reports of illnesses would need to be confirmed as caused by SARS-CoV-2 to be relevant. Epidemiological modeling suggests that the number of hypothetical cases needed to result in multiple hospitalized COVID-19 patients prior to December 2019 is incompatible with observed clinical, genomic, and epidemiological data[20].

The WIV possesses an extensive catalogue of samples derived from bats and has reportedly successfully cultured three SARSr-CoVs from bats, all of which are genetically distinct from SARS-CoV-2[30–32]. These viruses were isolated from fecal samples through serial amplification in

VeroE6 cells, a process that consistently results in the loss of the SARS-CoV-2 furin cleavage site[33–39]. It is therefore highly unlikely that these techniques would result in the isolation of a SARS-CoV-2 progenitor with an intact furin cleavage site. No published work indicates that other methods, including the generation of novel reverse genetics systems, were used at the WIV to propagate infectious SARSr-CoVs based on sequence data from bats. Gain-of-function research would be expected to utilize an established SARSr-CoV genomic backbone, or at a minimum a virus previously identified via sequencing. However, past experimental research using recombinant coronaviruses at the WIV has used a genetic backbone (WIV1) unrelated to SARS-CoV-2[32] and SARS-CoV-2 carries no evidence of genetic markers one might expect from laboratory experiments[40]. There is no rational experimental reason why a new genetic system would be developed using an unknown and unpublished virus, with no evidence nor mention of a SARS-CoV-2-like virus in any prior publication or study from the WIV[32,41,42], no evidence that the WIV sequenced a virus that is closer to SARS-CoV-2 than RaTG13, and no reason to hide research on a SARS-CoV-2-like virus prior to the COVID-19 pandemic. Under any laboratory escape scenario SARS-CoV-2 would have to have been present in a laboratory prior to the pandemic, yet no evidence exists to support such a notion and no sequence has been identified that could have served as a precursor.

A specific laboratory escape scenario involves accidental infection in the course of serial passage of a SARSr-CoV in common laboratory animals such as mice. However, early SARS-CoV-2 isolates were unable to infect wild-type mice[43]. While murine models are useful for studying infection *in vivo* and testing vaccines, they often result in mild or atypical disease[44–48]. These findings are inconsistent with a virus selected for increased pathogenicity and transmissibility through serial passage through rodents. Although SARS-CoV-2 has since been engineered[49] and adapted by serial passage[50–52], specific mutations in the spike protein, including N501Y, are necessary for such adaptation in mice[51,52]. Notably, N501Y has arisen convergently in multiple SARS-CoV-2 variants of concern in the human population, presumably being selected to increase ACE2 binding affinity[53–56]. If SARS-CoV-2 resulted from attempts to adapt a SARSr-CoV for study in animal models, it would likely have acquired mutations like N501Y for efficient replication in that model, yet there is no evidence to suggest such mutations existed early in the pandemic. Both the low pathogenicity in commonly used laboratory animals and the absence of genomic markers associated with rodent adaptation indicate that SARS-

CoV-2 is highly unlikely to have been acquired by laboratory workers in the course of viral pathogenesis or gain-of-function experiments.

Evidence from genomic structure and ongoing evolution of SARS-CoV-2

Considerable attention has been devoted to claims that SARS-CoV-2 was genetically engineered or adapted in cell culture or "humanized" animal models to promote human transmission[57]. Yet, since its emergence, SARS-CoV-2 has experienced repeated sweeps of mutations that have increased viral fitness[58,59]. The first clear adaptive mutation, the D614G substitution in the spike protein, occurred early in the pandemic[60,61]. Recurring mutations in the receptor binding domain of the spike protein, including N501Y, K417N/T, L452R, and E484K/Q—constituent mutations of the variants of concern—similarly enhance viral infectivity[54,55,62] and ACE2 binding[53,63], refuting claims that the SARS-CoV-2 spike protein was optimized for binding to human ACE2 upon its emergence[56]. Further, some pangolin-derived coronaviruses have receptor binding domains that are near-identical to SARS-CoV-2 at the amino acid level[40,64] and bind to human ACE2 even more strongly than SARS-CoV-2, showing that there is capacity for further human adaptation[65]. SARS-CoV-2 is also notable for being a host generalist virus[66], capable of efficient transmission in multiple mammalian species, including mink, tigers, cats, gorillas, dogs, raccoon dogs, ferrets, and large outbreaks have been documented in mink with spill-back to humans[67] and to other animals[68]. Combined, these findings show that no specific human "pre" adaptation was required for the emergence or early spread of SARS-CoV-2, and the claim that the virus was already highly adapted to the human host[57], or somehow optimized for binding to human ACE2, is without validity.

The genesis of the polybasic (furin) cleavage site in the spike protein of SARS-CoV-2 has been subject to recurrent speculation. Although the furin cleavage site is absent from the closest known relatives of SARS-CoV-2[40], this is unsurprising as the lineage leading to this virus is poorly sampled and the closest bat viruses have divergent spike proteins due to recombination[15,16,18]. Furin cleavage sites are commonplace in other coronavirus spike proteins, including some feline alphacoronaviruses, MERS-CoV, most but not all strains of mouse hepatitis virus, as well as in endemic human betacoronaviruses such as HCoV-OC43 and HCoV-HKU1[69–71]. A near identical nucleotide sequence is found in the spike gene of the bat coronavirus HKU9-1[72], and both SARS-CoV-2 and HKU9-1 contain short palindromic sequences immediately upstream of this sequence that are indicative of natural recombination break-points via template switching[72]. Hence, simple

evolutionary mechanisms can readily explain the evolution of an out-of-frame insertion of a furin cleavage site in SARS-CoV-2 (**Fig. 2**).

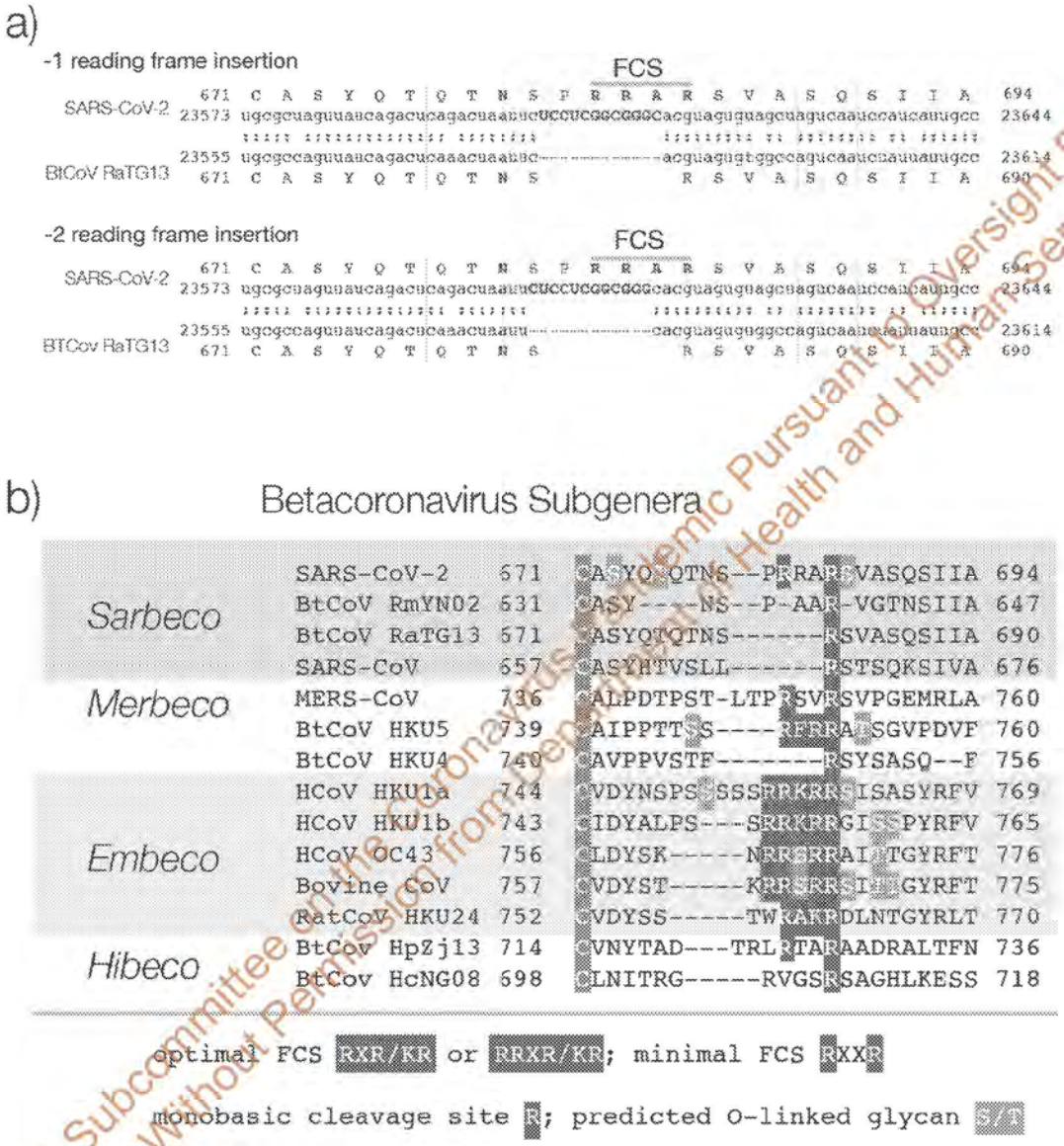

Figure 2 | Evolution of the furin cleavage site (FCS) in the spike protein of betacoronaviruses. (**a**) Sequence alignment of the region around the FCS in SARS-CoV-2 (NCBI accession MN908947) and bat coronavirus RaTG13 (NCBI accession MN996532) showing that the former was the result of an out-of-frame nucleotide sequence insertion. (**b**) Amino acid sequence alignment of the FCS region in representative members of the different subgenera of betacoronaviruses, highlighting the evolutionary volatility of this site and that the relevant amino acid motif (RRAR) in SARS-CoV-2 is functionally suboptimal. The residues predicted to be O-linked glycans are also marked. For more details see **supplementary information**.

The SARS-CoV-2 furin cleavage site (containing the amino acid motif RRAR) does not match its canonical form (R-X-R/K-R), is suboptimal compared to those of HCoV-HKU1 and HCoV-OC43, lacks either a P1 or P2 arginine (depending on the alignment), and was caused by an out-of-frame insertion (**Fig. 2**). The RRAR and RRSR S1/S2 cleavage sites in feline coronaviruses (FCoV) and cell-culture adapted HCoV-OC43, respectively, are not cleaved by furin[69]. There is no logical reason why an engineered virus would utilize such a poor furin cleavage site, which would entail such an unusual and needlessly complex feat of genetic engineering. The only previous studies of artificial insertion of a furin cleavage site at the S1/S2 boundary in the SARS-CoV spike protein utilized an optimal 'RRSRR' sequence in pseudotype systems[73,74]. Further, there is no evidence of prior research at the WIV involving the artificial insertion of complete furin cleavage sites into coronaviruses.

The recurring P681H/R substitution in the proline (P) residue preceding the SARS-CoV-2 furin cleavage site improves cleavage of the spike protein and is another signature of ongoing human adaptation of the virus[75]. The SARS-CoV-2 furin site is also lost under standard cell culture conditions[34,76], as is true of HCoV-OC43[73]. The presence of two CGG codons for arginines in the SARS-CoV-2 furin cleavage site is similarly not indicative of genetic engineering[77]. Although the CGG codon is rare in coronaviruses, it is observed in SARS-CoV, SARS-CoV-2 and other human coronaviruses at comparable frequencies[77]. Further, if low-fitness codons had been artificially inserted into the virus genome they would have been quickly selected against during SARS-CoV-2 evolution, yet both CGG codons are more than 99.8% conserved among the >1,800,000 near-complete SARS-CoV-2 genomes sequenced to date, indicative of strong functional constraints (**supplementary information, Table S1**).

Conclusions

As for the vast majority of human viruses, the most parsimonious explanation for the origin of SARS-CoV-2 is a zoonotic event. The documented epidemiological history of the virus is comparable to previous animal market-associated outbreaks of coronaviruses with a simple route for human exposure. The contact tracing of SARS-CoV-2 to markets in Wuhan exhibits striking similarities to the early spread of SARS-CoV to markets in Guangdong, where humans infected early in the epidemic lived near or worked in animal markets. Zoonotic spillover by definition selects for viruses able to infect humans. The laboratory escapes documented to date

have almost exclusively involved viruses brought into laboratories specifically because of their known human infectivity.

There is currently no evidence that SARS-CoV-2 has a laboratory origin. There is no evidence that any early cases had any connection to the WIV, in contrast to the clear epidemiological links to animal markets in Wuhan, nor evidence that the WIV possessed or worked on a progenitor of SARS-CoV-2 prior to the pandemic. The suspicion that SARS-CoV-2 might have a laboratory origin stems from the coincidence that it was first detected in a city that houses a major virological laboratory that studies coronaviruses. Wuhan is the largest city in central China with multiple animal markets and is a major hub for travel and commerce, well connected to other areas both within China and internationally. The link to Wuhan therefore more likely reflects the fact that pathogens often require heavily populated areas to become established[20].

We contend that there is substantial body of scientific evidence supporting a zoonotic origin for SARS-CoV-2. While the possibility of a laboratory accident cannot be entirely dismissed, and may be near impossible to falsify, this conduit for emergence is highly unlikely relative to the numerous and repeated human-animal contacts that occur routinely in the wildlife trade. Failure to comprehensively investigate the zoonotic origin through collaborative and carefully coordinated studies would leave the world vulnerable to future pandemics arising from the same human activities that have repeatedly put us on a collision course with novel viruses.

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Message

From: Myles, Renate (NIH/OD) [E] [redacted]
Sent: 9/14/2023 9:00:14 PM
To: Lauer, Michael (NIH/OD) [E] [redacted]
CC: Schwetz, Tara (NIH/OD) [E] [redacted]
Subject: RE: WIV

Thank you!

From: Lauer, Michael (NIH/OD) [E] [redacted]
Sent: Thursday, September 14, 2023 4:47 PM
To: Myles, Renate (NIH/OD) [E] [redacted]
Cc: Lauer, Michael (NIH/OD) [E] [redacted] Schwetz, Tara (NIH/OD) [E] [redacted]
Subject: WIV

Hi Renate – the SAM exclusion is here (see attached). As part of our standard pre-award assessment, we check the SAM exclusion list (as do all other government agencies). Thus, it should be impossible for them to receive any Federal funding.

WIV is indefinitely debarred.

Many thanks!

Mike

ECOHEALTH ALLIANCE BUDGET JUSTIFICATION

Note: we corrected this budget first to match the final budget as per the NoA. We then indicated which amounts we aim to renegotiate, and why, and which amounts will not be reallocated:

A. Senior/Key personnel:
The PD/PI, Dr. Peter Daszak, will commit 1 month per year in each year of this budget. He will be primarily responsible for overseeing the project, general management, communication and collaboration with subaward partners, as well as contributing to data analysis and manuscript writing.

Co-Investigator, Dr. Kevin Olival, will commit 1 month per year in each year of this budget. Dr. Olival will lead the design and implementation of the bat sampling fieldwork (Aim 1); facilitate overall project management; and train and oversee field teams. Dr. Olival will also oversee modeling and analyses under Aims 1 & 3, participate in regular conference calls, and help write manuscripts and reports.

Co-Investigator, Dr. Leilani Francisco, will commit 3 months per year in each year of this budget. Dr. Francisco will lead the implementation of the community and clinic-based surveillance (Aim 2), including adherence to study design, sampling methodology, and ethics in human subjects research; data collection instrument development; data management, cleaning, and analysis; and, findings dissemination.

Co-Investigator, Dr. Noam Ross, will commit 1 month per year in each year of this budget. Dr. Ross will lead modeling work and assist in with data analyses and manuscript writing. He will also advise on data management, statistical approaches, and computational work.

B. Other Personnel
Research Scientist, Ms. [redacted] will commit 9 months per year in each year of this budget. Ms. Li will coordinate the field and laboratory activities in China, maintaining the financial administration, results reporting, and data management, as well as work closely with Dr. Lili Ren at the Institute of Pathogen Biology to refine protocols, oversee field data collection, and perform data analysis for human study.

Research Scientist, Dr. [redacted], will commit 2 months per year in each year of this budget. Dr. Latinne will assist in with phylogenetic and phylogeographic analyses and manuscript writing. She will also advise on data management and field activities.

Research Scientist, Dr. [redacted], will commit 1 month per year in each year of this budget. Dr. Chmura will coordinate regular calls, reports, maintain EcoHealth Alliance and subaward budgets and both project and financial reporting, draft subcontracts, and set-up project databases, advise field activities, assist with statistical analysis, and manuscript writing.

Research Scientist, Ms. [redacted], will commit 4 months per year in each year of this budget. Ms. Hagan will assist with the development of human data collection instruments, testing, and implementation; advise on data storage, data analyses, and manuscript writing. She will also provide training for field teams conducting human subjects research.

Fringe benefits for Year 1 are calculated for EcoHealth Alliance's federally approved rate of 31.5% of base salary and is included in all subsequent years.

Personnel have been changed in our budget, replacing staff who have left, and replacing with staff who have the correct experience for the proposed work in our renegotiated Specific Aims.

C. Equipment
No Equipment costing more than $5,000 will be purchased

Commented [GS([1]: How has the roles and the work that each of these individuals changed since there will not be field work or animal studies? As well as a reduction in the # of subs. Please reference the revised Aims in the new justification

Commented [AC2R1]: See NEW version for updated text.

Commented [GS([3]: Why has this portion of the budget not changed? Several of the individuals had roles that involved field work or contact with subs that have been proposed to be removed as well as Human Subjects research. Please reference the revised Aims in the new justification

Commented [AC4R3]: Added to NEW version.

Commented [GS([5]: Revised budgets must reflect this change

Commented [AC6R5]: Done and see NEW version

D. Travel

Domestic Travel

$9,440 is requested annually for Years 1 through 5 for the PD/PI, 3 Co-Investigators, and 1 Research Scientist to attend and present on research results at the annual American Society for Tropical Medicine and Hygiene and the American Public Health Association meetings. 2 night and 3 day travel to Washington, DC is calculated as follows: $205 for hotels ($251 x 2 nights x 5 people x 2 trips = $5,020); $76 for meals and incidentals ($76 x 2.5 days x 5 people x 2 trips = $1,900); and $252 for round-trip train ($252 x 5 x 2 = $2,520).

Commented [AC7]: Updated in NEW version

Domestic travel is requested at the same level for the same activities.

International Travel

$11,998 is requested annually in Years 1 to 5. This will support round-trip flights from New York to Beijing and Wuhan for the annual meetings for 3 Senior/Key Personnel and 1 for the PD/PI (Daszak) at $1,055 each. Five nights and six days of hotels, meals, and incidentals for 3 Senior/Key Personal and 1 PD/PI are calculated at $1,944.50 per year: hotels at $258 per night (x 5 nights and 4 personnel = $5,160) and meals and incidentals at $119 per day (x 5.5 days and 4 personnel = $2,856).

The purpose of this portion of this international travel was for annual meetings with in-country collaborators. Given that we are now required to conduct twice-yearly in-person review of facilities, and we need to meet with our collaborators regularly to conduct review of results, we request that this full budget remains available for travel.

Commented [GS([8]: Will the same number of trips be conducted as originally planed and will the same number of people be traveling as originally planned, what are the accommodation costs broken out per person per year?

Commented [AC9R8]: Updated and clarified in NEW version

$17,960 is requested annually in Years 1 to 5 for EHA Research Scientists (Ms. [redacted] and Ms. [redacted]) who will travel to China for two field training and supervising visits per year for duration of 21 days each. Support for this request, annually, is $17,960 and is calculated as follows: 2 round trip flights = $4,400; hotel $258 x 20 nights x twice a year = $4,732; meals and incidentals at $119 per day x 20.5 days x twice a year = $3,570

The purpose of this portion of the travel budget was to conduct 1) field training and 2) supervising visits. There will be no international field work in our proposed renegotiated specific aims. However, we will require supervisory visits to ensure compliance with project goals. Therefore we request that 50% of this budget remains available for 1 staff member to conduct supervisory visits each year = $8,980 in each year 1 through 5.

Commented [GS([10]: Isn't this cost covered in the 11,998 above? What is the difference between this and the twice yearly in person review of facilities and the supervisory visits

Commented [PD11R10]: This is for project planning and for the archived sample coordinator to visit collaborator and arrange efficient sample identification, shipping and analysis

Commented [AC12R10]: Updated and clarified in NEW version

Our request is now for 4 people traveling to Singapore per year = $20,978, broken out as follows:

Annual Meetings

$11,998 is requested annually in Years 1 to 5. This will support round-trip flights from New York to Singapore for annual meetings for 2 Senior/Key Personnel and 1 for the PD/PI (Daszak) at $1,639 each. Five nights and six days of hotels, meals, and incidentals for 2 Senior/Key Personal and 1 PD/PI are calculated as follows: hotels at $278 per night (x 5 nights and 3 personnel = $4,170) and meals and incidentals at $129 per day (x 5.5 days and 3 personnel = $2,129). Additional travel costs are estimated per person for daily taxis Singapore ($8/ride twice per day = $16/day); airport (NYC $70.25/trip and SIN $12/trip) taxis.

Supervisory Visits

$8,980 is requested annually in Years 1 to 5 for EHA Research Scientist Ms. [redacted] to conduct supervision visits for 7 days twice per year. Support for this request is calculated as follows: 2 round trip flights = $3,318; hotel $278 x 6 nights x twice a year = $3,336; meals and incidentals at $129 per day x 6.5 days x twice a year = $1,677. Additional travel costs are estimated per person for daily taxis Singapore ($8/ride four times per day (hotel <-> laboratory and hotel <-> university) = $32/day); airport (NYC $70.25/trip and SIN $12/trip) taxis.

Commented [GS([13]: Can you clarify the calculations? Simplify it, what is in the cost? How many trips? The number of people going, the days and the total per trip. Or just list the cost per trip for all people. I don't need to know the math really. So hotel cost for 3 people 5 nights is 1,000. Instead of 278x5nights x 3 people.

Commented [AC14R13]: See NEW version for these edits per request above.

Commented [GS([15]: Same as above

Commented [AC16R15]: See NEW version.

E. Participant/Trainee Support Costs
There are no participant/trainee support costs.

F. Other Direct Costs
Materials & Supplies
We request $7,000 in Year 1 for sample collection materials to be shipped to China including bat catching equipment ($1,000); PPE ($2,000); and 1 liquid nitrogen dry shipper ($1,000) for Wuhan Institute of Virology in China to be used by Dr. Guanjian Zhu for field work.

Although no fieldwork will now be collected, we will require costs for archived samples to be aliquoted and sent frozen to Duke-NUS. We therefore request Yr 1 costs of liquid nitrogen, shipping equipment, sample vials and storage equipment and costs at $4,000. The previous allocations of $1,000 for bat catching equipment and $2,000 for PPE in Year 1 are not requested.

In Years 2 through 5, field and human sampling will be completely underway; we request support for PPE ($2,000) and other sample collection materials ($2,000) in each of these years.

Although no fieldwork will now be done, we will require costs for archived samples to be aliquoted and sent frozen to Duke-NUS. We therefore request Yr2-5 costs of liquid nitrogen, shipping equipment at $2,000 per year. The previous allocation of $2,000 for PPE per year are not requested.

Publication Costs
We request $6,000 per year for only Years 2 to 5 for publication fees required to publish research findings in peer-reviewed journals such as *Nature*, *Public Library of Science*, and other journals.

Subawards/Consortium/Contractual Costs
We are requesting consortium/contractual support for our three partners: Wuhan Institute of Virology (WIV), Institute of Pathogen Biology (IPB), and University of North Carolina (UNC). We have fully detailed these direct and indirect costs in their respective sub-award budgets.

Computers, Software, Reference Materials and Dataset Acquisition
We request support of $6,000 to permit two Research Scientists to purchase 1 laptop each (2 x $3,000 including insurance and software). We also request $1,000 per year in each year to cover software and reference materials, and an additional $1,000 per year in each year for acquisition of datasets.

Shipping
We will be shipping the materials and supplies detailed above to our subaward institutions in China (IPB and WIV). Shipping box and all taxes are estimated at $1,667 per shipment. We estimate 3 shipments of supplies and materials will be sent every year through the duration of this project.

Consultants
Dr. Linfa Wang, Co-Investigator/Consultant We request $10,000 per year for each year of the project for a consultancy for Dr. Linfa Wang who will focus on PCR development, serological testing strategy and virus characterization, and will also participate in regular meetings with collaborators. Dr. Wang has more than 20 years of research experience in designing and applying novel testing platforms to discover zoonotic pathogens.

Given the far more detailed analyses of recombination events, hotspot mapping of recombination and ecological drivers, detailed computer modeling of virus-host binding interactions and analyses of human behavioral risk, we request reallocation of this consultancy budget to a new consultant (not Dr. Linfa Wang) who will assist with Recombination analysis and phylogenetic analysis.

Dr. Guangjian Zhu, Co-Investigator/Consultant In total, we request $368,000 for the consultancy of Dr. Guanghan Zhu from Year 1 to Year 5 of the project including: $204,390 for field personnel, $124,750 for field

Commented [GS([17]: Where will the samples be sent from and who will be doing the Aliquoting?
Why is PPE needed and where will it be purchased and used?
Peter Daszak: This is work that will be done by the Research Scientist/archived sample coordinator, who will be based at EHA, organize the sample identification and shipping from here, with regular travel to Duke-NUS and other EHA collaborators. The samples will be sent from countries in SE Asia that EHA has previously collaborated with: Cambodia, China, India, Indonesia, Lao PDR, Malaysia, Myanmar, Thailand, Bangladesh, and Vietnam?

PPE is in EHA's F&A rate and would only be provided for clinical research or a clinical trial.
Reference: https://www.niaid.nih.gov/grants-contracts/ppe-allowable-direct-cost-certain-situations
The request looks to be for 4,000 provide the breakdown on the costs what is the other 3,000 for?

Commented [PD18R17]: 2nd part DONE

Commented [GS([19]: Where will the samples be sent from and who will be doing the Aliquoting? Why is PPE needed and Where will it be purchased and used?
Peter Daszak: This is work that will be done by the Research Scientist/archived sample coordinator, who will be based at EHA, organize the sample identification and shipping from here, with regular travel to Duke-NUS and other EHA collaborators. The samples will be sent from countries in SE Asia that EHA has previously collaborated with. (you can put a list in based on PREDICT and other former collaborators, including China).

PPE is in EHA's F&A rate and would only be provided for clinical research or a clinical trial.

Commented [AC20R19]: PPE is no longer in EHA's budget, but is in DUKE-NUS'. Please see NEW version.

Commented [GS([21]: In the final budget justification this needs to be updated

Commented [AC22R21]: Updated in the NEW version

Commented [GS([23]: this cost will be removed since there will be no shipments from or to China?

Peter Daszak: We expect that there will be shipments from China in the later years of the project, so please put this in for years 4&5

Commented [AC24R23]: Incorporated into total shipping in NEW justification.

Commented [GS([25]: What is their hourly rate and how many hours per year will they commit to the project?

Commented [AC26R25]: Entered in the New version.

travel; $33,548 for field supplies and materials, and $5,255 for other costs. Detailed expenses are calculated as the follows:

Personnel ($204,390)
Dr. Guangjian Zhu Co-Investigator/Consultant will oversee all field sampling activities in China by coordinating with local partners and stakeholders to lead the specimen collection and bats population monitoring at selected surveillance sites. Dr. Zhu is a zoologist and ecologist specializing in bats surveillance in southern and western China and has been leading EcoHealth Alliance's field surveillance work in China for more than 15 years. We request $51,850 annual stipend for Zhu, who will commit 5 months per year to this project in years 1-3 and increase time to 5.33 months per year for in years 4-5, since he will allocate more time to collaborating on peer-reviewed publications in the last two years of the project.

This consultant was tasked with "oversee… field sampling" as well as "coordinating with local partners… for specimen collection". We therefore request that 50% of this consultancy is reallocated to a staff member at EHA to coordinate archived sample identification and transport to Duke-NUS, and conduct oversight of that work, $10,802 per year for Yrs 7-8 & $11,515 per year for Yrs 9 & 10.

Research Assistant (TBD) will assist the Co-PI and Field Coordinator (Zhu) for project data management, reporting, and administration. We request $27,000 p.a. salary for this Research Assistant who will dedicate 2 months p.a. on this project from Years 1-5.

We request reallocation of this consultancy budget, which was originally for 'data management, reporting and administration'. We will use these funds for staff time at EHA to oversee data management and reporting.

Field Assistants (2 in each province, TBD) will assist all field surveillance activities including specimen collection and data entry and management. The assistants will commit a total of 50 days per year to this project from years 1-5. We request $6,000 per year to support each assistant for the field surveillance work.

We request partial reallocation of this budget, which originally include some funds for 'data entry and management'. We will use these funds for staff time at EHA to oversee data entry and management. We request 50% of the original budget of $12,000 (x 50% = $6,000)per year.

Travel ($124,750)
Inter-Province Travel. We request 1) $1,200 per year for all five years of this project to cover 3-per-year round-trip flights/trains each from Shanghai, to Yunnan, Guangdong, Guizhou, and Guangxi for Dr. Zhu to meet with collaborating institutions, train field teams, and ensure sample collection, storage, and shipments. Each round-trip flight is estimated at $400, in total $6,000 for 5 years; 2) $2,400 per year for all five years of this project to cover 2-per-year round-trip flights/trains for 2 field assists traveling to the field sites in Yunnan, Guangdong, Guizhou, and Guangxi for sampling work. Each round-trip flight is estimated at $400, in total $12,000 for 5 years.

We do not request reallocation of this budget, because there will be no field collection of samples in China.

Field Transportation. Field work will take place for 50 days per year for 5 years, the expenses of local transportation include 1) car rental at the rate of $79/car/day, with 1 car for 50 days, in total of $3,950 per year, and $19,750 for 5 years; 2) Gas and toll fee at the rate of $32/car/day, with 1 car for 50 days, in total of $1,600 per year, and $8,000 for 5 years.

Commented [GS([27]: This cost should be removed as the work is not the same. There will be no more collection of samples or field work there for the costs can not be rebudgeted
Additionally, these costs seem duplicative to costs in travel and materials and supplies

Commented [PD28R27]: The original description of this position included "coordinating with local partners" and "collaborating in peer reviewd publications". These are duties that will now be conducted by the Research Scientist/archived sample coordinator. Because no new fieldwork will be conducted, we request that only 50% of the salary costs are reallocated.

Commented [AC29R27]: See NEW justification.

Commented [GS([30]: The personnel section of the new budget should include the individual that will be conducting this work

Commented [AC31R30]: See NEW justification.

We do not request reallocation of this budget, because there will be no field collection of samples in China.

Meal and Lodging. We request 1) $6,400 to cover the expense of meals for 4 field team members in the field for 50 days per year, at the rate of $32/person/day, totaling $32,000 in 5 years; 2) $9,400 for lodging expenses of 4 field team members in the field for 50 days at the rate of $47/person/night, totaling $247,000 in 5 years.

We do not request reallocation of this budget, because there will be no field collection of samples in China.

Supplies and Materials ($33,548)
Biological sampling supplies ($25,165) We request $25,165 to purchase supplies for biological sampling during the 5 years of the project, including 1) puritan calcium alginate swabs $8,800 (5,000 IND); 2) viral sample collection tubes $6,875 (15,000 IND); 3) heparinized glass hematocrit tubes $190 (~4,000IND); 4) mist nets for bats trapping $2,200 (~500IND); 5) cloth bags for bats trapping $2,400 (~1,000IND); 6) Viral Transport Media $4,700 (~7,000 mL).
We request partial reallocation of this budget to cover the costs of identifying, aliquoting, storing in buffer and part of the costs for liquid nitrogen, then shipping on ice archived samples throughout each year. We do not request reallocation of the $8,800 costs for swabs or the $4,600 costs for 'mist nets' or 'cloth bags' specifically for fieldwork collecting bat samples. We therefore request reallocation of the remaining $11,765 for use throughout years 7-10 of the project.

Personal Protection Equipment ($4,336
): We request 1) $3,440 for 3M N95 respirators (~1,600IND) for field work across Year 1-5; 2) $470 for eye protection glasses (~100 IND) for the use in field across Year 1-5; 3) $426 for nitrile gloves (~3,000IND) for sampling work for Year 1-5.

We request reallocation of this budget to the subaward to Duke-NUS to provide part of the costs of PPE required to handle archived samples and conduct the testing at the foreign site in each year of the project.

Cold Chain Maintenance ($4,047): We request $4,047 to purchase 3 liquid nitrogen dry shippers for preserve biological samples in the field before transported an ultra-low temperature freezer. The expense is calculated at the rate of $1,349 each, with 1 purchased per year from Year 1-3, totaling $4,047.

We request reallocation of this budget to provide part of the costs of cold chain maintenance of archived samples for each year of the project.

Equipment ($0)
No equipment over $5,000 will be purchased.

Other Costs ($6,399)
We request 1) a total of $1,275 for specimen transportation or delivery from the field to partners' labs from Year 1-5, at the rate of $85/delivery with 1,000 tubes, with three times per year; and 2) a total of $3,990 for rabies and tetanus vaccination 4 field team members from Year 1-5, at the rate of $199/year/person.

Section 1) of these costs involves 'specimen transportation delivery'. We therefore request full reallocation of this budget to provide part of the costs of specimen transportation of archived

Commented [GS([32]: This cost has already been identified twice in this justification and in both instances it is written that the cost of shipping and liquid nitrogen are covered completely by the reallocation. How is this different? Provide the full required cost for shipping and cost of the samples

Commented [PD33R32]: We will add all of the archived sample shipping, aliquotting and other costs together and have it in one place. This work will be conduted by the Research Scientist/archived sample coordinator

Commented [AC34R32]: All shipping costs are consolidated in NEW version

Commented [GS([35]: This should be included in the sub to Duke as EHA would have the cost of PPE covered by your F&A Rate agreement. This also needs to be justified as to why PPE is needed at the site

Commented [PD36R35]: DONE

Commented [AC37R35]: There is no PPE in EHA NEW Version budget.

Commented [GS([38]: Will this work be conducted by EHA?

Commented [PD39R38]: Yes – organized and carried out by the Research Scientist/Archived sample coordinator

Commented [AC40R38]: See NEW version.

samples for each year of the project. Total $1,275 Section 2) of these costs involved the costs of vaccination of staff in our foreign collaborating institutions. We do not request reallocation of these costs.

H. Indirect Costs

We are requesting the EcoHealth Alliance federally approved indirect cost rate of 32.74% on all applicable direct costs. Indirect is taken only on the first $25,000 for each consortium/contractual agreement in each year. As there are 3 (Wuhan Institute of Virology, Institute of Pathogen Biology, and University of North Carolina), a total of $24,555 ($8,185 x 3) is requested as indirect costs on consortium/contractual/subaward agreements. This is not included as part of direct cost calculations and is only requested for year 1. In years 2-5 no indirect will be taken on consortium/contractual agreement subcontracts.

This renegotiated budget will now only have one subaward to Duke-NUS, so EccHealth Alliance will only apply its negotiated indirect cost to the first $25,000 or one subaward – not three subawards.

Commented [GS([41]: To and from where?

Commented [PD42R41]: As above – this will be from EHA collaborators in SE Asia to Duke NUS, organized and carried out by the Research Scientist archived sample coordinator.

Commented [GS([43]: This cost should be in the Duke budget and not the EHA budget then, also the justification should include how this cost meets the cost principles and citation that DUKE-NUS does not provide Fringe or Health Benefits to employees

Commented [PD44R43]: DONE

Commented [AC45R43]: See NEW version