From: Morens, David (NIH/NIAID) [E] [b6]
Sent: 5/24/2016 9:50:02 PM
To: b6
CC: Johnson Karl [b6]
Subject: bat questions

Hi Jon

when we spoke a few weeks ago about the role of bats in ebola i mentioned rhat Karl Johnson and I and colleagues were discussing the complcated bat data in rhe context of penning an wbola review

In following up on a suggestion of Karl's, is it possible that ebola viruses "bloom" in pregnant females? and we also wonder whether there migjt be seasonalty or other patterns when these bat species breed

The larger question is: are there any factors (such as sex or fighting between males) that might account for waxing and waning of viral infection? Otherwise, the epidemiology is hard to reconcile

Thanks, and i hope you will be coming down for the seminar on, what is it, the 3rd? Get Peter to put you up at the b6 and relax and take in DC

thanks as always

david

David M Morens MD
NIAID, NIH
Sent from my iPhone

From: Morens, David (NIH/NIAID) [E] [b6 b6]
Sent: 7/26/2020 12:22:48 AM
To: Jon Cohen [jcohen@aaas.org]
CC: Joel Breman [b6]; Gerald Keusch [b6]; Peter Daszak [b6]; Taubenberger, Jeffery (NIH/NIAID) [E] [b6]; Administrative Group (b6)
Subject: Re: Another Great article, thanks!

Thanks for your great stuff! Really. David

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

> On Jul 25, 2020, at 20:04, Jon Cohen <jcohen@aaas.org> wrote:
>
> Yes, I read. Many thanks to all of you. I'm going to see if I can add a link in my article.
>
> All the best,
>
> Jon
>
>> On Jul 25, 2020, at 4:36 PM, Morens, David (NIH/NIAID) [E] b6 wrote:
>>
>> [EXTERNAL EMAIL]
>>
>> Jon, Joel Breman, President of Am Soc Trop Med Hyg, called me today to ask me to bring to your attention the two publications, out this past Wednesday, in the ASTMH journal, which defend the work Of Peter and Chinese colleagues in a background review and a companion go-with editorial. Each of these papers is authored by senior internationally recognized experts And provide evidence in accord with your reporting. David
>>
>> Sent from my iPhone
>> David M Morens
>> OD, NIAID, NIH
>

From: Morens, David (NIH/NIAID) [E] [b6 b6]
Sent: 8/5/2021 12:09:13 PM
To: Jason Gale [j.gale@bloomberg.net]
CC: b6; Garry, Robert F [b6]; b6
BCC: Morens, David (NIH/NIAID) [E] [b6 b6]
Subject: Re: draft

Great piece!!!!!!! Kudos to you! dmm

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

On Aug 5, 2021, at 07:37, Jason Gale (BLOOMBERG/ NEWSROOM:) <j.gale@bloomberg.net> wrote:

Hi guys. Please keep this to yourselves. Thanks for trusting me with your perspectives and thoughts. Here's what I drafted. Every editor involved (and there's a bunch!) has a different idea on what the story should say at the top. I can't say I love this iteration, but it's bound to change anyway! (The original was a lot more colorful). Always glad to get your thoughts. Thanks again. Jason

By Jason Gale
(Bloomberg) --
The origin story of Covid-19 in China remains a mystery more than 18 months into the pandemic. Conjecture the virus escaped from a maximum security biology lab in Wuhan has piqued the interest of foreign intelligence services, despite no supporting evidence that's surfaced publicly.
A more plausible theory, some scientists contend based on past coronavirus outbreaks, is that an infected animal brought the virus to a Wuhan seafood and produce market, where many of the early cases of Covid-19 were traced back to in late 2019.
Chinese authorities have shot down that theory as steadfastly as the lab-leak hypothesis, insisting there were never any wild animals sold at the market.
Yet a just-published study by researchers in China and at the University of Oxford containing photographic evidence of Wuhan's wildlife trade suggests otherwise. Minks, civets, raccoon dogs and other mammals known to harbor SARS-CoV-2 and related coronaviruses were sold for food and as pets in plain sight in shops across Wuhan for years, including the Huanan Seafood

Wholesale Market, considered ground zero of the global health crisis.

The evidence, collected by a scientist working at a research lab affiliated with China's Ministry of Education, gathered dust for a year and a half, buried under layers of bureaucracy and obfuscation. The delay allowed Chinese officials to weave alternative narratives in which the virus could not have possibly evolved in an animal market, and that the threat was likely imported from elsewhere. Meanwhile, controversial speculation that the virus had escaped from a nearby lab gained traction.

"It is unclear why earlier initiatives within China to locate source animals for SARS-CoV-2 were curtailed, and now appear unfortunately to have stopped," said Robert F. Garry, a professor of microbiology and immunology at Tulane University's School of Medicine in New Orleans. "Instead, the focus is on highly implausible origins scenarios. If we continue to place politics over science, humanity will again be unprepared for the next emergence of a pandemic virus."

The U.S. Intelligence Community is slated to report its own findings later by Aug. 24, but Garry and others say that with only circumstantial evidence remaining, scientists are unlikely to get to the bottom of what caused the outbreak. They are left wondering whether among the dozens of species of exotic animals sold live across Wuhan, animals existed that may have acted as intermediate hosts between the pandemic strain and its closest known relative -- a virus collected from a bat cave in Yunnan province nine years ago.

Quickly unraveling Covid's genesis could have yielded more than valuable lessons in how to ensure new infectious diseases don't trigger catastrophic outbreaks; it could have averted a raging political debate that's already caused a trade war between China and Australia, as nations demand to know how SARS-CoV-2 emerged.

The evidence that scientists needed to solve the mystery of Covid's origins may have been in the hands of Xiao Xiao, a scientist whose roles straddled epidemiology and animal research at the Hubei University of Traditional Chinese Medicine and the government-funded Key Laboratory of Southwest China Wildlife Resources Conservation. Xiao routinely surveyed 17 shops selling live wild animals across four wholesale and retail centers from May 2017 through November 2019 -- finishing just weeks before the discovery of mysterious pneumonia cases at the Huanan market heralded the start of the pandemic.

Seven of the shops Xiao surveyed were in the Huanan market, which was linked two of the three earliest documented Covid-19 cases.

On each of his monthly visits, Xiao asked vendors what species they had sold over the preceding month and in what numbers and at what price. It wasn't the novel coronavirus that Xiao was hunting, but the source of a tick-borne disease that had spread in Hubei province years earlier.

Xiao checked the animals for injuries and disease, noting that almost a third bore trapping and shooting wounds, and that none of the shops displayed an origin or quarantine certificate, making the trade "fundamentally illegal." Of the 38 animal species Xiao documented, 31 were protected. Traders caught violating China's wild animal conservation law face fines and up to three years imprisonment.

As an objective observer unconnected to law enforcement, Xiao was granted "unique and complete access to trading practices," he and his colleagues noted. Xiao's list of animals included masked palm civets and raccoon dogs -- both involved in the 2003 SARS outbreak -- and other species susceptible to coronavirus infections, including bamboo rats, minks, hog badgers and hedgehogs.

The shop owners gave written consent for the research, but for the most part, their animal-wares were displayed openly, "caged, stacked and in poor condition," Xiao observed. Over the 30-month survey period, he estimated 47,381 wild animals were sold in Wuhan -- one of the 10 most-surveilled cities in the world, according to Comparitech Ltd., a U.K.-based security researcher which estimates there are 339 CCTV cameras per square mile in Wuhan.

The live animals weren't a cheap form of bushmeat, akin to the remains of animals killed in the jungles and savannas of Africa, Xiao said. These were luxury food items priced at up to $25 a kilogram ($11/pound) -- or more than four times costlier than pork, China's main meat staple. Most of the shops offered custom, onsite butchering services.

Remarkably Xiao's findings -- and broad awareness of Wuhan's flourishing wildlife trade -- didn't surface until June 2021 -- 18 months after Covid surfaced and four months after a 17-person international team of experts convened by the World Health Organization completed a four-week mission in Wuhan in February to study Covid's origins.

It wasn't like Xiao and his colleagues -- Zhou Zhaomin, a researcher from a wildlife resources laboratory affiliated with China's Ministry of Education, and three seasoned scientists from the University of Oxford's Wildlife Conservation Research Unit -- held onto their research. A manuscript was submitted to a journal in February 2020. The authors anticipated "support and swift publication," enabling the data to be widely shared, co-author Chris Newman, a zoologist with some 177 publications to his credit, recalled in an email.

Instead, an indepedent expert assessing the paper as part of the peer-review process publications are typically subjected to "cast aspersions onto the veracity of our dataset, both in terms of Dr. Xiao's surveying and the extent to which these data might accurately reflect all species sold in the markets," Newman said. A revised version was met with a second round of questions that led to further delays. At the end of September 2020, the journal rejected the paper outright.

“They did not think it would have widespread appeal,” Newman said. “It caused us, especially our Chinese co-authors, concern that these data would not be taken seriously.”

The manuscript was revised a third time to include data on China’s pangolin trade networks, and sent the following month to Scientific Reports. Springer Nature AG & Co., the journal’s publisher submitted it directly to the WHO shortly after it was received as part of an agreement with the agency, said Ed Gerstner, Springer Nature’s director of journals, policy and strategy.

The paper, cryptically titled “Pangolin trading in China: Wuhan’s alibi in the origin of Covid-19” went to a generic email address at WHO for receiving unpublished papers, with a copy sent to Maria van Kerkhove, the organization’s technical lead for Covid-19. There, the paper languished amid the tens of thousands of manuscripts that have flooded the Geneva-based agency since January last year.

Newman said he was grateful Nature Scientific Reports ultimately published the paper after it was revised yet again, trimmed of the pangolin element, and recast to focus once more on the wildlife trade in Wuhan. Still, the process took eight months, held up by a common struggle journals faced finding scientists to review other researchers’ manuscripts amid intense demands from the pandemic, he said.

Van Kerhove found the process “very frustrating,” she said, adding that she regretted there was no direct follow up from the journal during the eight-month review process or by the authors themselves to inform the WHO-convened global study of the origins of SARS-CoV-2 that began in mid-January 2021.

“It’s a shame this important information was not shared directly with the mission team while the team was in Wuhan and visited the markets,” she said in an email. “This paper would certainly have added great value to the mission team.”

Zhaomin Zhou, a scientist working across two government-affiliated labs in Nanchong, Sichuan province who was nominated to act as spokesman on the publication, said the paper had been rejected by several journals by the time it was submitted to Scientific Reports. “We were unwilling to disclose it to any other parties, unless the peer reviewers think the paper is almost ready,” he said in an email in June.

Newman said the data weren’t his to share, but belonged to Xiao, a recent collaborator in China. “These were his data and his contacts in the markets,” Newman said. “Plus we were sensitive to not wanting to compromise our Chinese authors.”

Xiao didn’t respond to emails requesting comment. Newman said he “has essentially disappeared off of our radar, although we remain in close contact with my good friend Zhaomin.”

The China-based authors had to be cautious. On Feb. 25, the China CDC issued supplementary regulations prohibiting scientists working on Covid-related research from sharing their data and requiring them to receive permission before conducting any studies or publishing the results. Days later, a State

Council panel with oversight of coronavirus research took control of all publication work related to the pandemic for "coordinated deployment."

Newman's Chinese co-authors never told him why they didn't take their data directly to the WHO, he said, adding that it's possible they were more comfortable writing a report on market surveys for publishing in a journal. "But to take their data to the WHO directly would have required them to go through line management channels that would not be typical to their normal roles in their universities," Newman said.

"It was unfortunate that this paper had a chequered publication history," he said.

In the first months of the epidemic, researchers in China asserted that the new coronavirus resembled a spill-over from animals, reminiscent of the emergence of the SARS virus in wet markets in the nation's southern province of Guangdong almost 20 years ago.

Hedgehogs, badgers, snakes and birds were among "a variety of live wild animals" as well as animal carcasses and animal meat available for sale in Wuhan's Huanan market before the outbreak began, scientists from national and municipal health authorities and Chinese universities wrote in a study in the journal Nature in early February 2020.

Many of the earliest known Covid-19 cases were exposed to wild animals at the market, scientist from four Chinese universities wrote in a paper in the Journal of Medical Virology on Jan. 22, the day before Wuhan was placed under a 76-day lockdown (later extended later to the whole of Hubei province, stranding 35 million residents during the heavy-travel Chinese Spring Festival holidays.)

"Wild animals carry the risk of exposing people to new viruses," Xu Jianguo, head of an evaluation committee advising the Chinese government, told the journal Science a month earlier. "We should have more strict regulations and inspections of markets that sell wild animals."

In mid-January CNN broadcast unverified footage reportedly recorded inside the market in early December showing caged deer, marmots and raccoon dogs. Photographs of a menu board advertising the price and availability of exotic animals circulated online.

Yikai Luo
@YikaiLuo

A SARS-like #coronavirus is rapidly spreading in China and potentially abroad because some people in Wuhan were obsessed with eating wild animals. (If you read in Chinese you'll see the menu has a whole ZOO.) Not a teleologist but it does seem nature is taking its revenge.

Sent via Twitter for Android.
View original tweet.
The market was shuttered and its 678 stalls emptied and sanitized in the early hours of Jan. 1 to stem the spread. Authorities, though, had sprayed disinfectant around the market on at least two nights before it closed, Beijing News reported.
China CDC disease detectives arriving from Beijing on the first day of 2020 ordered environmental samples to be collected from the market. Some 585 specimens were tested, including extra samples gathered on Jan. 12, two days after scientists published the first genetic sequence of SARS-CoV-2. Thirty-three of the samples were positive for SARS-CoV-2, and all were from 22 stalls and a garbage truck, state news broadcaster CCTV reported on Jan. 26.
All but two of the positive specimens were concentrated in a dark, cavernous, poorly ventilated section of the market's western wing, where many shops sold animals -- a feature that the Beijing-based Caixin news organization said added to suspicions that "the epidemic is related to the wildlife trade."
"We have found out which stalls on the seafood market in Wuhan had the virus," Tan Wenjie, a researcher at China CDC's viral disease control and prevention institute, was quoted telling state-owned China Daily newspaper also on Jan. 26. "It is an important discovery, and we will investigate which animal was the source."
China responded decisively the same day, temporarily banning the wildlife trade -- a market worth an estimated 520 billion yuan ($80 billion) in 2016. Then a month later, trading and consumption of terrestrial, or land-dwelling, wild animals for food was banned permanently.
A WHO-China Joint Mission to Wuhan in February reported that an effort was underway to collect detailed records on the source and type of wildlife species sold at the Huanan market and the destination of those animals after the market was closed.
But there is no record of that happening.
Health officials and emergency and security services personnel dressed in protective clothing conducted an additional deep clean and purge of the market in early March 2020, Beijing News reported. Wild animals had already been removed by China CDC staff, it said.
References to wildlife in publications by Chinese scientists also began to disappear.
After describing the Huanan complex as a wholesale seafood and "animal" market in publications in the New England Journal of Medicine on Jan. 24 and Feb. 20, by March, when Covid was declared a pandemic, China CDC Director George Gao was seeding doubt about the role of the market and the existence of its live animals.
Wild animals were "purportedly available," the Oxford-educated virologist and colleagues wrote in the New England Journal of Medicine on March 26. "From the very beginning, everybody thought the origin was the market," Gao said in an interview

with Science published the next day. "Now, I think the market could be the initial place, or it could be a place where the virus was amplified."

Data on what animals were present in the market, let alone tested weren't publicly released.

"Unfortunately, the apparent lack of direct animal sampling in the market may mean that it will be difficult, perhaps even impossible, to accurately identify any animal reservoir at this location," Zhang Yongzhen and Edward C. Holmes, the scientists who published the first genetic sequence of SARS-CoV-2, wrote in a commentary piece published in the journal Cell on March 26.

One explanation was that there was no live wildlife on sale in the Huanan market -- or anywhere in China -- to begin with.

On April 23, then U.S. Secretary of State Mike Pompeo used part of his Earth Day message to call on China to close its wildlife wet markets to "reduce risks to human health inside and outside of China and discourage the consumption of trafficked wildlife and wildlife products." Days earlier, Australia called for a global inquiry into the origins of the pandemic, including China's handling of the initial outbreak in Wuhan.

In response to Pompeo, Geng Shuang, a spokesman for China's Foreign Ministry denied such activity occurred in China or that "wildlife wet markets" even existed there. "The sale of wildlife at farmers' markets and seafood markets is illegal in China," Xinhua, the nation's official state-run press agency, quoted Geng as saying in an article titled "There are no so-called 'wildlife wet markets' in China."

Chinese government researchers now dismiss the market hypothesis completely: "SARS-CoV-2 could not have possibly evolved in an animal market in a big city and even less likely in a laboratory," they wrote in a paper released last month ahead of publication. A more recent one by Gao and colleagues contends that the virus may have been imported to the market from multiple locations worldwide, including parts of Europe where mink are raised in areas in inhabited also by horseshoe bats.

"The official narrative changed not because the evidence changed," said Tulane's Garry. "A spillover from a wet market was what caused SARS and embarrassingly for China, those wet markets were never shut down."

Members of the WHO-convened research team that visited Wuhan from Jan. 14 to Feb. 10 suspected so too, according to three scientists familiar with the mission.

But by the time the WHO-led team visited the Huanan market in the afternoon of Jan. 31 -- more than a year after its closure -- little remained to assist the kind of epidemiological detective work that led SARS investigators to Himalayan palm civets, raccoon dogs and Chinese ferret-badgers sold in live-animal markets in Guangdong almost two decades ago.

The researchers noted a mixed smell of animals and disinfectant in some areas of the market, but were told by the market's manager what they were probably smelling was the lingering

stench of rotten meat and sewage, according to a joint WHO-China report.

Ten shops had been found to be selling frozen "domesticated" wild animals, including bamboo rats -- some sourced from Yunnan province, where scientists found a coronavirus that most closely matches SARS-CoV-2 from horsehoe bats. But no live animals had been seen before the market was closed, the official said. It was further stated that no live animals were sold and no animals were butchered on the premises.

The researchers saw nothing in the market to dispute that, including any sign of the cages used to house mammals like the raccoon dogs that University of Sydney researcher Edward Holmes photographed in the market in October 2014. Unpublished information and unverified photographs and videos in media reports weren't included in the research.

Instead, scientists were invited to quiz two Wuhan residents who had responded to an invitation to participate in a meeting. According to the report, both had shopped regularly in the market for 20 to 30 years and provided similar accounts: "Nothing out of the ordinary noticeable, all vendors had certificates and inspection certificates displayed in their stalls, they had never witnessed any live animals being sold, the market was kept clean and tidy and they had not noticed any stray cats or dogs, and there had been no confirmed cases in their residential block."

Earlier the same day, the international research team visited the larger Baishazhou Market in Wuhan where Xiao had been regularly surveying two shops selling live wild animals for 2 1/2 years. Yet, the group was told no live animals were sold there either; only frozen food, ingredients and kitchenware.

Liang Wannian, an epidemiologist who headed the Chinese experts collaborating with the WHO-convened team, said Xiao's data weren't known to his group either. "In January-February, when the team was working in Wuhan, we were not aware of that information," he told reporters last month in response to questions about the June study in Scientific Reports. "Scientists should always communicate with each other in a common pursuit of truth," he said.

Among the earliest clusters of infections recorded in Wuhan, one involved three Covid cases among staff working at a stall in the Huanan market that sold "frozen products such as pastry, and soy products." One of the employees, a 32-year-old who fell ill with Covid on Dec. 19, "purchased goods from the Baishazhou market and Huanan Market back and forth."

A confirmed case linking two markets known to sell live wild animals permissive to SARS-CoV-2 is "very intriguing," said Stephen Goldstein, a research associate in evolutionary virology at the University of Utah in Salt Lake City. But tracing any contact the employee might have had with infected animals is impossible now. The animals are long gone, along with any evidence.

“It seems to me, at a minimum, that local or regional authorities kept that information quiet deliberately,” Goldstein said. “It’s incredible to me that people theorize about one type of coverup, but an obvious coverup is staring them right in the face.”

From: Morens, David (NIH/NIAID) [E] [b6 ([b6])]
Sent: 12/29/2019 11:32:30 PM
To: Ellen Carlin [b6]
Subject: Fwd: Lancet Infect Dis: Preparedness for emerging epidemic threats: a Lancet Infectious Diseases Commission http://bit.ly/39oQH5N

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

Begin forwarded message:

From: "Folkers, Greg (NIH/NIAID) [E]" b6
Date: December 29, 2019 at 15:00:59 MST
Subject: Lancet Infect Dis: Preparedness for emerging epidemic threats: a Lancet Infectious Diseases Commission http://bit.ly/39oQH5N

<!--[if !vml]--> <!--[endif]-->
Volume 20, Issue 1, January 2020, Pages 17-19

Comment

Preparedness for emerging epidemic threats: a *Lancet Infectious Diseases* Commission

Author links open overlay panelVernon JLee[ab]
XimenaAguilera[c]DavidHeymann[d]AnneliesWilder-Smith[d]for The
Lancet Infectious Diseases Commission
Author links open overlay panelVernon J.LeeXimenaAguileraDavid L.HeymannAnneliesWilder-SmithDaniel G.BauschSylvieBriandChristianneBruschkeEduardo H.CarmoSeanCleghornLalitDandonaChristlDonnellyIbrahima SocéFallJaneHaltonRichardHatchettFeliciaHongPeterHorbyChikwelhekweazuMichaelJacobsKamranKhan YijunLinGabrielLeungConstanceLowBethan F.McDonaldZiad A.MemishRyanMorhardDeborah HLNgJohnNkengasongJunxiongPangStephen C.ReddKarenTanWen QingYeo
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Available online 23 December 2019.

At any time, an emerging, lethal, and highly transmissible pathogen might pose a risk of being spread globally because of the interconnectedness of the global population.1, 2 Emerging epidemic threats are occurring with increasing scale, duration, and effect, often disrupting travel and trade, and damaging both national and regional economies.3, 4 Even geographically limited outbreaks such as the Ebola virus disease in Africa might have a global effect.

Preparing for epidemic threats is not a static or binary (prepared or unprepared) exercise, but a dynamic state reflecting the constantly changing world. Countries prepare in different ways based on their interpretation of disease risks and international agreements such as the International Health Regulations (IHR). The IHR were introduced in 1969 to prevent spread of specific serious diseases between countries and set out preparedness measures at international borders to stop disease spread. The 2005 revisions to the IHR reflect changes across multiple dimensions, requiring countries to develop preparedness capacities to detect and respond to outbreaks where and when they occur, supported by international partners to respond when outbreaks cannot be contained locally.[5] However, disruptive factors have emerged at a greater pace over the past decade, creating a new ecology that requires novel strategies for preparedness. These factors include dealing with the increasing human population density and connectivity, harnessing novel data streams and new technological advances to manage epidemics, mitigating false information on social networks, to creating informal technical networks that can work together when political forces fail to do so.

Do the recent outbreaks of Ebola virus disease, Middle East respiratory syndrome coronavirus, and yellow fever reflect this changing context of disruptions requiring dynamic responses? These outbreaks show that countries are at various stages of preparedness, and many have underdeveloped preparedness plans and response capabilities with weak or non-existent strategies to mitigate disruptive factors.6, 7 Many countries face severe difficulties in providing universal health coverage, for example, and might overlook timely investments for threats that demand greater health-care facility or workforce requirements.8, 9 Other challenges include shifts in within-country and between-country cooperation, the evolving need for transdisciplinary, cross-sectoral approaches and social participation,2, 3, 8, 9 and effective leadership, coordination, and financing of local national and international partners.[10]

Against this backdrop, the *Lancet Infectious Diseases* Commission on Preparedness for Emerging Epidemic Threats was formed in mid-2019 to examine the importance of this new ecology and its disruptive factors that have resulted in an underprepared world, whether current planning assumptions still hold, and what mitigation measures need to be introduced.

A sample of the new ecology, its disruptive factors, and how they manifest are shown in the table. Preparedness plans must take these factors into account to succeed and those that do not will not have the resilience and capability to fully respond. These factors are political and institutional factors that include influential stakeholders and decision-making forces; social factors that link individuals and communities, through exchange of goods and information, and building relationships that ensure societal cohesiveness; environmental factors that influence pathogens and hosts, contribute to biodiversity and how diseases emerge and spread, these factors affect interaction between humans, vertebrate animals, and arthropod vectors, and influence human development and health systems; and

pathogenic factors that define the biological basis of epidemic emergence and antimicrobial resistance, host–pathogen interactions, and available interventions to address these epidemics.

Table. Examples of disruptive factors and their manifestations that require mitigation for effective preparedness

	Disruptive factors	Examples of manifestations
Political and institutional	National governments; international agencies; non-governmental organisations and charities; corporate entities; academic institutions	Weakness in behavioural change guidance from national and international organisations; scarcity of sustainable leadership and financing in failed states leading to neglected or uncoordinated health systems; increasing duration and frequency of insecurity or conflict zones hindering efforts to recognise and respond to health threats; failure of countries to report disease outbreaks because of fear of economic consequences
Social	Travel patterns, migration, and interconnectivity; trade; technology and digital revolution, including those that affect human interaction; expansion and control of information; patterns of communication including social media; expectations and definition of expertise; social conflict and privacy	Failure of host countries to protect the health of refugees and migrants; epidemic of devastating rumours and fake news on social media due to increased digital connectivity; emergence of social influencers exerting influence on politicians and institutions; increased resistance and hesitancy within communities to health interventions because of opposition by local experts
Environment	Geography affecting biological diversity; planned and unplanned urbanisation; climate change; interaction between humans, animals, and vectors; human development; state of the economy; state of health systems	Climate change resulting in increased flooding with failed sanitation and safe water; altered distribution of zoonotic disease reservoirs and vectors; emerging zoonosis with increased agricultural production and human encroachment into animal environments; changing national priorities resulting in sharply reduced investment in health systems
Pathogenesis	Changing disease biomes; relationship between hosts and pathogens; pathogen evolution and changes; technologies such as synthetic biology, and the risks of manufacturing pathogens and their accidental or deliberate release; characteristics of a population such as underlying disease condition	Increased opportunities for mutation or reassortment of infectious agents; increasingly reduced effectiveness of conventional vaccines and therapeutics for prevention and treatment of diseases; failure of conventional control measures to break the chain of transmission of infectious agents

The *Lancet Infectious Diseases* Commission will discuss disruptive factors and how preparedness planning must consider this new ecology by exploring current preparedness platforms and their vulnerability to disruptive factors; by addressing key disruptions, identifying possible solutions, and providing recommendations for countries to strengthen preparedness; by developing a multidisciplinary approach including a strong role for social sciences and innovative technology; by challenging leaders and stakeholders to create sustainable preparedness platforms through collaborations and investment in established and novel recommendations; and by creating a community of practice to share new ideas and monitor outcomes.

To tackle the wide-ranging issues, the Commission has brought together experts from academic, public health, policy making, international, non-governmental, and corporate institutions. They bring local and global knowledge and experience, including policy-making and field response, human and animal health (including One Health) approaches, and novel developments in communications, information technology, analytics, public health, diagnostics, and therapeutics. The Commission aims to deliver the report by 2021 and will include key recommendations for countries and international stakeholders, and monitoring indicators to evaluate the effectiveness of preparedness initiatives over time.

The Mok Hing Yiu Charitable Foundation is the sole sponsor for the *Lancet Infectious Diseases* Commission meetings and travel for some commissioners. The foundation is not involved in the technical discussions, data analysis, and drafting of the report. This Comment was written on the behalf of the *Lancet Infectious Diseases* Commission on Preparedness for Emerging Epidemic Threats; see appendix (pp 1–2) for the Commissions author list.

Supplementary Material

Download : Download Acrobat PDF file (112KB)

Supplementary appendix.

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1

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View Abstract

From: Jon Epstein [b6]
Sent: 12/11/2020 8:56:30 PM
To: Morens, David (NIH/NIAID) [E] [b6]
b6]
CC: Peter Daszak ([b6]) [b6]; Keusch, Gerald T [b6]
Subject: Re: FW: NYT [Opinion]: The Virus and Bats /They probably spread the virus that's killing humans. We almost certainly spread the fungus that's killing them.

Thanks, David. David Quammen is such a great storyteller and one of the best at describing the issues around zoonotic disease emergence and the role of people, more so than wildlife, as the main driver. It's refreshing to see an article in the paper focused on the importance of bats, rather than just as a source of SARS-COV-2.

Cheers,
Jon

On Fri, Dec 11, 2020 at 12:54 PM Morens, David (NIH/NIAID) [E] b6 wrote:

Guys, great story, congrats!

David

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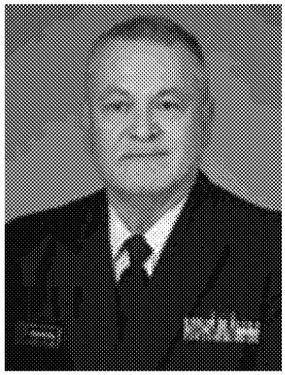


From: Folkers, Greg (NIH/NIAID) [E] b6
Sent: Friday, December 11, 2020 11:54 AM
Subject: NYT [Opinion]: The Virus and Bats /They probably spread the virus that's killing humans. We almost certainly spread the fungus that's killing them.

The Virus and Bats

They probably spread the virus that's killing humans. We almost certainly spread the fungus that's killing them.

By David Quammen

Mr. Quammen is the author of "Spillover: Animal Infections and the Next Human Pandemic."

- Dec. 11, 2020

Credit...Wesley Allsbrook

The order of animals known as Chiroptera, the bats, enjoys a mixed reputation among humans. I'm putting this politely: They have been calumniated and abused for centuries.

Some people, mainly from the comfort of distance and ignorance, find bats repellent and spooky. Some people fear them, with or without rational grounds. Bats are sometimes slaughtered in large numbers, defenseless at their collective roosts, when people deem them menacing, inconvenient, noxious or desirable as food.

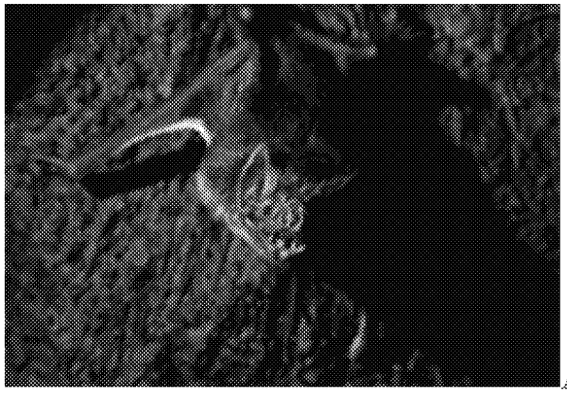
The idea of bat soup or roasted bat may induce cringes in sensitive Western eaters, but that's no consolation to the tens of thousands of flying foxes (as the largest of the Old World fruit bats are known) that have been legally hunted for meat and sport in Malaysia in recent years. Or to the Mariana fruit bat, pushed toward oblivion not just by habitat loss in Guam and neighboring islands, but also by the introduction of a tree snake that preys upon them and a tradition among the local Chamorro people of eating them as a celebratory meal. Almost 200 bat species around the world are threatened with extinction.


A young grey-headed flying fox in Victoria, Australia. Ancient literature and folklore record a long list of anti-bat beliefs. Some people also blame bats for carrying dangerous pathogens, including, potentially, the precursor of the new coronavirus.Credit...Annette Ruzicka

And this pattern of antipathy will only be made worse by the Covid-19 pandemic — given molecular evidence showing bats as the likely origin of the new coronavirus — unless we recognize the merits and beauties of these creatures, as well as the biases against them.
Ancient literature and folklore record a long list of anti-bat beliefs: that they were turncoats in the primordial battle between Birds and Beasts, that they curdled the eggs of storks, that they gouged bites out of hams hung for curing, that they entangled themselves in women's hair, that they were accomplices to Satan in his effort to seize control of human nature, that bat blood could serve as an antidote to snakebite and all manner of other silly stuff.

The association of vampirism with bats, though, is no myth. Three species of small, sneaky New World bats are adapted to feeding exclusively on blood from birds and oblivious mammals — originally wildlife, but now also cows, horses and humans asleep with their feet exposed. The most conspicuous of them is the common vampire bat, Desmodus rotundus, known from Uruguay to Mexico and especially abundant in southeastern Brazil. These sanguinivorous bats have heat sensors in their noses for locating capillary concentrations, sharp incisors for slicing flesh, anticoagulant saliva — the whole deal. Like furry mosquitoes.

The “rotundus” (portly) in their scientific name reflects the fact that after they’ve crept across the ground to nip the ankles of cattle and drink blood, they become so fat from a night’s meal (burp), that they must piss away the plasma, retaining the red cells, before they can be airborne and get back to their roost. From there it’s a short flight to “Dracula.”


A vampire bat, Desmodus rotundus. Bat viruses spill into humans; they don’t climb into us. And the spilling generally happens when we intrude upon bats in their habitats.Credit...Stephen Dalton/Avalon, via Alamy

Some people also blame bats for the dangerous pathogens they carry — including, potentially, the precursor of the new coronavirus, SARS-CoV-2. That virus may have gotten into us from one of the several kinds of horseshoe bat from southern China. If so, the fateful event probably had more to do with what some human wanted from bats than with what some bat wanted from humans.

Bat viruses *spill* into humans; they don’t *climb* into us. They don’t seek us out. And the spilling generally happens when we intrude upon bats in their habitats, excavating their guano for fertilizer, capturing them, killing them or transporting them live to markets, or otherwise initiating a disruptive interaction.

Scientists haven’t yet discovered (and they may never) just which such encounter brought this coronavirus to humanity. But you can be confident that it didn’t happen because some Chinese rufous horseshoe bat flew into Wuhan and bit a poor man on the toe.

II.

The most lethal of bat-borne viruses, for humans, is rabies, now recognized as one member of a diverse group called the lyssaviruses (as in Lyssa, the Greek goddess of frenzy and rage), most of them associated with bats. Humans have been aware of rabies at least since Democritus, in the fifth century B.C. We’ve seen it in our dogs, sometimes driven mad, like Old Yeller, and occasionally in an unlucky person who got bit. The fatality rate for rabies, absent prompt post-exposure vaccination, is nearly 100 percent, and the disease still kills tens of thousands of people each year.

But from what original source did rabies get into dogs or raccoons or skunks or the other carnivores from whose saliva it drips into a bite wound? The first clue to that mystery came in 1911, when rabies virus was reported among bats by an Italian scientist in Brazil, Antonio Carini, who noted the odd detail that it didn’t seem to make the bats sick. That suggested a long relationship between the bats and the virus, which had perhaps reached a mutual accommodation: a secure habitat for the virus, no symptoms for the host.

Although rabies was the topic that dominated research in this field for much of the 20th century, a few other bat-borne viruses turned up, mostly as incidental discoveries by scientists studying something else. Rio Bravo virus, for instance, found among some California bats in 1954 and related

to the yellow fever virus, was one. Tacaribe virus, carried by both bats and mosquitoes in Trinidad, was another. These viruses yielded scientific papers but not newspaper headlines, because they weren't causing human deaths.

Soon, too, there appeared some new killer viruses, though without (at first) any clear linkage to bats. Marburg virus as well as the most lethal and infamous of the Ebolas, now known as Zaire ebolavirus, caused gruesome illness and death with their first recognized outbreaks among humans, during the late 1960s and 1970s. But their confirmed (Marburg) or probable (Zaire ebolavirus) connections to bats as reservoirs were not established by science until later.
Then, in 1994, a strange new bug spilled out of certain flying foxes in eastern Australia, burned its way horrifically through a stable of racehorses and killed one of the three men who had labored, shoulder-deep in bloody froth, to save those horses. A second man, a stable hand, got very sick but survived. The third man was a tall veterinarian named Peter Reid.

"That's it," Dr. Reid told me, a dozen years later, as we sat in his car amid a sprawl of new tract houses near Brisbane, gazing at a solitary fig tree left standing in a traffic circle. "That's the bloody tree." The suburb, in 1994, was a horse pasture. The bats came for the figs. The first infected horse shaded herself beneath this tree, feeding on grass splotched with virus-laced bat feces. From her it passed to the other horses and to the men.

That virus got the name Hendra, after the Brisbane suburb where the horse deaths occurred. This was before it became politically unacceptable to name a nasty new virus after a place.

Nipah virus, in 1998, in Malaysia, also emerged from bats, also passed through an amplifier host (pigs), also killed people and also was named for a place: the village of Sungai Nipah, home to a 51-year-old pig farmer from whose cerebrospinal fluid the virus was first isolated.

The original SARS virus appeared shortly thereafter, in 2002. It, too, arose from a bat, passed possibly through palm civets, and began sickening people in Shenzhen, China. It spread alarmingly fast to other countries in 2003, with several superspreading events and a high fatality rate, but it was controlled thanks to strong public health measures, and it killed "only" 774 people.

The SARS outbreak of 2002-03 was a galvanizing event for disease scientists, who recognized that it could have brought about a disastrous pandemic if just a few factors had differed: a slower response by public health officers, disorganized efforts of containment, or maybe a similar coronavirus but capable of spreading from asymptomatic cases. (Does all that sound familiar? It should.) Discovery of the bat-SARS link two years later moved bat-virus research, according to the eminent virologist Charles H. Calisher, "from serendipitous, fragmented, and local, to well-planned, methodical, and global," with attention focused ever more strongly on bats as the reservoirs from which many nefarious viruses have emerged.

That's a long list of animosities, scurrilities, grudges and indictments. So what can be said for bats, these feared and detested creatures?
Plenty can be said for them.

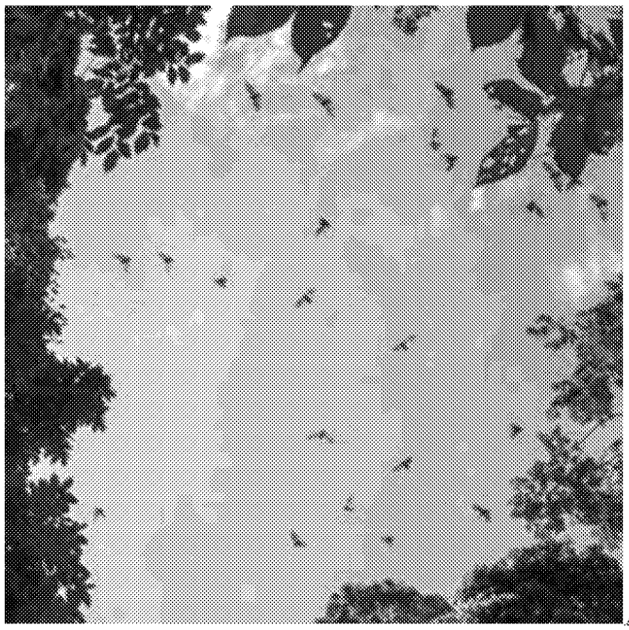
III.

To grasp the majesty of bats, start by imagining this: You are on a small cargo boat, chartered for 25 bucks, puttering southward across open sea among the small islands east of Komodo, in central Indonesia. There are scarcely any villages, scarcely any people, and certainly no hotels in this remote, austere bit of the archipelago. It's twilight and you're hurrying toward a safe anchorage at the lee of one of these islands, where you and the boat captain and his two sons, who constitute his crew, can

sleep the night. Just before dark, a great flock of fruit bats comes out of the west, flying high, maybe a thousand of them, each as large as a raven.

Most likely they are Sunda fruit bats, Acerodon mackloti, a species endemic to Indonesia, and whatever viruses they may carry have not yet caused any known harm to people. Their wings flap in easy rhythm as they move in procession, full of purpose, like migrating geese, toward their nocturnal feeding grounds on some island eastward. The dipping sun warms the sky with a last peach-colored wash. The moon is a thin crescent, and the bats cross it in silhouette, minding their own business. They are magnificent.

The Sunda fruit bat is just one of what scientists tally as more than 1,400 living species of bat. That's more than any other mammalian order except the rodents and constitutes about 20 percent of all mammals. Think of it: One in every five mammals on earth, by count of species, is a bat. They must be doing something right.



A colony of fruit bats flying above the rainforest in West Sumatra, Indonesia. Almost 200 bat species around the world are threatened with extinction.Credit...Leisa Tyler/LightRocket, via Getty Images

By another standard, bats are more diverse even than rodents if you consider the variousness of their ecological, physiological and behavioral traits, as well as the sheer count of species. They live on every continent except Antarctica, from north of the Arctic Circle to Tierra del Fuego, and on some of the world's most remote islands. Their diets include insects, small mammals, reptiles, amphibians, fish taken by skimming over water, fruit, flowers, nectar, pollen, leaves, scorpions and blood.

Some of them migrate, traveling long distances for seasonal food or mild temperatures. Some of them hibernate, notably in caves, to avoid the hardships of winter. Many bats of the temperate zones are also capable of daily torpor, reducing their body temperature and oxygen consumption while they are inactive, to save energy. When they perk up again and take flight, their metabolic rate can increase quickly by a factor of 14. All of these traits relate to the two great adventures that evolution opened to early bats: They colonized the air and they embraced the dark. Nowadays they sleep by day and fly by night.

They were the first, and are still the only, mammals capable of powered flight. That's big: By opening a third spatial dimension to them, a vast new realm of activity scarcely explored by other mammals, flight may be what enabled such extraordinary diversification.

Another factor is the duration of their lineage. The earliest known bat fossil dates to about 50 million years ago, and because it resembles a modern bat, the dawning of bats must have occurred well before that. The earliest flying squirrel may not have appeared until 30 million or 40 million years later, by which time bats were the mammalian masters of the air.

To function at night, performing the aerial dives and swoops necessary to catch flying insects, without going hungry or continually knocking themselves silly against tree limbs or rock walls, they acquired another crucial capacity: echolocation. They became able to blast out pulses of high-frequency sound, some of them through their noses, like silent screams, and receive back the echoes with acutely sensitive ears. This allows their brains to assemble dynamic images of the size, shape, distance and motion of the zigzagging moths and plummeting katydids that are their prey.

Certain of the nostril shriekers, including the horseshoe bats and the leaf-nosed bats, developed elaborate nasal structures that help focus their sonic pulses. Some others, by evolutionary increments, grew huge ears. Tomes's long-eared bat, native to forests in Central and South America, has combined both — towering, wide ears shaped like the spinnaker on a yacht, plus a nose like the prow of a Viking ship. This makes for a face of peculiar distinction — I would say, a face only a mother could love, except that chiroptophiles love it, too — while the poor little animal is just trying to locate dinner.


A horseshoe bat. Thanks to elaborate nasal structures, it can blast out pulses of high-frequency sound, like silent screams, and receive back the echoes. This allows the bat to assemble dynamic images of the size, shape, distance and motion of the zigzagging moths and plummeting katydids it preys on.Credit...Charles M. Francis/Bat Conservation International

Bat superlatives are both wide and long: Besides showing great collective diversity, bats also have high life expectancy. If an infant bat gets past its first birthday, it has a good prospect of surviving to 7 or 8. Much longer than a mouse. On average, according to one study, a bat lives more than three times as long as a nonflying mammal about the same size, and some can reach 30 years, even in the wild.

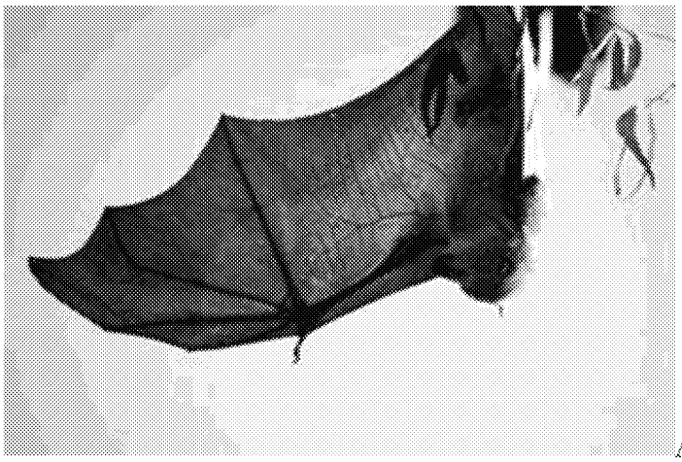
This longevity is not just because of torpor and hibernation, giving long periods of rest. Even non-hibernating bats live to be old, possibly in part because flight allows them escape from predators, possibly also because escape from predators, lengthening life, has given Darwinian natural selection the time and reasons to eliminate negative mutations that might cause congenital disease in middle-aged bats — a positive feedback loop. But these are guesses that invite more investigation.

Another conundrum now at the forefront of bat research, with potential medical value for humans, is how their immune systems tolerate viral infection with such aplomb. Bats carry many viruses, and yet they generally don't suffer symptoms themselves.
In at least some cases, the concentration of virus in their blood tends to be low. They don't mount the same inflammatory responses as other mammals, which is good for their longevity, because excessive inflammatory responses can be dangerous, sometimes overwhelming the body with a reaction worse than the cause. The sequencing of the genomes of several bat species has revealed that they carry about half as many immunity-related genes as a human does.

Why would evolution dampen down immune reactions in bats? One hypothesis is that it's a trade-off for flight: Flying entails such physiological stress that an alert immune system might react against unstable molecules produced by the animal's own exertion. In this view, it's better for the bat to ignore the presence of viruses than to suffer autoimmune symptoms from flying. So, could bats help medical researchers understand autoimmune disease in humans? That's an open question.

IV.

Although the earliest bats were small insect-eaters, the big fruit bats diverged at least 35 million years ago, when chance and evolutionary opportunity led them to abandon echolocation (mostly) for good eyesight, and agile insectivory for vegetarianism and bulk. The largest are the flying foxes, stately creatures with broad wingspans, dog-like faces, molars for crushing fruit pulp and, in some species, long tongues for lapping up nectar.


A grey-headed flying fox in Melbourne, Australia. One in every five mammals on earth, by count of species, is a bat. They must be doing something right.Credit...Annette Ruzicka

A few of them are lovely, russet-bodied with umber wings, occasionally a golden collar. They roost mainly in trees, such as the tall karoi surrounding a certain derelict warehouse, in southern Bangladesh, where a wildlife veterinarian named Jonathan Epstein, along with his field crew and me, in 2009 found a roosting colony of 4,000 to 5,000 Indian flying foxes. Dr. Epstein had come to trap some of these animals and sample them for Nipah virus.

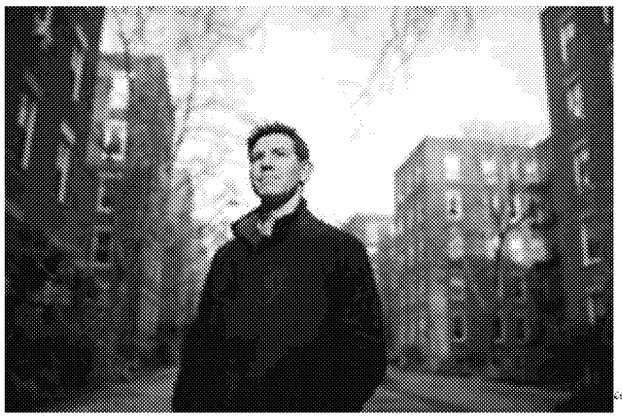
On the first afternoon, as Dr. Epstein's two agile net-riggers climbed high into one tree, the bats stirred, woke and, spooked, rose into the sky, one after another, with what seemed calm caution, to escape the disturbance. Soon, the whole flock was airborne, circling out to the northeast, then back in, out again, back, riding the thermals with minimal wing beats, like flotsam going around in a great river eddy. I gawked up in awe and Dr. Epstein reminded me — I can't remember if it was then or later — that a wide-open gape beneath a caldron of such bats might be a good way to get a mouthful of Nipah-laced guano.

In the wee hours of the night we returned, climbed a rickety bamboo ladder to the warehouse roof, wearing masks and goggles and gloves and headlamps, and were in position when the first bat — now returning from its nocturnal foraging — hit the net. Dr. Epstein, hands protected in welder's gloves from the sharp claws and teeth, held the animal in a firm grip behind its neck while a colleague untangled it. That one went into a cloth bag, and so had, by dawn, five others. Then, in a makeshift field lab, Dr. Epstein and his crew took blood samples and cheek swabs from the bats, now anesthetized, being careful not to hurt them.


Dr. Jonathan Epstein and his team capturing an Indian flying fox in Bangladesh in 2015 as part of a long-term study to understand Nipah virus and how it jumps from bats to humans.Credit...Eco Health Alliance 2020

At full daylight, we all marched outside. By now a small crowd of people, adults and children, had gathered to watch the strange business. Dr. Epstein released each animal gently: He raised an arm high, letting the bat free its wings and legs and then drop of its own accord, catching itself with wing beats just above ground, and then slowly flap away. With one of his crew members translating, Dr. Epstein addressed the gathering: "You're very fortunate to have so many bats." They pollinate plants, they spread seeds, they generate fruit trees, he explained. Implied but unmentioned was this message: If you leave them alone, if you keep your distance, you probably won't get Nipah-virus disease.

Dr. Epstein — one of those cross-trained experts with a veterinary degree, a Ph.D. in ecology and a master's in public health — is now a vice president at EcoHealth Alliance, a research and conservation organization devoted to animal and human health. He reminded me during a recent conversation, as he had those villagers in Bangladesh, of the benefits ledger for bats.


"Bats are too important to lose," said Dr. Epstein, a vice president at EcoHealth Alliance, a research and conservation organization devoted to animal and human health.Credit...Karsten Moran for The New York Times

They play a huge role in the perpetuation of tropical hardwood forests. They eat a vast tonnage of insects each year. In Thailand, wrinkle-lipped bats provide protection against a major rice pest. In Indonesia, other bats reduce the insect burden on shade-grown cacao. A single colony of big brown bats in the American Midwest, by consuming 600,000 cucumber beetles in a year, prevents 33 million cucumber beetle larvae from feeding on the next year's crop. Mexican free-tailed bats eat cotton bollworm moths in Texas. By one estimate, from 2011, bat predation on insects was saving $23 billion annually for agriculture in the United States. The global total is incalculable. "Bats are too important to lose," Dr. Epstein said.

V.

Yet they *are* being lost in many parts of the world, because of habitat destruction and direct killing — and, at a cataclysmic rate in North America over the past 14 years, because of a new problem: a contagious disease. It's called white-nose syndrome, and it's caused by a pathogenic fungus that seems to have arrived from Europe. In this case, humans are the vector, and bats are the victims.

Winifred Frick is the chief scientist of Bat Conservation International and has studied white-nose syndrome almost from the start. The disease first showed itself at a tourist-destination cave west of Albany, N.Y., in February 2006, where a caver photographed some hibernating bats with powdery white fuzz on their muzzles, like frost on the beard of a skier. A year later, biologists for New York State found thousands of dead bats with similar growths in another cave nearby. By 2008, Dr. Frick, among others, was at work on the problem, which grew into a crisis for the hibernating bats of North America.

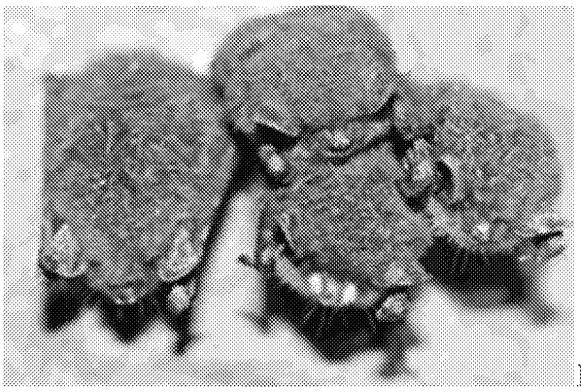

Dr. Winifred Frick, the chief scientist of Bat Conservation International. "You can almost think of them as being like little cold Petri dishes," Dr. Frick said of

hibernating bats exposed to white-nose syndrome, a deadly fungus.Credit...Cayce Clifford for The New York Times

"It spread really rapidly," she told me recently by Skype, walking on her treadmill as we spoke. I knew Dr. Frick already as a multitasking scientist a decade ago, having met her when a group of us shared dinner in a grand venue at the close of an international bat conference in Berlin and she brought along her 4-month-old son, Darwin. By now, white-nose syndrome is in 33 U.S. states and Canadian provinces, she told me, having caused a 90 percent decline in the known populations of three bat species, plus losses among at least four others. Millions of bats have died.

One of the three hardest-hit species, the northern long-eared bat, she said, was "totally gone," within three years, from some areas where it used to hibernate. North America's hibernating bat populations could be nearly or completely wiped out.

The fungus thrives in cold, damp environments such as caves, and it takes hold on bats during their periods of torpor and hibernation, when their immune systems are inattentive, not just to viruses but also to other infections. "You can almost think of them as being like little cold Petri dishes," Dr. Frick said. The fungus grows robustly, causes irritation and rouses the bats in midwinter, whereupon they fly out, expend crucial fat reserves searching for insect food that isn't there and die.



Bats with white-nose syndrome. It's caused by a pathogenic fungus that seems to have arrived from Europe. In this case, humans are the vector, and bats are the victims.Credit...Michael Schirmacher/Bat Conservation International

The same fungus is commonly found on bats in Europe, but with relatively mild effect and no evidence of mass mortality, possibly because it's long familiar and those populations have adapted. How did it get to North America? No one knows for sure, Dr. Frick said. "We don't have a smoking gun," but "the most parsimonious explanation is that it came over on somebody's boots." An invisible smudge of the fungal spores, on the footwear of a casual tourist or a serious caver lately returned from spelunking in northeastern France or Germany, could have been enough. Bats don't fly between Europe and America, but people do.

I'm sure you see the analogy here, the gruesome symmetry that brings consolation to no one: Covid-19 is a disease catastrophe for humans, with its likely origin in bats, triggered by human action; white-nose syndrome is a disease catastrophe for bats, with its origin who knows where, triggered again by human action. We humans are one species, abundant and wondrous and powerful. Bats are many species, diverse and wondrous and vulnerable.

That puts some responsibility upon us. Our lives and our health are entangled with theirs. If we could speak to bats, offering armistice, seeking concord, I'd suggest six words for a start: "Thank you. No hard feelings. Sorry."

Credit...Annette Ruzicka

David Quammen is an author and journalist whose books include "Spillover: Animal Infections and the Next Human Pandemic."

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

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Sent: 7/11/2021 5:05:30 PM
To: Peter Daszak ([b6]) [[b6]]; Keusch, Jerry ([b6]) [[b6]]
Subject: FW: Science Media Center: Expert reaction to a preprint reviewing the evidence on the origins of SARS-CoV-2 https://bit.ly/3hRzCpX

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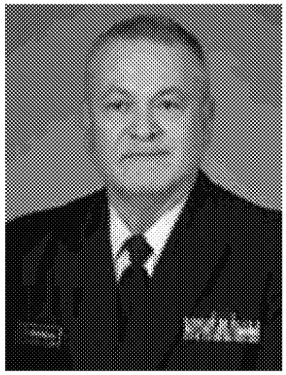

From: Folkers, Greg (NIH/NIAID) [E] [b6]
Sent: Friday, July 9, 2021 3:42 PM

Subject: Science Media Center: Expert reaction to a preprint reviewing the evidence on the origins of SARS-CoV-2 https://bit.ly/3hRzCpX

you are here: science media centre > roundups for journalists > expert reaction to a preprint reviewing the evidence on the origins of SARS-CoV-2

July 8, 2021

Expert reaction to a preprint reviewing the evidence on the origins of SARS-CoV-2

A preprint, an unpublished non-peer reviewed study, critically reviews the current scientific evidence on the origins of SARS-CoV-2.

Please note this is a comment from one of the authors, NOT a third party comment, but sending out in case useful as there wasn't a press release: **Prof David L Robertson, MRC Investigator, Head of CVR Bioinformatics MRC-University of Glasgow Centre for Virus Research (CVR), said:**

"In a review of the evidence as a group of experts in virus evolution and molecular virology we concluded the most parsimonious explanation for the origin of SARS-CoV-2 is a zoonotic spillover event. The contact tracing of early cases in Wuhan, obtained from the WHO report earlier this year, exhibits striking similarities to the early spread of the first SARS-virus, where humans infected early in the epidemic lived near or worked in animal markets. While the intermediate animal species has not been found, there is clear evidence of susceptible animals being present in the Wuhan market throughout 2019, and related viruses have been found circulating in horseshoe bats, again very similar to the first SARS-virus. Altogether the evidence points to a zoonotic event and not a leak from a laboratory in Wuhan. The "lab leak" scenario alternates between it was made in a lab and it was an accidental release of a natural virus, neither of which there's any evidence for. It's of critical importance to understand the origin of SARS-CoV-2 so we can assess the risk of future spillover events."

Prof James Wood, Head of Department of Veterinary Medicine, University of Cambridge, said:

"This manuscript represents a very considered review of all virological and epidemiological evidence regarding the origins of the cause of the COVID-19 pandemic, SARS-COV-2. The authors, who are acknowledged experts in their fields, concluded that there is a substantial body of scientific evidence supporting a zoonotic origin for SARS-CoV-2.

"They considered the uncertainties that invariably persist around retrospective investigations of this nature and also noted that a laboratory accident could not be entirely ruled out, but that this was highly unlikely relative to an origin involving human and animal contact.

"While nothing can be absolutely certain regarding the origin of the pandemic, it is important that we note the conclusions of this review and start to act to introduce changes that can reduce the likelihood of further events occurring. Regulation of laboratory experimentation will not do this. Trade in and markets for live animals, especially involving the mixing of wildlife species need banning or tightly regulating and we should work to reduce biodiversity loss, an important underlying driver for zoonotic disease emergence. Biodiverse areas should be protected, recognising that humans are an important part of biodiversity; recognising land rights of indigenous peoples can make important contributions to protecting ecoystems."

Dr Jonathan Stoye, Group Leader, Retrovirus-Host Interactions Laboratory, The Francis Crick Institute, said:

"The debate about the origins of SARS-CoV-2 is becoming increasingly acrimonious. The failure to detect a potential natural host has stimulated suggestions by some that the COVID-19 pandemic has resulted from the escape of an engineered virus from a lab in Wuhan, China. However, there is little or no evidence for such an event and lab leak theories remain essentially speculative, at times verging on conspiratorial.

"By contrast, the current preprint provides a refreshingly clear and reasoned description of the virological events that have taken place during the emergence of the pandemic virus. It makes a strong case for the natural origin of the virus followed by on-going adaptation in humans. The continuing evolution of the virus to give new variants, highlighted by the independent acquisition of the N501V change on multiple occasions, is clearly inconsistent with the notion of a purposely manipulated virus optimized for growth on human cells. While there are still gaps in our knowledge that should be explored further, particularly regarding events that occurred before December 2019, the conclusions reached here seem entirely consistent with those in the WHO report released earlier this year."

'The Origins of SARS-CoV-2: A Critical Review' by Edward Holmes et al. is a preprint available here:
https://doi.org/10.5281/zenodo.5075888

All our previous output on this subject can be seen at this weblink:

www.sciencemediacentre.org/tag/covid-19

From: Morens, David (NIH/NIAID) [E] [b6] ([b6])
Sent: 8/2/2021 3:23:58 PM
To: Peter Daszak ([b6]) [[b6]]; Keusch, Jerry ([b6]) [[b6]]; Taubenberger, Jeffery (NIH/NIAID) [E] ([b6]) [[b6]]; Jason Gale (BLOOMBERG/ NEWSROOM:) [[b6]]; Eddie Holmes ([b6]) [[b6]]; Kessler, Robert ([b6]) [[b6]]; Wang Linfa [[b6]]
Subject: FW: House report on Origins
Attachments: ORIGINS-OF-COVID-19-REPORT (1).pdf

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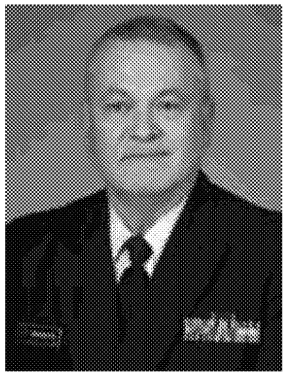
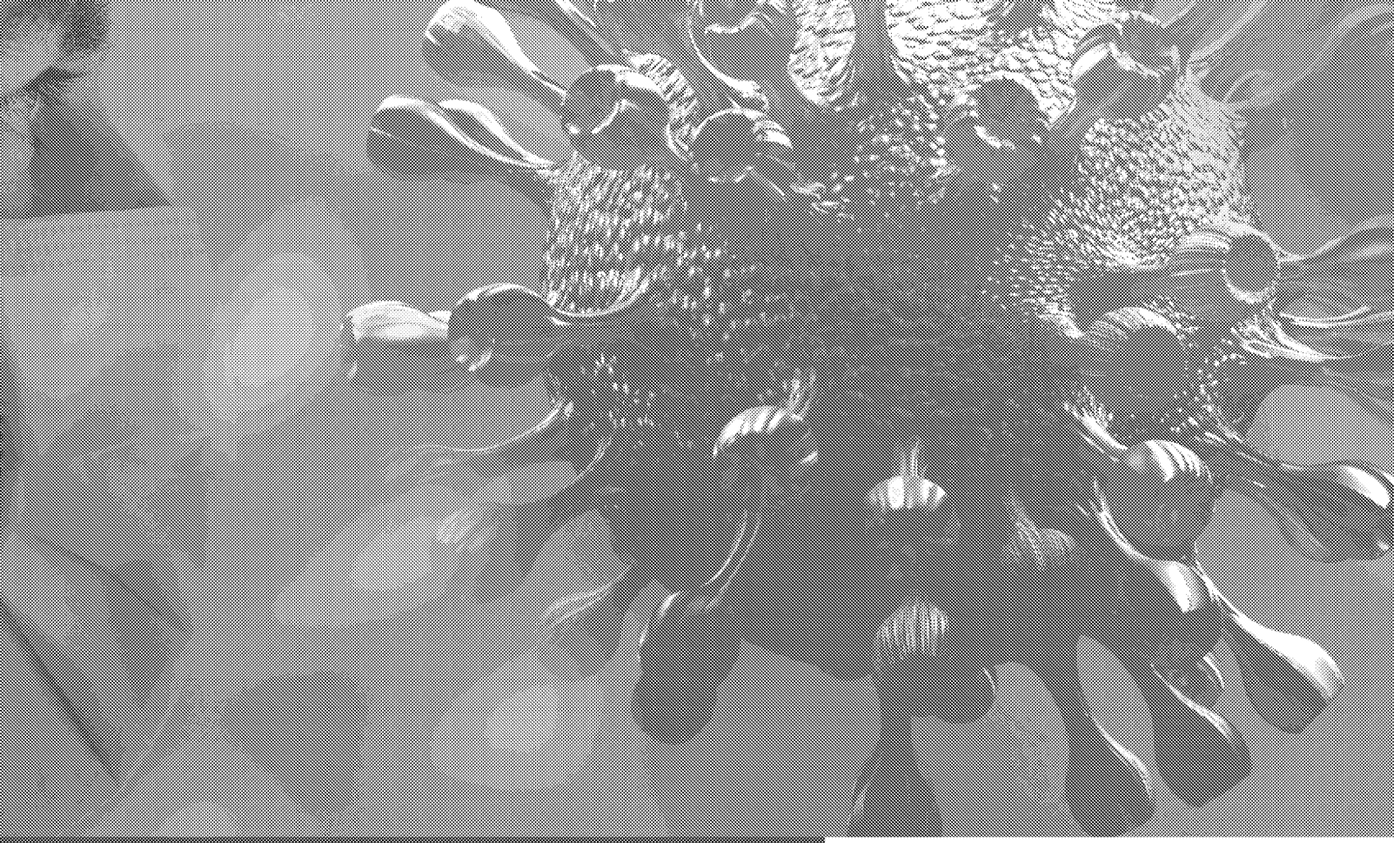


From: Embry, Alan (NIH/NIAID) [E] b6
Sent: Monday, August 2, 2021 11:19 AM
To: NIAID OD AM <NIAIDODAM@niaid.nih.gov>
Subject: House report on Origins



AUGUST 2021

THE ORIGINS OF COVID-19:

AN INVESTIGATION OF THE WUHAN INSTITUTE OF VIROLOGY

HOUSE FOREIGN AFFAIRS COMMITTEE
REPORT MINORITY STAFF

LEAD REPUBLICAN MICHAEL T. MCCAUL

ONE HUNDRED SEVENTEENTH CONGRESS

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INTRODUCTION

Five hundred and four days ago, on March 16, 2020, Committee Minority Staff began its investigation into the origins of SARS-CoV-2 and the COVID-19 global pandemic at the direction of Ranking Member Michael T. McCaul. The House Foreign Affairs Committee Minority Staff Final Report on The Origins of the COVID-19 Global Pandemic, Including the Roles of the Chinese Communist Party and the World Health Organization was published in late September 2020. At the time of its release, there were an estimated 30.8 million cases of COVID-19 around the world, and a death toll of approximately 958,000. Today, the cumulative count stands at more than 196.4 million cases and 4,194,061 dead.

The House Foreign Affairs Committee Minority Staff has continued to investigate the origins of COVID-19, examining new information as it became available, including through expert testimony. We have done so because approximately 48 million of our population are under the age of 12 and without access to a vaccination, while others remain unvaccinated due to underlying medical conditions, leaving a large portion of American citizens at risk of infection. We prepared this addendum as reports increase regarding various strains around the globe, and as PRC authorities continue to withhold critical information about the early months of the pandemic. We have strongly urged our Majority colleagues to take this investigation seriously and conduct a full bipartisan investigation into the origins of COVID-19, and will continue to do so. President Biden has said he wants to discover how the pandemic began, and it is our duty to the American people to use all the tools in our arsenal in pursuit of that goal. As always, we stand ready to address this and other foreign policy challenges together and in a bipartisan manner. We must not let up on pressing General Secretary Xi and CCP authorities for answers.

Here we share the result of these efforts in an addendum to our September 2020 Final Report. In particular, this update focuses on whether the virus may have leaked from a medical research laboratory in Wuhan, Hubei Province, PRC, and the efforts to conceal such a leak. The evidence used to inform this report is based upon open source information and includes published academic work, official PRC publications (both public and confidential), interviews, emails, and social media postings.

Since the publication of the September 21, 2020 Final Report new questions have been raised pertaining to the origins of COVID-19. The PRC's continued lack of transparency resulted in President Joseph R. Biden, Jr.'s May 26, 2021, order to the United States Intelligence Community to prepare a report in 90 days on the origins of COVID-19, "including whether it emerged from human contact with an infected animal or from a laboratory accident." [1]

[1] "Statement by President Joe Biden on the Investigation into the Origins of COVID-19." The White House, 26 May 2021, www.whitehouse.gov/briefing-room/statements-releases/2021/05/26/statement-by-president-joe-biden-on-the-investigation-into-the-origins-of-covid-19/.

INTRODUCTION

Based on the material collected and analyzed by the Committee Minority Staff, the preponderance of evidence suggests SARS-CoV-2 was accidentally released from a Wuhan Institute of Virology laboratory sometime prior to September 12, 2019. The virus, or the viral sequence that was genetically manipulated, was likely collected in a cave in Yunnan province, PRC, between 2012 and 2015. Researchers at the WIV, officials within the CCP, and potentially American citizens directly engaged in efforts to obfuscate information related to the origins of the virus and to suppress public debate of a possible lab leak. It is incumbent on these parties to respond to the issues raised herein and provide clarity and any exonerating evidence as soon as possible. Until that time, it must be assumed General Secretary Xi and the Chinese Communist Party, prioritizes preserving the Party over the lives of its own people and those around the global suffering the effects of the COVID-19 pandemic.

EXECUTIVE SUMMARY

More than one year after the World Health Organization declared a pandemic, the world is still reeling from the emergence of the SARS-CoV-2 virus and the disease it causes, COVID-19. More than four million people have lost their lives worldwide, including more than 612,000 Americans, while economies around the world have been devastated by the fallout. This report investigates the origin of this virus and looks at how it became a deadly pandemic.

The Wuhan Institute of Virology

Last September, the House Foreign Affairs Committee Minority Staff, under the direction of Ranking Member Michael T. McCaul, released a report on the origins of the COVID-19 pandemic. That report highlighted the possibility SARS-CoV-2 could have leaked from the Wuhan Institute of Virology (WIV). However, as we continued our investigation and uncovered more information, we now believe it's time to completely dismiss the wet market as the source of the outbreak. We also believe the preponderance of the evidence proves the virus did leak from the WIV and that it did so sometime before September 12, 2019.

This is based upon multiple pieces of evidence laid out in the report, including:

- The sudden removal of the WIV's virus and sample database in the middle of the night on September 12, 2019 and without explanation;
- Safety concerns expressed by top PRC scientists in 2019 and unusually scheduled maintenance at the WIV;
- Athletes at the Military World Games held in Wuhan in October 2019 who became sick with symptoms similar to COVID-19 both while in Wuhan and also shortly after returning to their home countries;
- Satellite imagery of Wuhan in September and October 2019 that showed a significant uptick in the number of people at local hospitals surrounding the WIV's headquarters, coupled with an unusually high number of patients with symptoms similar to COVID-19;
- The installation of a People's Liberation Army's bioweapons expert as the head of the WIV's Biosafety Level 4 lab (BSL-4), possibly as early as late 2019; and
- Actions by the Chinese Communist Party and scientists working at or affiliated with the WIV to hide or coverup the type of research being conducted at there.

EXECUTIVE SUMMARY

Genetic Modification

This report also lays out ample evidence that researchers at the WIV, in conjunction with U.S. scientists and funded by both the PRC government and the U.S. government, were conducting gain-of-function research on coronaviruses at the WIV, at times under BSL-2 conditions. Much of this research was focused on modifying the spike protein of coronaviruses that could not infect humans so they could bind to human immune systems. The stated purpose of this work was to identified viruses with pandemic potential and to create a broad-spectrum coronavirus vaccine. In many instances, the scientists were successful in creating "chimeric viruses" – or viruses created from the pieces of other viruses – that could infect human immune systems. With dangerous research like this conducted at safety levels similar to a dentist's office, a natural or genetically modified virus could have easily escaped the lab and infected the community.

Committee Minority Staff has also identified scientists who are directly tied to the WIV, and who worked on gain-of-function research in the years prior to the start of the current pandemic, who had the ability to modify genetically modify coronaviruses without leaving any trace evidence. An American scientist, Dr. Ralph Baric, assisted in creating a method to leave no trace of genetic modification as early as 2005. And as early as 2016, scientists working at the WIV were able to do the same. This makes it clear that claims by the scientific community that SARS-CoV-2 could not be man-made because it has no genetic modification markers are disingenuous.

We conclude there is ample proof that the virus could have been genetically manipulated, and that it is vitally important we fully investigate this hypothesis to determine if that happened here.

The Cover-Up

In the original report, we laid out many of the ways the Chinese Communist Party (CCP) and the World Health Organization (WHO) went to great lengths to cover up the initial epidemic, and how their cover-up likely turned what could have been a local outbreak into a global pandemic. The CCP detained doctors in order to silence them, and disappeared journalists who attempted to expose the truth. They destroyed lab samples, and hid the fact there was clear evidence of human-to-human transmission. And they still refuse to allow a real investigation into the origins. At the same time, the WHO, under Director General Tedros, failed to warn the world of the impending pandemic. Instead, he parroted CCP talking points, acting as a puppet of General Secretary Xi.

In this addendum, we have uncovered further evidence of how top scientists at the WIV and Dr. Peter Daszak, an American scientist, furthered that cover-up. Their actions include bullying other scientists who questioned whether the virus could have leaked from a lab; misleading the world about how a virus can be modified without leaving a trace; and, in many, instances directly lying about the nature of the research they were conducting, as well as the low-level safety protocols they were using for that research.

These actions not only delayed an initial investigation into the possibility of a lab leak costing valuable time, but provide further proof the virus likely leaked from the WIV. These actions also call into question the way in which U.S. government grants are used in overseas labs and call for more oversight of those grants.

Next Steps

After this extensive investigation, we believe it is time to call Peter Daszak to testify before Congress. There are still many outstanding questions about the type of research he funded at the WIV that only he can answer. In addition, we believe there is legislation Congress can pass that would not only hold those responsible accountable but also help to prevent a future pandemic, including but not limited to:

- Institute a ban on conducting and funding any work that includes gain-of-function research until an international and legally binding standard is set, and only where that standard is verifiably being followed.
- Sanction the Chinese Academy of Sciences and affiliated entities.
- List the Wuhan Institute of Virology and its leadership on the Specially Designated Nationals and Blocked Persons List and apply additional, appropriate secondary sanctions.
- Authorize new sanctions for academic, governmental, and military bioresearch facilities that fail to ensure the appropriate levels of safety and information sharing.

GLOSSARY OF TERMS

Gain-of-Function Research	"Research that improves the ability of a pathogen to cause disease." – U.S. Department of Health and Human Services
Spike Protein	A protein structure on the surface of an enveloped virus responsible for anchoring the virus to the host cell's surface and enabling the injection of the virus' genetic material into the host cell.
RBD	Receptor-Binding Domain. The specific short fragment in a spike protein of a virus that binds the virus to a specific receptor on the host cell.
Primary Author	The first listed author of an academic paper, usually the person who contributes the most to a paper.
Corresponding Author	The point of contact for editors and outside readers who have questions about an academic paper.
USAID Predict	An epidemiological research grant program funded by the United States Agency for International Development. PREDICT provided funding for biological sampling aimed at virus identification and collection. The program provided grant funding to EcoHealth Alliance.
SARS	Severe Acute Respiratory Syndrome. A viral respiratory disease caused by SARS-CoV, a betacoronavirus. First identified as the cause of a 2002-2003 epidemic.
MERS	Middle East Respiratory Syndrome. A viral respiratory disease caused by MERS-CoV, a betacoronavirus. First identified as the cause of a 2012 outbreak.
SARS-CoV-2	The betacoronavirus that causes COVID-19.
Coronavirus	An RNA virus that causes disease in mammals and birds. Range in severity from the common cold to SARS-CoV-2.
Betacoronavirus	One of the four subclassifications of coronaviruses. Found in bats and rodents, this is the genus includes SARS, MERS, and SARS-CoV-2.
Biosafety Level 1 (BSL1)	Designed for work on microbes not known to cause disease in healthy adults and present minimal potential hazard to laboratorians and the environment. Work can be performed on an open lab bench or table.

GLOSSARY OF TERMS

Biosafety Level 2 (BSL2)	For work with microbes that pose moderate hazards to laboratorians and the environment. The microbes are typically indigenous and associated with diseases of varying severity. Personal protective equipment includes lab coats and gloves. Work can be performed in the open or in a biological safety cabinet. Commonly compared to the level of safety observed in a dentist's office.
Bio Safety Level 3 (BSL3)	For work with microbes that are either indigenous or exotic, and that can cause serious or potentially lethal disease through respiratory transmission. Respiratory transmission is the inhalation route of exposure. Researchers should be under medical surveillance and potentially immunized for the microbes they work with. Respirators may be required, in addition to standard personal protective equipment. Work must be performed within a biological safety cabinet. Exhaust air cannot be recirculated, and the laboratory must have sustained directional airflow by drawing air into the laboratory from clean areas towards potentially contaminated areas.
Biosafety Level 4 (BSL4)	This is the highest level of biological safety. The microbes in a BSL-4 lab are dangerous and exotic, posing a high risk of aerosol-transmitted infections. Infections caused by these microbes are frequently fatal and without treatment or vaccines. Researchers must change clothing prior to entering the lab, shower upon exiting, and decontaminate all materials before exiting. All work with microbes must be performed in a Class III biological safety cabinet or while wearing a full body, air-supplied, positive pressure suit. The lab must be in a separate building or in a restricted zone, and must have a dedicated supply and exhaust air, as well as vacuum lines and decontamination systems.
Wuhan Institute of Virology (WIV)	A research institute in Wuhan, PRC focused on focused on virology, that consists of at least two facilities – the Wuhan National Biosafety Laboratory and the Wuhan Institute of Virology Headquarters."

GLOSSARY OF TERMS

Wuhan National Biosafety Laboratory	The WIV's new campus, located in the Zhengdian Scientific Park in Jiangxia District, Wuhan. The location of the WIV's Biosafety Level 4 laboratory space.
WIV Headquarters	The older WIV facility, located in Wuchang District, Wuhan near the Wuhan Branch of the Chinese Academies of Science.
Chinese Academy of Sciences	The national academy for natural sciences in the PRC. Reports to the State Council of the People's Republic of China.
WIV1	The first novel coronavirus isolated by WIV researchers. Isolated from bat fecal samples in 2013. A SARS like coronavirus.
WIV16	The second coronavirus isolated by WIV researchers. Isolated from a single bat fecal sample in 2016. A SARS like coronavirus.
Rs4874	The third coronavirus isolated by WIV researchers. Isolated from a single bat fecal sample in 2017. A SARS like coronavirus.
ID4491/RaTG13	A SARS like coronavirus collected in 2013 in a mining cave. 96.1% similar to SARS-CoV-2.
ACE2	Angiotensin-converting enzyme-2, found on the surface of certain cells in a variety of animals, including humans, mice, and civets. The entry point for coronaviruses.
hACE2	The human version of ACE2. Primarily found on the surface of cells and tissues throughout the human body, including the nose, mouth, and lungs. In the lungs, hACE2 is highly abundant on type 2 pneumocytes, an important cell type present in chambers within the lung called alveoli, where oxygen is absorbed, and waste carbon dioxide is released. The primary entry point for SARS-CoV-2 into human cells.
Chimeric Virus	An artificial, man-made virus. Created by joining two or more viral fragments.
Natural Virus	A virus found in nature; "wild type."

GLOSSARY OF TERMS

Reverse Genetics System	A method in molecular genetics that is used to help understand the function(s) of a gene by analyzing the phenotypic effects caused by genetically engineering specific nucleic acid sequences within the gene. Can be used to create chimeric viruses indistinguishable from natural viruses.
Furin Cleavage Site	An enzyme in the spike protein of SARS-CoV-2 that increases how infectious the virus is in humans. SARS-CoV-2 is the only betacoronavirus to have this structure.
Phylogenetic Analysis	The study of the evolutionary development of a species or a group of organisms or a particular characteristic of an organism. Used to identify the relationship between different viruses in the same family.
CGG Double Codon	"CGG-CGG." This group of six nucleotides (a group of three nucleotides is also know as a codon) is half of the 12 nucleotides that create the furin cleavage site. The CGG double codon is relatively rare in coronaviruses, and SARS-CoV-2 is the only coronavirus in its family to have one.

KEY PEOPLE

Dr. Wang Yanyi	Director General of the Wuhan Institute of Virology.
Dr. Yuan Zhiming	Director of the WNBL BSL-4 lab. General Secretary of the Chinese Communist Party Committee within the Wuhan Branch of the Chinese Academy of Sciences, to which the WIV belongs.
Dr. Shi Zheng-li	Senior scientist as the Wuhan Institute of Virology (WIV). Serves as Director, Research Center for Emerging Infectious Diseases; Director, Chinese Academy of Sciences Key Laboratory of Special Pathogens; Director, Biosafety Working Committee; and Deputy Director of the Wuhan National Biosafety Laboratory's Biosafety-Level 4 lab.
Dr. Ben Hu	WIV researcher and former doctoral student of Shi Zheng-li. Deeply involved in the WIV's coronavirus research.
Dr. Linfa Wang	PRC national, Director and Professor of the Program in Emerging Infectious Diseases at the Duke-NUS Graduate Medical School in Singapore. Chair of the Scientific Advisory Board for the Center for Emerging Diseases at the WIV.
Dr. Peter Daszak	CEO of EcoHealth Alliance. Longtime collaborator of Shi and others at the WIV. Provided subgrants to the WIV to help fund coronavirus research.
Dr. Ralph Baric	Researcher at the University of North Carolina at Chapel Hill who has collaborated with Shi and other WIV researchers on coronavirus research.

ADDENDUM TO THE REPORT

I. THE CITY OF WUHAN: EPICENTER OF A PANDEMIC

Wuhan is the epicenter of the coronavirus pandemic. Located in central PRC where the Yangtze River, the PRC's longest river, and the Han River meet, Wuhan is the capital city of Hubei Province and boasts a population of about 11.1 million in about 3,280 square miles. [2] It is home to the PRC's tallest skyscrapers, multiple colleges and universities, including the prominent Wuhan University, major historical and cultural sites, and an influential research laboratory, the Wuhan Institute of Virology (WIV). To put the scale of Wuhan in perspective, the city covers an area five times the size of Houston and has a larger population than New York City and Chicago combined.

Wuhan is home to the Hankou railway station, central PRC's biggest European-style Railway station, and two other major train stations. Hankou Station connects directly to the Tianhe International Airport, the busiest airport in central PRC and the geographic center of the PRC's airport network. From the Tianhe airport, travelers can fly direct to New York City, San Francisco, Paris, Milan, Rome, Hamburg, Bangkok, Tokyo, Seoul, and Dubai, among many other destinations around the world.

The PRC calls Wuhan one of its nine "National Central Cities," an official state label that means it leads the way, along with the capital Beijing, Shanghai, and other major cities, in developing culture, politics, and the economy.[3] An August 2016 report by the Netherlands Enterprise Agency, a government agency that operates under the auspices of the Ministry of Economic Affairs and Climate Policy, identified Wuhan as a major hub not just within the PRC, but also globally within the Chinese "One Belt One Road" initiative due to its accessibility.[4] The city is also home to significant railway commerce. A 2018 report from Xinhua news expected an estimated 500 freight trains from Wuhan to Europe for the export of goods.[5]

France, the U.S., the Republic of Korea, and the UK maintain Consulates in the city, which was selected to host the 7th International Military Sports Council (CISM) Military World Games. During the games, more than 9,000 military personnel from over 100 countries stayed in Wuhan in accommodations at an athletes' village built specifically for the games.

2 "WHO-convened Global Study of Origins of SARS-CoV-2: China Part." Joint WHO-China Study. 30 March 2021, https://www.who.int/health-topics/coronavirus/origins-of-the-virus

3 Xu, Zongwei. "China Unveils National Central City Strategy." *China Watch,* 29 Mar. 2018, www.chinawatch.cn/a/201803/29/WS5ad061d6a310cc9200067c6c.html.

4 Van de Bovenkamp, Judith and Yuan Fei. "Economic Overview of Hubei Province." *Neatherlands Business Support Office Wuhan,* Aug. 2016, https://www.rvo.nl/sites/default/files/2016/08/Economic-overview-Hubei-province-China.pdf

5 "Central China-Europe Rail Freight to Surge in 2018." *Xinhua*, 1 Feb. 2018. http://www.china.org.cn/china/Off_the_Wire/2018-02/01/content_50372222.htm

II. EVIDENCE OF A LAB LEAK

As discussed in the previously issued report, the WIV continues to be a focal point of debate concerning the origins of SARS-CoV-2 and the COVID-19 pandemic. In recent months, new information about the WIV has come to light, enabling us to better understand the institute, the type of research conducted by scientists working there, and its ties to the CCP and their military, the People's Liberation Army (PLA). We now believe the preponderance of evidence shows the virus accidentally leaked from one of the WIV's facilities.

The Wuhan Institute of Virology

The WIV was founded in 1956 as the Wuhan Microbiology Laboratory and has operated under the administration of the Chinese Academy of Sciences since 1978.[6] The institute currently occupies at least two campuses – the much-discussed Wuhan National Biosafety Laboratory (WNBL) in Zhengdian Scientific Park (see Figure 1), and the older facility (hereafter WIV Headquarters) located in the Xiaohongshan park in the Wuchang District of Wuhan (see Figure 2). The WNBL is a large complex with multiple buildings that house 20 Biosafety Level II (BSL-2) laboratories, two Biosafety Level III (BSL-3) laboratories, and 3000 square meters of Biosafety Level IV (BSL-4) space, "including four independent laboratories areas and two animal suites."[7] Construction was completed in 2015, but due to delays the BSL-4 space did not become operational until early 2018.[8]

Fig. 1: Wuhan National Biosafety Laboratory (WNBL)

Missing from the majority of public debates regarding the WIV is the research conducted at the WIV Headquarters, the older location in the Wuchang District of Wuhan. Located 12 miles northeast of the WNBL, in the Wuchang District, this facility remains the administrative headquarters of the WIV. In addition to the BSL-2 labs at this location, the WIV constructed a BSL-3 laboratory at the facility in 2003.[9]

6 "History." *Wuhan Institute of Virology*, http://english.whiov.cas.cn/About_Us2016/History2016/.

7 World Health Organization. "WHO Consultative Meeting on High/Maximum Containment (Biosafety Level 4) Laboratories Networking." Meeting Report, Lyon, France, 13-15 Dec. 2018. https://apps.who.int/iris/bitstream/handle/10665/311625/WHO-WHE-CPI-2018.40-eng.pdf

8 Zhiming, Yuan. "Current status and future challenges of high-level biosafety laboratories in China." *Journal of Biosafety and Biosecurity,* 1 Sept. 2019, 1(2): 123-127. https://doi.org/10.1016/j.jobb.2019.09.005

9 Zheng Qianli, "Jiang Xia plays new essays and plays Yoko on the crane——The construction and research team of P4 laboratory of Wuhan Institute of Virology, Chinese Academy of Sciences." *Chinese Journal of Science,* 1 Jan. 2018, https://archive.is/V3GHk#selection-517.35-517.202

It was here, in the center of Wuhan, that Dr. Shi Zheng-li and her team conducted gain-of-function research on coronaviruses in the years leading up to the COVID-19 pandemic.

Fig. 2: WIV Headquarters in Wuchang

According to the WIV's website, Shi Zheng-li serves as the Director of the WIV's Research Center for Emerging Infectious Diseases, the Deputy Director of the WNBL BSL-4 lab, the Director of the BSL-3 lab, and the Director of the Biosafety Working Committee.[10] Shi is also the Director of the Chinese Academy of Sciences (CAS) Key Laboratory of Special Pathogens and Biosafety,[11] which includes the majority of scientists who are conducting gain-of-function research on coronaviruses at the WIV.

It should be noted that the WIV has a Chinese Communist Party Committee within the institute, as well as a Commission for Discipline Inspection. The Party Committee is divided into four party branches, which are then divided into subbranches organized around the individual WIV departments, research centers, and offices. Each subbranch has its own Propaganda Committee. Committee Minority Staff were able to identify eight WIV researchers on these committees, including several who are affiliated with the Key Laboratory that Shi directs.

WIV Researcher	Lab Affiliation	Propaganda Committee[12]
Liu Qiaojiue	Key Laboratory of Special Pathogens and Biosafety[13]	Party Branch of Research Center for Emerging Infectious Diseases
Zhang Xiaowei	Key Laboratory of Special Pathogens and Biosafety and Key Laboratory of Virology[14]	Party Branch of the Research Center for Microbiology and Nanobiology

10 "Shi Zhingli." Wuhan Institute of Virology, http://www.whiov.cas.cn/sourcedb_whiov_cas/zw/rck/200907/t20090718_2100074.html

11 "Prof. SHI Zhengli elected a fellow of the American Academy of Microbiology." *Wuhan Institute of Virology,* http://english.whiov.cas.cn/ne/201903/t20190308_206697.html

12 "Party Branch." Wuhan Institute of Virology, http://www.whiov.cas.cn/djkxwh/dqzz/dzb/

13 Wang Q, et. al. "Structural Basis for RNA Replication by the SARS-CoV-2 Polymerase." *Cell,* 23 July 2020, 182(2):417-428.e13, https://pubmed.ncbi.nlm.nih.gov/32526208/

14 Zhang, Xiaowei et al. "Tick-borne encephalitis virus induces chemokine RANTES expression via activation of IRF-3 pathway." *Journal of Neuroinflammation,* 30 Aug. 2016, 13(1):209. https://pubmed.ncbi.nlm.nih.gov/27576490/

Shen Xurui	Key Laboratory of Special Pathogens and Biosafety [15]	Graduate Party Branch of the Research Center for Emerging Infectious Diseases
Tang Shuang	State Key Laboratory of Virology [16]	Party Branch of the Research Center for Microbial Resources and Bioinformatics
Wu Yan	State Key Laboratory of Virology [17]	Party Branch of Molecular Virus and Pathology Research Center
He Lihong	State Key Laboratory of Virology [18]	Party Branch of the Research Center for Microbial Resources and Bioinformatics
Wang Qingxing	State Key Laboratory of Virology [19]	Graduate Party Branch of the Research Center for Molecular Viruses and Pathology
Yang Mengsi	State Key Laboratory of Virology [20]	Graduate Party Branch of the Research Center of Microbiology and Nanobiology

Table 1: WIV Researchers on CCP Propaganda Committees

The Committee for Discipline Inspection is charged with "the implementation of the party's line, policy, party discipline, relevant laws and regulations, and the institute's rules and regulations."[21]

In addition to the researchers serving on propaganda committees, other key figures at the WIV also serve as CCP officials. Dr. Wang Yanyi serves as the Director of the WIV and joined the China Zhi Gong Party, a CCP controlled minority party, in 2010. In 2018, the same year she became the Director General of the WIV, she was elected the Deputy Director of the Wuhan Municipal Party Committee.

15 Zhou, Peng et al. "A pneumonia outbreak associated with a new coronavirus of probable bat origin." *Nature* March 2020, 579(7798): 270-273. https://pubmed.ncbi.nlm.nih.gov/32015507/

16 Abudurexiti, Abulikemu, et al. "Taxonomy of the order Bunyavirales: update 2019." *Archives of Virology,* July 2019, 164(7): 1949-1965. https://pubmed.ncbi.nlm.nih.gov/31065850/

17 Su, Hai-Xia et al. "Anti-SARS-CoV-2 activities in vitro of Shuanghuanglian preparations and bioactive ingredients." *Acta Pharmacologica Sinica,* September 2020, 41(9): 1167-1177. https://pubmed.ncbi.nlm.nih.gov/32737471/

18 Shao, Wei et al. "Functional Characterization of the Group I Alphabaculovirus Specific Gene ac73." *Virologica Sinica,* Dec. 2019, 34(6): 701-711. https://pubmed.ncbi.nlm.nih.gov/31317397/

19 Su, Haixia et al. "Identification of pyrogallol as a warhead in design of covalent inhibitors for the SARS-CoV-2 3CL protease." *Nature Communications,* 15 June 2021, (2(1): 3623. https://pubmed.ncbi.nlm.nih.gov/34131140/

20 Zhang, Juan, et. al. "Passive cancer targeting with a viral nanoparticle depends on the stage of tumorigenesis." *Nanoscale,* 8 July 2021, 13(26):11334-11342, https://pubmed.ncbi.nlm.nih.gov/34165123/

21 "Commission for Discipline Inspection." *Wuhan Institute of Virology,* http://www.whiov.cas.cn/djkxwh/dqzz/jw/

Until late 2019, the BSL-4 lab was managed by Dr. Yuan Zhiming. Yuan is the General Secretary of the Chinese Communist Party Committee within the Wuhan Branch of the Chinese Academy of Sciences, to which the WIV belongs. Local CCP leaders not only run the WIV itself but also directly managed the BSL-4 lab.[22]

Director Wang's 2021 New Year's speech makes reference to the Party Committee of Wuhan Institute of Virology, pledging that the party committee will "effectively play the role of a battle fortress of grassroots party organizations."[23] The WNBL also has its own party branch, the Zhengdian Laboratory Party Branch, which was "awarded the title of 'Red Flag Party Branch' by the Hubei Provincial Party Committee and Provincial Organization Working Committee, effectively playing an advanced and exemplary role."[24] Notably, in discussing the COVID-19 pandemic, Director Wang's 2021 speech takes pains to address questions of lab safety – "The institute's high-level biosafety laboratory operates safely for more than 300 days throughout the year."[25] Her 2020 address, posted sometime after April 2020, makes no such mention.

The WNBL's BSL-4 lab was constructed as a result of an agreement between the PRC and France that was signed after the 2003 SARS pandemic.[26] At the time, all BSL-3 labs in the PRC were controlled by the PRC's People's Liberation Army (PLA). Then-President of France, Jacques Chirac, and his Prime Minister, Jean-Pierre Raffarin, approved the project despite concerns from both the French Ministry of Defense and French intelligence services – Raffarin himself described it as "a political agreement."[27] The PRC was suspected of having a biological warfare program, and the military and intelligence services were worried that the dual-use technology required to build a BSL-4 lab could be misused by the PRC government. The uneasy compromise reached within the French government was that the agreement would require joint PRC-France research to be conducted in the lab, with French researchers present.[28]

In 2016, the PRC requested dozens of the containment suits required to work in the lab. The French Dual-Use Commission, tasked with considering exports of sensitive equipment, rejected their request. According to French reporting, the request was "well above the needs of the Wuhan [lab]."[29] **This continued to fuel concerns within the French Ministry of Defense that the PRC was seeking to engage in military research or open a second BSL-4 lab for military means.** Despite the agreement that the BSL-4 lab would be a site of joint research, and an announcement at the 2017 inauguration by then Prime Minister Bernard Cazeneuve of €5 million in funding, there has only been one French scientist assigned to the lab. His tour ended in 2020.[30]

22 Izambard, Antoine. "L'histoire Secrète Du Laboratoire P4 De Wuhan Vendu Par La France à La Chine." *Challenges*, 30 Apr. 2020 www.challenges.fr/entreprise/sante-et-pharmacie/revelations-l-histoire-secrete-du-laboratoire-p4-de-wuhan-vendu-par-la-france-a-la-chine_707425.

23 "New Year's Speech by the Director in 2021." *Wuhan Institute of Virology*, http://www.whiov.cas.cn/gkjj/szzc_160220/

24 "New Year's Message from the Director in 2020." *Wuhan Institute of Virology*, https://web.archive.org/web/20200701032318/http://www.whiov.cas.cn/gkjj/szzc_160220/

25 *Ibid.*

26 "About WIV." *Wuhan Institute of Virology*, http://english.whiov.cas.cn/About_Us2016/Brief_Introduction2016/.

27 Izambard, Antoine. "L'histoire Secrète Du Laboratoire P4 De Wuhan Vendu Par La France à La Chine." *Challenges*, 30 Apr. 2020, www.challenges.fr/entreprise/sante-et-pharmacie/revelations-l-histoire-secrete-du-laboratoire-p4-de-wuhan-vendu-par-la-france-a-la-chine_707425.

28 *Ibid.*

29 *Ibid.*

30 Izambard.

Safety Concerns and Unusual Maintenance

There have been several reports of safety concerns at PRC labs starting as early as 2004, when it was discovered SARS leaked from a lab in Beijing. Several other accidental releases have happened in the years since.

As discussed in our original report released last year, in 2018 U.S. State Department officials sent cables to Washington, D.C. highlighting concerns with safety issues at the WIV. The cables reported that scientists at the WIV noted "a serious shortage of appropriately trained technicians and investigators needed to safely operate this high-containment laboratory."[31] The cables also questioned the PRC's commitment to prioritizing the important research for which the lab was designed.

(b)(6) **Thus, while the BSL-4 lab is ostensibly fully accredited, its utilization is limited by lack of access to specific organisms and by opaque government review and approval processes. As long as this situation continues, Beijing's commitment to prioritizing infectious disease control - on the regional and international level, especially in relation to highly pathogenic viruses, remains in doubt.**

Fig. 4: Excerpt from January 19, 2018 Cable from the U.S. Embassy in Beijing to State Department Headquarters in Washington, D.C.

One year later, in June 2019, George Gao, the Director of the Chinese Center for Disease Control and Prevention, expressed concerns about safety protocols at the WIV. In an almost prophetic statement published in *Biosafety and Health*, Gao wrote (emphasis added):

> Advances in biomedical technologies, such as genome editing and synthetic biotechnology, have the potential to provide new avenues for biological intervention in human diseases. These advances may also have a positive impact by allowing us to address risks in new approaches. **However, the proliferation of such technologies means they will also be available to the ambitious, careless, inept, and outright malcontents, who may misuse them in ways that endanger our safety.** For example, while CRISPR-related techniques provide revolutionary solutions for targeted cellular genome editing, it can also lead to unexpected off-target mutations within genomes or the possibility of gene drive initiation in humans, animals, insects, and plants. Similarly, genetic modification of pathogens, which may expand host range as well as increase transmission and virulence, may result in new risks for epidemics. For example, in 2013, several groups showed that influenza H5N1 viruses with a few nucleotide mutations and H7N9 isolates reasserted with 2009 pandemic H1N1 virus could have the ability for airborne transmission between ferrets. **Likewise, synthetic bat-origin SARS-like coronaviruses acquired an increased capability to infect human cells. Thus, modifying the genomes of animals (including humans), plants, and microbes (including pathogens) must be highly regulated.** [32]

Three months later, in September 2019, Yuan Zhiming, the Director of the BSL-4 lab at the WNBL and Shi's superior, published an article in the *Journal of Biosafety and Biosecurity.*

31 Rogin, Josh. "Opinion | State Department Cables Warned of Safety Issues at Wuhan Lab Studying Bat Coronaviruses." *The Washington Post,* 14 Apr. 2020, www.washingtonpost.com/opinions/2020/04/14/state-department-cables-warned-safety-issues-wuhan-lab-studying-bat-coronaviruses/.

32 Gao, George F. "For a better world: Biosafety strategies to protect global health." *Biosafety and Health,* June 2019, 1(1): 1-3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7147920/

Entitled, "Current status and future challenges of high-level biosafety laboratories in China,"[33] the article discusses at length the construction of the WNBL. Yuan identifies multiple key issues, including inadequate biosafety management systems, insufficient resources for efficient laboratory operation, and deficiency of professional capacity. With a surprising level of transparency, Yuan admits that the enforcement of pathogen, waste, and laboratory animal management regulations "needs to be strengthened."[34] Discussing the insufficient level of resources being provided by the PRC government, he stated:

> **The maintenance cost is generally neglected; several high-level BSLs have insufficient operational funds for routine yet vital processes. Due to the limited resources, some BSL-3 laboratories run on extremely minimal operational costs or in some cases none at all.**[35]

Yuan also raised concerns about a lack of specialized biosafety managers and engineers to run the labs.[36] **It is important to note that researchers at the WIV had previously conducted gain-of-function research on coronaviruses at the BSL-2 and BSL-3 levels. This is important given that both the head of the China CDC and the head of the WIV's BSL-4 labs had expressed concern about the safety of this research and the labs in which it was being conducted.**

Interestingly, there appears to have been ongoing maintenance and repairs projects occurring at the WIV in 2019, before Yuan published his article raising these concerns. It is important to note that at the time of the hazardous waste treatment system renovation project, the WNBL had been operational for less than two years. Such a significant renovation so soon after the facility began operation appears unusual. Procurement announcements published on the PRC's government procurement website provide evidence of ongoing work at what appears to be both WIV locations.

Project Name	**Location**	**Date**	**Budget (USD)**
Maintenance Project of P3 Laboratory and Laboratory Animal Center in Zhengdian Park[37]	WNBL	March 1, 2019	$401,284.10
Procurement of Positive Pressure Protective Clothing [38]	WNBL	March 21, 2019	$177,161.40
Hazardous Waste Treatment System Renovation Project [39]	WNBL	July 31, 2019	$1,521,279.28

33 Yuan Zhinming. "Current status and future challenges of high-level biosafety laboratories in China." *Journal of Biosafety and Biosecurity,* Sept. 2019, 1(2): 123-127. https://www.sciencedirect.com/science/article/pii/S2588933819300391#b0080

34 *Ibid.*

35 *Ibid.*

36 *Ibid.*

37 "Announcement of Competitive Consultation on Maintenance Project of P3 Laboratory and Laboratory Animal Center in Zhengdian Park, Wuhan Institute of Virology, Chinese Academy of Sciences." *China Government Procurement Network,* 1 March 2019, https://archive.is/7eCPU#selection-229.0-229.185

38 "Announcement of a single source for the purchase of positive pressure protective clothing project by Wuhan Institute of Virology, Chinese Academy of Sciences." *China Government Procurement Network,* 21 March 2019, https://archive.is/VUcNA#selection-229.0-229.157

39 "Announcement on the transaction of the hazardous waste treatment system renovation project in Zhengdian Park, Wuhan Institute of Virology, Chinese Academy of Sciences." *China Government Procurement Network,* 31 July 2019, https://archive.is/3CW03#selection-229.0-229.166

Procurement Project of The Environmental Air Disinfection System and The Scalable Automated Sample Storage Management System [40]	Unclear	August 14, 2019	$132,200,025.47
Security Service Procurement Project [41]	WNBL	September 12, 2019	$1,281,022.33
Central Air Conditioning Renovation Project [42]	Unclear	September 16, 2019	$606,382,986.11
Procurement of Air Incinerator and Testing Service [43]	Unclear	December 3, 2019	$49,388.81

Table 2: WIV Procurement Projects in 2019

The references to maintenance at the BSL-3 and animal center at the WNBL, the procurement of an environmental air disinfection system, and renovations to the hazardous waste treatment system and central air conditioning system all raise questions about how well these systems were functioning in the months prior to the outbreak of COVID-19.

The Disappearing Database

On September 12, 2019 the WIV's online, public database of samples and virus sequences was taken offline in the middle of the night between 2:00AM and 3:00AM local time.[44] The database contained more than 22,000 entries consisting of sample and pathogen data collected from bats and mice. The database contained key information about each sample, including what type of animal it was collected from, where it was collected, whether the virus was successfully isolated, the type of virus collected, and its similarity to other known viruses.

[40] "Announcement of winning the bid for the procurement project of the environmental air disinfection system and the scalable automated sample storage management system of the Wuhan Institute of Virology, Chinese Academy of Sciences." *China Government Procurement Network,* 14 Aug. 2019, https://archive.is/1nXLD#selection-229.0-229.228

[41] "Competitive consultation on the procurement project of security services in Zhengdian Science Park, *Wuhan Institute of Virology,* Chinese Academy of Sciences." *China Government Procurement Network, 12* Sept. 2019,https://archive.is/tUi75#selection-229.0-229.156

[42] "Competitive Consultation on Central Air Conditioning Renovation Project of Wuhan Institute of Virology, Chinese Academy of Sciences." *China Government Procurement Network,* 16 Sept. 2019, https://archive.is/bfoTD#selection-229.0-229.131

[43] "The Wuhan Institute of Virology of the Chinese Academy of Sciences plans to use a single-source procurement method to publicize the procurement of air incineration devices and test service projects." *China Government Procurement Network,* 3 Dec. 2019, https://archive.is/Jifqr#selection-229.0-229.197

[44] "Status breakdown of the database of characteristic wild animals carrying virus pathogens (September 2019)." *Scientific Database Service Monitoring & Statistics System.* https://archive.is/AGtFv#selection-1553.0-1567.2

Table 1 Virus data display of bat samples

Data element name	Example
Sample ID	1423878
Sample tissue type	Anal
Animal type	bat
Source species	*Rousettus leschenaultii*
Species molecular identification	*Rousettus* sp.
Collection date	2016-08-21
country	China
province	Yunnan
city	Mazonb village, Mengla county, Xishuangbanna
GPS information	101.51944,21.78127
Whether high-throughput sequencing	No
Whether the virus is isolated	No
publishing	Luo Y, Li B, Jiang RD, et al. Virol Sin. 2018;33(1):87-95. doi:10.1007/s12250-018-0002-2
Remarks	
Detection method	PCR-based
Virus name	Coronaviridae
Test results	Positive
Blast result	btcov HKU9
Virus classification	HKU9
Virus sequence	See references for details
Similarity	94%
Sequence length	398bp
Sequence encoded gene	Partial RdRp

Fig. 6: Example Database Entry [45]

To date, there has been no consistent answer provided as to why the database was removed or when or if it will be put back online.

Shi is listed as the data correspondence author for the project. When questioned about the database being taken offline, Shi has given several conflicting answers. During a December 2020 interview with *BBC*, Shi said the database was taken offline for "security reasons" after cyberattacks against the work and personal emails of WIV staff. She also insisted that WIV virus sequences were saved in the GenBank database, run by the National Center for Biotechnology Information. Shi stated, "It's completely transparent. We have nothing to hide." [46]

In a January 26, 2021 email to someone inquiring about the database, however, Shi stated the database was taken down due to cyberattacks "during [the] COVID-19 pandemic."[47] She also claimed that researchers had "only entered a limit[ed] data in this database" despite it having more than 22,000 entries.

45 "Database of pathogens of bat and murine viruses." *Wikisource*, https://zh.wikisource.org/zh-hant/%E8%9D%99%E8%9D%A0%E6%BA%90%E5%92%8C%E9%BC%A0%E6%BA%90%E7%97%85%E6%AF%92%E7%97%85%E5%8E%9F%E6%95%B0%E6%8D%AE%E5%BA%93

46 Sudworth, John. "Covid: Wuhan Scientist Would 'Welcome' Visit Probing Lab Leak Theory." *BBC News*, 21 Dec. 2020, www.bbc.com/news/world-asia-china-55364445.

47 Cleary, Tommy. "Prof Zheng-Li Shi Replied to Me, to CNRI,中文DOI运维 I Can Only Conclude @PeterDaszak & the Rest of the @WHO Organisation Were given the Same Information Access Ultimatum:No Trust, No Conversation.@SciDiplomacyUSA Has Its Work Cut Out.Data Hostage? Pic.twitter.com/KhiFs42U7j." *Twitter*, 10 Mar. 2021, https://twitter.com/tommy_cleary/status/1369689088790425602?s=20.

In an apparent contradiction of her *BBC* interview, Shi admitted that "access to the visitors is limited,"[48] but maintains:

> **...all our work regarding the different type of bat coronavirus (partial sequences or full-length genome sequences) have been published and the sequence and sample information have been submitted to GenBank.**[49]

At the end of her email, Shi writes, "I'll not answer any of your questions if your curiosity is based on the conspiracy of 'man made or lab leak of SARS-CoV-2' or some non-sense questions based on your suspicion. **No trust, no conversation**"[50] (emphasis added).

New Leadership and PLA Involvement

The WIV's website indicates that Yuan Zhiming serves as the Dean of the Wuhan Branch of the Chinese Academy of Sciences and director of the WNBL BSL-4 lab.[51] However, news posted on Weibo Douban, a PRC website, on February 7th, 2020 stated that PLA officials were dispatched to assume control of the response. **The report says PLA Major General Chen Wei, an expert in biology and chemical weapon defenses , was deployed to Wuhan in January 2020 and took control of the WNBL BSL-4 lab.** The posting of this information to Douban is significant given the website's history of censoring posts critical of the CCP, including censoring words related to the Tiananmen Square Massacre.[54] The post's survival on a heavily CCP censored site confirms its legitimacy.

48 Sudworth.

49 *Ibid.*

50 *Ibid.*

51 "Yuan Zhiming." *Wuhan Institute of Virology*, http://www.whiov.cas.cn/sourcedb_whiov_cas/zw/rck/200907/t20090718_2100080.html

52 Gertz, Bill. "Chinese Maj. Gen. Chen Wei TAKES Leading Role in Coronavirus Fight." *The Washington Times,* 16 Feb. 2020, www.washingtontimes.com/news/2020/feb/16/chinese-maj-gen-chen-wei-takes-leading-role-in-cor/.

53 Guli. "Major General Chen Wei, China's Chief Biochemical Weapons Expert, Takes Over Wuhan P4 Virus Laboratory." *Radio France Internationale,* https://www.rfi.fr/cn/%E4%B8%AD%E5%9B%BD/20200208-%E4%B8%AD%E5%9B%BD%E9%A6%96%E5%B8%AD%E7%94%9F%E5%8C%96%E6%AD%A6%E5%99%A8%E4%B8%93%E5%AE%B6%E9%99%88%E8%96%87%E5%B0%91%E5%B0%86%E6%8E%A5%E7%AE%A1%E6%AD%A6%E6%B1%89p4%E7%97%85%E6%AF%92%E5%AE%9E%E9%AA%8C%E5%AE%A4

54 Honorof, Marshall. "China Marks Tiananmen Massacre with 'Internet Maintenance Day.'" *NBC News,* 4 June 2013, https://www.nbcnews.com/id/wbna52096871

Committee Minority Staff have also received testimony from a former senior U.S. official that Gen. Chen actually took control of the WNBL BSL-4 lab in late 2019, not January 2020 as was publicly reported. Gen. Chen taking over part of the WIV demonstrates the CCP was concerned about the activity happening there as news of the virus was spreading. If she took control in 2019, it would mean the CCP knew about the virus earlier, and that the outbreak began earlier – a topic discussed further in this section.

Gen. Chen is a researcher at the Academy of Military Medical Sciences in Beijing, and served as a delegate to the 12th National People's Congress.[55] In January 2018, Gen. Chen was made a member of the 13th National Committee of the Chinese People's Political Consultative Conference (CPPCC). According to the U.S.-China Economic Security Review Commission, the CPPCC is a "critical coordinating body that brings together representatives of China's other interest groups and is led by a member of China's highest-level decision-making authority, the CCP's Politburo Standing Committee." [56]

According to a January 15, 2021 fact sheet published by the State Department, in the years leading up to the pandemic, researchers at the WIV were engaged in classified research, including experiments on animals, on behalf of the PLA.[57] Dr. Shi has repeatedly denied any involvement of the PLA at the WIV. During a lecture hosted only by Rutgers Medical School, Shi stated:

> We—our work, our research is open, and we have a lot of international collaboration. And from my knowledge, all our research work is open, is transparency. So, at the beginning of COVID-19, we heard the rumors that it's claimed in our laboratory we have some project, blah blah, with army, blah blah, these kinds of rumors. But this is not correct because I am the lab's director and responsible for research activity. I don't know any kind of research work performed in this lab. This is incorrect information.[58]

This statement is demonstrably false. The WIV had multiple connections to PLA researchers prior to the COVID-19 pandemic; several were listed on the WIV's English language website. The Academic Committee of State Key Laboratory of Virology at the WIV included a Deputy Director from the Second Military Medical University and a member from the 302 Military Hospital of China. The Scientific Advisory Committee for the Center for Emerging Infectious Diseases had among its members a researcher from the Institute of Military Veterinary at the Academy of Military Medical Sciences.[59] This website was scrubbed on May 28, 2020, and the lists of committee members removed. However, archived copies of the website are available online.

[55] "List of Deputies to the Twelfth National People's Congress of the People's Republic of China." *Sohu,* http://news.sohu.com/20130227/n367313787.shtml

[56] Bowe, Alexander. "China's Overseas United Front Work: Background and Implications for the United States." *U.S.-China Economic and Security Review Commission,* 24 Aug. 2018, https://www.uscc.gov/sites/default/files/Research/China%27s%20Overseas%20United%20Front%20Work%20-%20Background%20and%20Implications%20for%20US_final_0.pdf

[57] United States, Department of State. "Fact Sheet: Activity at the Wuhan Institute of Virology." 15 Jan. 2021, https://2017-2021.state.gov/fact-sheet-activity-at-the-wuhan-institute-of-virology/index.html

[58] Eban, Katherine. "The Lab-Leak Theory: Inside the Fight to Uncover COVID-19's Origins." *Vanity Fair,* 3 June 2021, www.vanityfair.com/news/2021/06/the-lab-leak-theory-inside-the-fight-to-uncover-covid-19s-origins.

[59] "Committees." *Wuhan Institute of Virology,* https://web.archive.org/web/20200527045823/http://english.whiov.cas.cn/About_Us2016/Committees/

Academic Committee of State key laboratory of virology, WIV, CAS

Director: Zihe RAO, Tsinghua University, China.

Deputy Directors: Hongyang WANG, The Second Military Medical University, China.

Hongbin SHU, Wuhan University, China.

Members:

Jianfang GUI, Institute of Hydrobiology, Chinese Academy of Sciences, China.

Fusheng WANG, 302 Military Hospital of China, China.

Hualan CHEN, Harbin Veterinary Research Institute, Chinese Academy of Agricultural Sciences, China.

Zhenghong YUAN, Fudan University, China.

Ningshao XIA, Xiamen University, China.

Linqi ZHANG, Tsinghua University, China.

Musheng ZENG, Sun Yat-sen University, China.

Jianguo WU, Wuhan University, China.

Xinwen CHEN, Wuhan Institute of Virology, Chinese Academy of Sciences, China.

Ke LAN, Wuhan University, China.

Fig. 3: Archived Versions of the WIV Committees Page

This raises the obvious question of why Shi, who served on one of the committees, would lie about military researchers working with the WIV. **Her denial and the scrubbing of the website appear to be obvious attempts to obfuscate the PLA's involvement with the WIV.**

Geospatial Analysis of Traffic Patterns at Wuhan Hospitals Near the WIV

Around the time the WIV's virus database went offline, car traffic at hospitals in downtown Wuhan began to increase. Researchers from Boston University School of Public Health, Boston Children's Hospital, and Harvard Medical School used satellite imagery to examine parking lot volume of hospitals in Wuhan for the two and a half years prior to December 2019. They found that five of six hospitals analyzed had the highest relative daily volume of cars in the parking lot in September and October 2019, before the first reported cases of COVID-19.

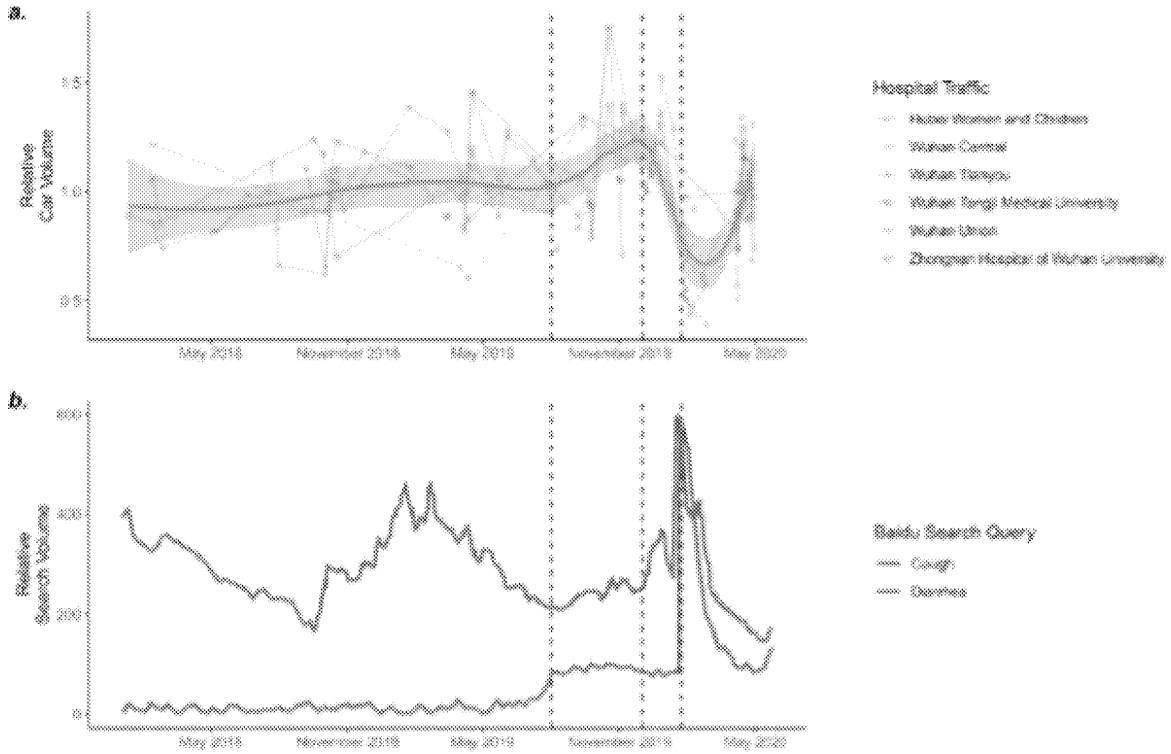


Fig. 7: Time-series of Different Influenza-like Illnesses, Symptoms and Surveillance signals[62]

This peak corresponded with an increase in searches for "cough" and "diarrhea" in Wuhan on Baidu, a Chinese search engine.[60] According to the CDC, both cough and diarrhea are symptoms of COVID-19.[61] This study suggests a virus with similar symptoms as COVID-19 was circulating in Wuhan in September and October.

The Initial Outbreak's Proximity to the WIV

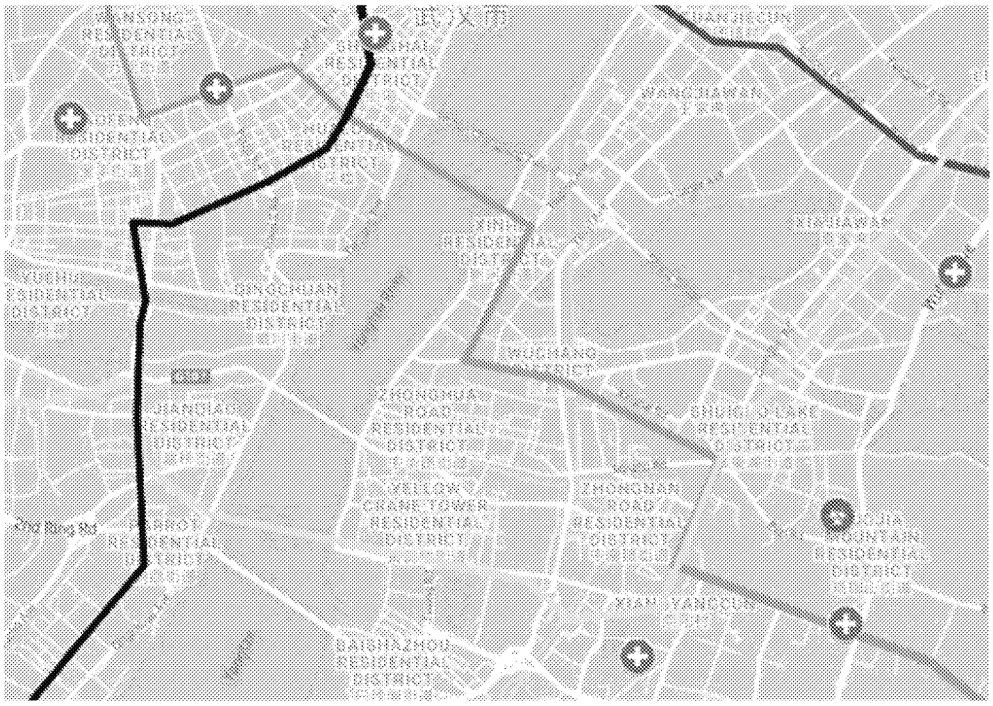
When people get sick, they are likely to seek healthcare near their home or work. Each of the hospitals that saw a rise in traffic with patients complaining of COVID-19 symptoms are located within 6.5 miles of the WIV Headquarters and are connected by public transit lines. The below map shows the location of the WIV Headquarters (in red) and the six hospitals (in blue) which experienced increase vehicle traffic in September and October 2019. When plotted on a map, these six hospitals are clustered around the WIV Headquarters in Wuchang, Wuhan, and are connected to that facility via the Wuhan Metro – various lines are shown in black, yellow, pink, and green on the map. The pink line represents Line 2, whose daily passenger volume exceeded one million trips in 2017.[63]

60 Nsoesie, Elaine Okanyene, et. al. "Analysis of hospital traffic and search engine data in Wuhan China indicates early disease activity in the Fall of 2019 (2020)." *Digital Access to Scholarship at Harvard,* 2020. http://nrs.harvard.edu/urn-3:HUL.InstRepos:42669767

61 "Symptoms of COVID-19." *Centers for Disease Control and Prevention.* https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

62 Nsoesie

63 "Wuhan Metro is bursting with passengers, breaking records for two consecutive days." 5 April 2017, https://web.archive.org/web/20170825184909/http://ctjb.cnhubei.com/html/ctjb/20170405/ctjb3089625.html



Map 1: Harvard Study Hospitals in Relation to the WIV Headquarters

It is also important to note, according to an Australian scientist who worked in the BSL-4 lab, a daily shuttle bus transfers WIV researchers from the Wuhan Branch of the Chinese Academy of Sciences to the WNBL facility and back again.[64] According to public mapping data, the shuttle pick up and drop off point is less than 500 meters from the WIV Headquarters. As such, it is likely that researchers from both the WIV Headquarters, as well as the WNBL, used the Wuhan metro and/or the WNBL shuttle bus, as part of their daily work commute.

Therefore, it is reasonable to conclude, based on the WIV's extensive sample library and history of genetically manipulating coronaviruses, that in early September, one or more researchers became infected with SARS-CoV-2 in the lab and carried it out into the city. Based on the WIV's publications, researchers could have been exposed while experimenting with a natural virus collected from the wild or infected with a virus they genetically manipulated. Those researchers likely traveled to and from the WIV via the Wuhan metro or via the shuttle service, providing a vector for the virus to spread. This corresponds with the first signs of a growing wave of ill people in Wuhan centered around the WIV's Wuchang facility.

The 2019 Military World Games and Sick Athletes

The 7th International Military Sports Council Military World Games (MWGs) opened in Wuhan on October 18, 2019. The games are similar to the Olympic games but consist of military athletes with some added military disciplines. The MWGs in Wuhan drew 9,308 athletes, representing 109 countries, to compete in 329 events across 27 sports. Twenty-five countries sent delegations of more than 100 athletes, including Russia, Brazil, France, Germany, and Poland.[65]

64 Cortez, Michelle Fay. "The Last—And Only—Foreign Scientist in the Wuhan Lab Speaks Out." *Bloomberg*, 27 June 2021, www.bloomberg.com/news/features/2021-06-27/did-covid-come-from-a-lab-scientist-at-wuhan-institute-speaks-out.

65 "Military Games to Open Friday in China." *China Daily,* 17 Oct. 2019, www.china.org.cn/sports/2019-10/17/content_75311946.htm.

The PRC government recruited 236,000 volunteers for the games, which required 90 hotels, three railroad stations, and more than 2,000 drivers.[66] An archived version of the competition's website from October 20, 2019, lists the more than thirty venues that hosted events for the MWGs across Wuhan and the broader Hubei province.[67] The live website is no longer accessible – it is unclear why it was removed.

During the games, many of the international athletes became sick with what now appear to be symptoms of COVID-19. In one interview, an athlete from Luxembourg described Wuhan as a "ghost town,"[68] and recalls having his temperature taken upon arriving at the city's airport. In an interview with *The Financial Post,* a Canadian newspaper, one member of the Canadian Armed Forces who participated in the games said (emphasis added):

> **This was a city of 15 million people that was in lockdown. It was strange, but we were told this was to make it easy for the Games' participants to get around. [I got] very sick 12 days after we arrived, with fever, chills, vomiting, insomnia.... On our flight to come home, 60 Canadian athletes on the flight were put in isolation [at the back of the plane] for the 12-hour flight. We were sick with symptoms ranging from coughs to diarrhea and in between.**[69]

The service member also revealed his family members became ill as his symptoms increased,[70] a development that is consistent with both human-to-human transmission of a viral infection and COVID-19. Similar claims about COVID-19 like symptoms have been made by athletes from Germany, France, Italy,[71] and Sweden.[72]

[I got] very sick 12 days after we arrived, with fever, chills, vomiting, insomnia.... On our flight to come home, 60 Canadian athletes on the flight were put in isolation [at the back of the plane] for the 12-hour flight. We were sick with symptoms ranging from coughs to diarrhea and in between.

- Canadian Athlete

By cross referencing the listed MWG venues with publicly available mapping data, it is possible to visualize the venues (in black) in relation to the WIV Headquarters (in red) and the above-mentioned hospitals (in blue). The green figures represent athletes who have publicly expressed their belief they contracted COVID-19 while in Wuhan and are mapped at the venues which hosted the events in which they competed. Some of these athletes resided in the military athletes' village.

66 "2019 Military World Games Kicks off in Central China's Wuhan." *CISION*, 17 Oct. 2019, www.prnewswire.com/news-releases/2019-military-world-games-kicks-off-in-central-chinas-wuhan-300940464.html.

67 "Competition Venues." *Wuhan 2019 Military World Games*, https://web.archive.org/web/20191020154108/en.wuhan2019mwg.cn/html/Competition_venues/.

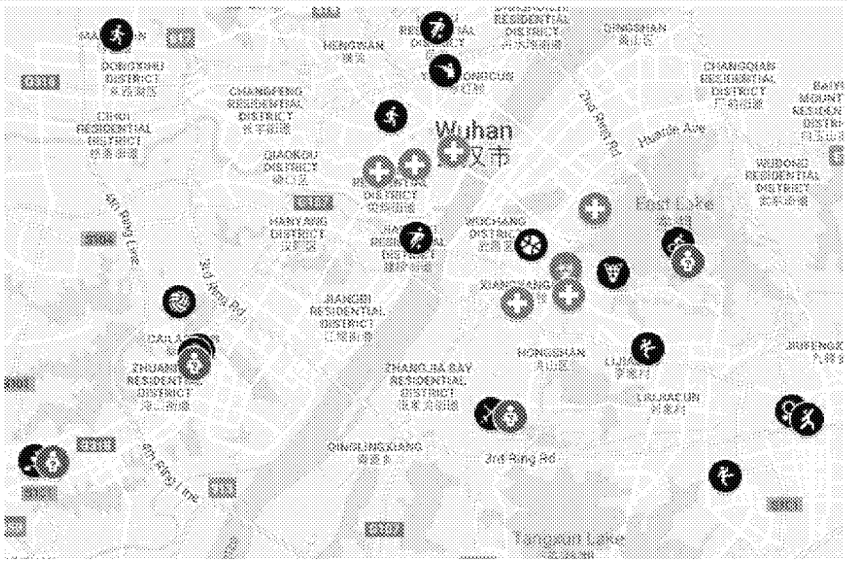
68 Houston, Michael. "More athletes claim they contracted COVID-19 at Military World Games in Wuhan." *Inside the Games,* 17 May 2020, https://www.insidethegames.biz/articles/1094347/world-military-games-illness-covid-19

69 Francis, Diane. "Diane Francis: Canadian Forces Have Right to Know If They Got COVID at the 2019 Military World Games in Wuhan." *Financial Post,* 25 June 2021, https://financialpost.com/diane-francis/diane-francis-canadian-forces-have-right-to-know-if-they-got-covid-at-the-2019-military-world-games-in-wuhan.

70 *Ibid*.

71 Houston.

72 Liao, George. "Coronavirus May Have Been Spreading since Wuhan Military Games Last October." *Taiwan News*, 13 May 2020, www.taiwannews.com.tw/en/news/3932712.



Map 2: WIV Headquarters, Hospitals, MWG Venues, and Sick Athletes

At least four countries who sent delegations to the MWGs have now confirmed the presence of SARS-CoV-2 or COVID-19 cases within their borders in November and December 2019, before the news of an outbreak first became public.

1. Italy. In February 2021, researchers from Italy published a research letter in the CDC's Emerging Infectious Diseases journal describing a case involving a 4-year-old boy from Milan. A retrospective analysis of samples taken in 2019 identified the boy, who developed a cough on November 21, 2019, as having been infected with SARS-CoV-2 three months before Italy's first reported case. The boy had no reported travel history.[73]

2. Brazil. A March 2021 article by researchers in Brazil examined wastewater samples from October to December 2019. Previous studies have confirmed that humans infected with the virus can experience prolonged viral shedding via their gastrointestinal tract. **A sample from November 27th tested positive for SARS-CoV-2 RNA**, confirming the virus was circulating in Santa Catarina, Brazil months before January 21, 2020, when the first case in the Americas was reported.[74]

3. Sweden. Sweden's Public Health Agency said it is likely that individuals in the country were infected with SARS-CoV-2 as early as November 2019.[75]

73 Amendola, Antonella¸ et. al. "Evidence of SARS-CoV-2 RNA in an Oropharyngeal Swab Specimen, Milan, Italy, Early December 2019." *Emerging Infectious Diseases,* Feb. 2021, 27(2). https://doi.org/10.3201/eid2702.204632

74 Fongaro, Gislaine et al. "The presence of SARS-CoV-2 RNA in human sewage in Santa Catarina, Brazil, November 2019." *The Science of the Total Environment,* 8 March 2021, 778: 146198. https://dx.doi.org/10.1016%2Fj.scitotenv.2021.146198

75 "Coronavirus May Have Arrived in Sweden in November: Public Health Agency." *The Local,* 5 May 2020, www.thelocal.se/20200505/the-coronavirus-may-have-arrived-in-sweden-in-november/.

4. France. Researchers in France also re-tested samples from late 2019 in an effort to identify early COVID-19 cases. They identified a 42-year-old male who presented to the emergency room on December 27th with an influenza-like illness. He had no connection to the PRC and no recent travel history. Upon re-testing, the patient's samples were positive for SARS-CoV-2. It should be noted that one of his children also had similar symptoms before the man became sick, suggesting that the first case in France was likely earlier than December 27th.[76]

As stated above, athletes from France, Italy, and Sweden also complained of illnesses with symptoms similar to COVID-19 while at the MWGs in Wuhan. **The presence of SARS-CoV-2 in four countries, on two separate continents, suggests a common source. If, as presumed, SARS-CoV-2 first infected humans in Wuhan before spreading to the rest of the world, the 2019 Military World Games in Wuhan appears to be a key vector in the global spread – it other words, potentially one of the first "super spreader" events.**

Conclusion

While much of the public debate was initially focused on the Huanan seafood market in Wuhan as the origin of the pandemic, the preponderance of evidence now suggests that the virus leaked from the Wuhan Institute of Virology. Given the WIV's demonstrated history of conducting gain-of-function experiments on coronaviruses, including genetically manipulating viruses specifically to make them infectious to humans in BSL-2 labs, as well as their possession of one of the world's largest collections of coronaviruses, it is completely plausible that one or more researcher(s) was accidentally infected and carried the virus out of the lab. The evidence outlined above, combined the cover-up conducted CCP authorities, strongly suggest the Wuhan Institute of Virology as the source of the current pandemic.

III. EVIDENCE OF GENETIC MODIFICATION

The other topic of debate is whether the virus could have been genetically modified. The WIV was conducting gain-of-function research on coronaviruses and testing them against human immune systems in the months leading up to the emergence of SARS-CoV-2, however the scientific community has claimed it is not possible it was anything but a naturally occurring virus. But, as this report lays out, we believe it is a viable hypothesis that the virus could have been modified.

> **"You can engineer a virus without leaving any trace. The answers you are looking for, however, can only be found in the archives of the Wuhan laboratory."**
>
> **– Dr. Ralph Baric**

76 Deslandes, A et al. "SARS-CoV-2 was already spreading in France in late December 2019." *International Journal of Antimicrobial Agents*, 3 May 2020, 55(6): 106006. https://dx.doi.org/10.1016%2Fj.ijantimicag.2020.106006

77 Stahl, Lesley. "What Happened In WUHAN? Why Questions Still Linger on the Origin of the Coronavirus." *CBS News*, 28 Mar. 2021, www.cbsnews.com/news/covid-19-wuhan-origins-60-minutes-2021-03-28/.

Research Regarding SARS Like Coronaviruses from 2004-2017

The WIV's work on bat coronaviruses dates back to the aftermath of SARS in the early 2000s. Shi met Peter Daszak, an American citizen, in 2004 during an effort to find the origins of the 2002 SARS pandemic. Daszak is the CEO of EcoHealth Alliance, a New York-based NGO that funds scientific research around the world.[78] For the last year and a half, questions have been raised about how and why EcoHealth Alliance provided the WIV with U.S. taxpayer dollars. Those funds were provided to EcoHealth Alliance in the form of grants from the Department of Health and Human Services (HHS), National Institutes of Health (NIH), National Science Foundation (NSF), and the United States Agency for International Development (USAID).

Beginning in 2005, and continuing over the next 16 years, Shi and Daszak have collaborated on coronavirus research. Together, they "led dozens of expeditions to caves full of bats, to collect samples and analyze them."[79] They have identified more than 500 novel coronaviruses, including roughly 50 related to SARS or MERS, and they have repeatedly engaged in gain-of-function research on coronaviruses designed to make them more infectious in humans.[80] As discussed below, the vast majority of the most relevant scientific publications that have emerged from the WIV regarding coronaviruses was conducted with funding provided by Peter Daszak through EcoHealth Alliance.

Article and Publication: "Bats Are Natural Reservoirs of SARS-Like Coronaviruses," in Science (2005).

Participants: Li Wendog, primary author; Shi, second author and one of three corresponding authors; Peter Daszag; additional scientists from Australia and China.

Funding: The paper was supported in part by funding from the PRC government, who provided a special grant for Animal Reservoirs of SARS-CoV from the State Key Program for Basic Research (grant no. 2005CB523004) and the State High Technology Development Program (grant no. 2005AA219070) from the Ministry of Science and Technology.

78 Zaugg, Julie. "In Wuhan with Bat Woman, at the origins of the Covid-19." *L'Illustre*, 22 Jan. 2021, https://www.illustre.ch/magazine/a-wuhan-avec-bat-woman-aux-origines-du-covid-19

79 *Ibid.*

80 *Ibid.*

It was also funded by the U.S. government, through the NIH and NSF, who provided funding in the form of an 'Ecology of Infectious Diseases'' award (no. R01-TW05869) from the John E. Fogarty International Center and the V. Kann Rasmussen Foundation.

Purpose: The scientists hoped to identify the origins of SARS by identifying species of bats which are a natural host for SARS-like coronaviruses.

Conclusion: "These findings on coronaviruses, together with data on henipaviruses (23–25, 28), suggest that genetic diversity exists among zoonotic viruses in bats, increasing the possibility of variants crossing the species barrier and causing outbreaks of disease in human populations. It is therefore essential that we enhance our knowledge and understanding of reservoir host distribution, animal-animal and human-animal interaction (particularly within the wet-market system), and the genetic diversity of bat-borne viruses to prevent future outbreaks."[81]

Relevance: This conclusion would drive the next fifteen years of collaboration between the WIV and Peter Daszak, with Shi directing the laboratory work.

In 2006, Shi and Daszak collaborated with a researcher in Australia to publish "Review of bats and SARS" in Emerging Infectious Diseases, a peer-reviewed journal published monthly by the U.S. Centers for Disease Control and Prevention. Shi was again listed as the second author,[82] and the work was funded by the same PRC and NIH/NSF grants referenced above. The following year, these grants supported the publication of "Evolutionary Relationships between Bat Coronaviruses and Their Hosts" in Emerging Infectious Diseases. Shi is listed as the sixth author, followed by another WIV researcher, and Peter Daszak is listed as one of two corresponding authors.[83]

In 2007, Shi and several other WIV researchers joined additional scientists in publishing another paper on coronaviruses.

Article and Publication: "Difference in Receptor Usage between Severe Acute Respiratory Syndrome (SARS) Coronavirus and SARS-Like Coronavirus of Bat Origin" in Journal of Virology.

Participants: WIV researchers and Linfa Wang. Shi is listed as the corresponding author.

Funding: This work was funded by the PRC government and grants from Australia and the European Commission.

Purpose: This study focused on the receptors used by the spike protein of SARS-like coronaviruses, which are the major surface structures that enable coronaviruses to bind to receptors on cells. To test this, researchers created multiple chimeric viruses by inserting different sequences of the SARS-CoV spike protein into the spike protein of the SARS-like virus being examined, and tested them against bat, civet, and human ACE2 expressing cells.

Conclusion: One of these chimeric viruses was able to enter cells through the human ACE2 receptor. ACE2 is an abbreviation for angiotensin converting enzyme-2, which is a protein found on the surface of cells and tissues throughout the human body,

81 *Ibid.*

82 Wang L-F, Shi Z, Zhang S, Field H, Daszak P, Eaton BT. "Review of bats and SARS." *Emerg Infect Dis,* Dec. 2006; 12(12): 1834-1840., http://dx.doi.org/10.3201/eid1212.060401

83 Cui J, et. al. "Evolutionary relationships between bat coronaviruses and their hosts." *Emerg Infect Dis*., Oct. 2007; 13(10):1526-32. https://wwwnc.cdc.gov/eid/article/13/10/07-0448_article

including the nose, mouth, and lungs. "In the lungs, ACE2 is highly abundant on type 2 pneumocytes, an important cell type present in chambers within the lung called alveoli, where oxygen is absorbed and waste carbon dioxide is released."[84] ACE2 is also the location where SARS-CoV-2's spike protein binds to human cells. Researchers concluded that "a minimal insert region" is "sufficient to convert the SL-COV S [SARS-like coronavirus spike protein] from non-ACE2 binding to human ACE2 binding."[85]

Relevance: In other words, WIV researchers were able to take a SARS-like coronavirus that does not infect humans and modify it so it was able to do so. Also importantly, this work was done under BSL-2 conditions.

Shi and Daszak do not appear as coauthors on a paper again until 2013.

Article and Publication: "Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor" in *Nature*.[86]

Participants: WIV and EcoHealth researchers, including Hu,. Shi, Daszak, and Wang who are credited for designing the experiments. Shi and Daszak listed as corresponding authors.

Funding: The study was funded by grants from the PRC government (including grant no. 2013FY113500), as well as the National Institute of Allergy and Infectious Diseases (NIAID) (no. R01AI079231), a NIH/NSF "Ecology and Evolution of Infectious Diseases" award (no. R01TW005869), an award from the NIH Fogarty International Center supported by International Influenza Funds from the Office of the Secretary of the Department of Health and Human Services (no. R56TW009502), and USAID's Emerging Pandemic Threats PREDICT program.[87]

Purpose: This work marked "the first recorded isolation of a live SL-CoV"[88] [SARS-live coronavirus], which researchers isolated from bat fecal samples and named WIV1. Additionally, they identified two novel bat coronaviruses (SCH014 and Rs3367) and reported "the first identification of a wild-type bat SL-CoV capable of using ACE2 as an entry receptor."[89]

Conclusion: "Finally, this study demonstrates the public health importance of pathogen discovery programs targeting wildlife that aim to identify the 'known unknowns'—previously unknown viral strains closely related to known pathogens. These programs, focused on specific high-risk wildlife groups and hotspots of disease emergence, may be a critical part of future global strategies to predict, prepare for, and prevent pandemic emergence."[90]

Relevance: By isolating a wild-type (common strain in nature) SARS-like coronavirus that binds to ACE2, and testing it in human lung tissue, the authors proved that bat coronaviruses are capable of infecting humans directly, without having to pass through an intermediate host.

84 Sriram, Krishna, et al. "What Is the ACE2 Receptor, How Is It Connected to Coronavirus and Why Might It Be Key to Treating COVID-19? The Experts Explain." The Conversation, 25 May 2021, https://theconversation.com/what-is-the-ace2-receptor-how-is-it-connected-to-coronavirus-and-why-might-it-be-key-to-treating-covid-19-the-experts-explain-136928.

85 Ren.

86 Ge, Xing-Yi et al. "Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor." *Nature,* 30 Oct. 2013, 503(7477): 535-8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5389864/

87 *Ibid.*

88 *Ibid.*

89 *Ibid.*

90 *Ibid.*

In 2014, Shi and Daszak coauthored two more joint WIV-EcoHealth Alliance papers. The lead author for one of the papers, entitled "Detection of diverse novel astroviruses from small mammals in China," was Ben Hu, a WIV researcher who was a coauthor of earlier Shi/Daszak papers. Shi is listed as the corresponding author, and the paper was again jointly funded by the PRC government (including grant no. 2013FY113500) and USAID's PREDICT program.[91]

The next year, in 2015, Shi provided Ralph Baric and other researchers at the University of North Carolina at Chapel Hill with spike protein sequences and plasmids of SCH014, one of the viruses Shi, Daszak, and WIV researchers identified in bat feces samples in 2013. American researchers used those samples to create "a chimeric virus expressing the spike of bat coronavirus SHC014 in a mouse-adapted SARS-CoV backbone."[92] **In other words, they removed the spike protein from SHC014 and inserted it into a SARS coronavirus that was genetically manipulated to better infect mice.** This work was done under BSL-3 conditions. The newly created virus was then shown to bind to ACE2 in humans, replicate "efficiently"[93] in primary human airways cells, and withstand antibodies and vaccines. Researchers concluded that the work "suggests a potential risk of SARS-CoV re-emergence from viruses currently circulating in bat populations."[94] This research was funded by NIAID and the NIH under multiple awards (nos. U19AI109761, U19AI107810, AI085524, F32AI102561, K99AG049092, DK065988), USAID's PREDICT program via EcoHealth Alliance, and the PRC government. Baric was the corresponding author.[95]

2015 also saw the publication of another Shi/Hu/Wang/Daszak paper. Entitled "Isolation and Characterization of a Novel Bat Coronavirus Closely Related to the Direct Progenitor of Severe Acute Respiratory Syndrome Coronavirus," it was published in the *Journal of Virology*. Nine of the twelve authors were WIV researchers, including Hu and Shi, who was the corresponding author. Here the WIV reported the successful isolation of a second novel coronavirus, WIV16. The SARS-like coronavirus was isolated from a single sample of bat fecal matter collected in Kunming, Yunnan Province of the PRC in July 2013. Like previous papers, this work was supported by a NIAID grant (no. R01AI110964) and by grants from the PRC government (including grant no. 2013FY113500).[96]

In addition to her aforementioned work with researchers at UNC Chapel Hill, Shi also provided them with additional bat coronavirus sequences and plasmid of WIV1's spike protein. The resulting paper, "SARS-like WIV1-CoV poised for human emergence," was published in the Proceedings of the National Academy of Sciences of the United States of America in March 2016. While neither Shi nor Daszak (nor any WIV researcher) are listed as coauthors, Baric was the corresponding author.

91 Hu, Ben, et. al. "Detection of diverse novel astroviruses from small mammals in China." *J Gen Virol.* Nov 2014, 95(Pt 11): 2442-2449. https://pubmed.ncbi.nlm.nih.gov/25034867/

92 Menachery, Vineet, et. al. "A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence." *Nat Med,* 9 Nov. 2015, 21:1508–1513. https://doi.org/10.1038/nm.3985

93 Menachery

94 *Ibid.*

95 *Ibid.*

96 Yang, Xing-Lou et al. "Isolation and Characterization of a Novel Bat Coronavirus Closely Related to the Direct Progenitor of Severe Acute Respiratory Syndrome Coronavirus." *Journal of Virology,* 30 Dec. 2015, 90(6): 3253-6. https://dx.doi.org/10.1128%2FJVI.02582-15

This paper is significant because the authors discuss moving from disease surveillance to creating chimeric viruses as a means of pandemic preparedness; "this manuscript describes efforts to extend surveillance beyond sequence analysis, constructing chimeric and full-length zoonotic coronaviruses to evaluate emergence potential." [97]

During this work, researchers produced chimeric viruses created by inserting the spike protein from WIV1 into a strain of SARS-CoV adapted to infecting mice. They subsequently tested this chimeric virus in human airway epithelial cells as well as in mice.[98] In addition to standard BALB/c mice (a strain of albino, lab-breed house mice used in experimentation[99]), researchers genetically manipulated the mice to create a strain of mice expressing the human ACE2 (hACE2) receptor. While hACE2 was found primarily in the lungs of the mice, it was also present in the brain, liver, kidneys, and gastrointestinal tract. The WIV1 chimeric virus was then tested in these hACE2 expressing mice, proving that the chimeric virus could infect humans. This work was funded by NIAID and NIH awards (nos. U19AI109761, U19AI107810, AI1085524, F32AI102561, K99AG049092, DK065988, AI076159, and AI079521).[100]

In 2016, Shi and Daszak also coauthored two additional papers focused on infectious diseases that year. One, entitled "Bat Severe Acute Respiratory Syndrome-Like Coronavirus WIV1 Encodes an Extra Accessory Protein, ORFX, Involved in Modulation of the Host Immune Response," was coauthored by Wang and represents a major step forward in the WIV's work. While working on this project, WIV researchers created a reverse genetics system and used it to genetically modify WIV1, the live coronavirus that was successfully isolated in 2013 and that UNC researchers manipulated months earlier. WIV researchers created multiple versions of this virus by deleting or adding genetic information to the virus' RNA. According to the paper, all experiments with live virus for this paper were done under BSL-2 conditions, which does not require respirators or biological safety cabinets. Nine of the eleven authors are WIV researchers, and Shi is the corresponding author. The experimentation for the paper was supported by a grant from NIAID (no. R01AI110964) and funding from the PRC government.[101]

The following year, Ben Hu was the lead author of a paper entitled "Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus." As with previous papers, the overwhelming majority (14 out of 17) of the authors worked at the WIV. Daszak, Shi, and Wang are all listed as coauthors. Hu is the lead author and Shi is one of two corresponding authors. Daszak is credited for "funding acquisition."[102]

Additionally, using the reverse genetics system they debuted the previous year, WIV researchers created eight separate chimeric viruses by inserting the spike protein of various SARS-like coronaviruses into WIV1. Two of these chimeric viruses (WIV1-Rs4231S and WIV1-Rs7327S), and one natural virus, Rs4874, all replicated within hACE2 expressing cells.[103]

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97 Menachery, Vineet, et al. "SARS-like WIV1-CoV poised for human emergence." *Proceedings of the National Academy of Sciences of the United States of America,* 14 March 2016, 113(11): 3048-53. https://dx.doi.org/10.1073%2Fpnas.1517719113

98 *Ibid.*

99 "Inbred Strains: BALB." MGI, www.informatics.jax.org/inbred_strains/mouse/docs/BALB.shtml.

100 Menachery 2016.

101 Zeng, Lei-Ping et al. "Bat Severe Acute Respiratory Syndrome-Like Coronavirus WIV1 Encodes an Extra Accessory Protein, ORFX, Involved in Modulation of the Host Immune Response." *Journal of Virology,* 24 June 2016, 90(14): 6573-6582. https://dx.doi.org/10.1128%2FJVI.03079-15

102 Hu, Ben et al. "Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus." *PLOS Pathogens,* 30 Nov. 2017, 13(11). https://dx.doi.org/10.1371%2Fjournal.ppat.1006698

103 Hu, 2017.

To reiterate, WIV researchers created chimeric coronaviruses able to infect humans in 2017, before the WNBL BSL-4 lab became operational. This work was jointly funded by NIAID (no. R01AI110964), USAID's PREDICT program, and the PRC government (including grant no. 2013FY113500).

Research Regarding SARS-Like Coronaviruses at the WIV or in Conjunction with WIV Scientists from 2018-2019

While Shi and Daszak coauthored several additional papers in 2018 and 2019 regarding coronaviruses, none include gain-of-function research on SARS-like coronaviruses designed to make them more infectious to humans. This is especially odd given that in 2018 the Chinese Academy of Science launched a new special project titled "Pathogen Host Adaption and Immune Intervention."[104] One of the five subprojects was titled "Research on Virus Traceability, Cross-Species Transmission, and Pathogenic Mechanism," – Shi is listed as one of the two scientists in charge.[105] This subproject had three areas of focus: 1) the traceability, evolution and transmission mechanism of new pathogens; 2) molecular mechanisms of viral cross-species infection and pathogenicity, and 3) the interaction mechanism between virus and host.

A second WIV scientist, Cui Zongqiang, was one of two researchers in charge of another subproject entitled, "New methods and new technologies for infection and immune research."[106] This project focused on, among other things, evaluating new vaccines and establishing "humanized small animal models"[107] for in vitro pathogen testing.[108]

In January 2018, Shi was appointed Principal Investigator for a new Strategic Priority Research Program of the Chinese Academy of Sciences (grant no. XBD29010101, $1.35 million USD),[109] investigating "genetic evolution and transmission mechanism of important bat-borne viruses." This project, especially with its focus on transmission mechanisms, aligns with the first focus area mentioned above. That same month, Shi began work on a project titled "Study on the evolutionary mechanism of bat SARS-like coronavirus adapted to host receptor molecules and the risk of cross-species infection."[110] The project was funded at a value of roughly $850,000 USD (grant no. 31770175) and is slated to run until December 2021.[111] This grant aligns with the second focus area, the description of which specifically mentions replicating and modifying coronaviruses (emphasis added):

> For important emerging emergencies and virulent viruses (influenza virus, Ebola virus, coronavirus, Marburg virus, arenavirus, etc.), by studying **their ability to invade different host cells and their ability to replicate in different host cells,** analyze the key molecules affecting their cross-species infections and their pathogenic mechanisms. Including: virus invasion, virus replication and assembly, and infection model.[112]

104 "Guidelines for the application of the 'Pathogen Host Adaptation and Immune Intervention' project of the Chinese Academy of Sciences Strategic Leading Technology." Chinese Academy of Sciences, 6 Sept. 2018, https://archive.is/spmNg#selection-3389.0-3389.160

105 *Ibid.*

106 *Ibid.*

107 *Ibid.*

108 *Ibid.*

109 Shi, Zheng-li. "Curriculum Vitae." https://www.ws-virology.org/wp-content/uploads/2017/11/Zhengli-Shi.pdf
"Study on the evolutionary mechanism of bat SARS-like coronavirus adapted to host receptor molecules and the risk of cross-species infection."

110 *MedSci*, https://archive.is/g35C6#selection-1425.0-1425.139

111 *Ibid.*

112 "Guidelines for the application of the 'Pathogen Host Adaptation and Immune Intervention' project of the Chinese Academy of Sciences Strategic Leading Technology." *Chinese Academy of Sciences,* 6 Sept. 2018, https://archive.is/spmNg#selection-3389.0-3389.160

Shi did not publish any papers funded by this grant before the start of the pandemic. As such, it is impossible to know what experiments she was conducting in the months prior to the pandemic.

Further evidence expands on Shi's work in 2018 and 2019. In January 2019, Shi and several other scientists were awarded a National Natural Science Award Second Prize for a project entitled, "Research on Important Viruses Carried by Chinese Bats."[113] Five out of the six researchers on the award were coauthors of the previously discussed 2013 paper entitled, "Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor."

In January 2019, Ben Hu, was awarded $385,850 in grant money (grant no. 31800142) by the Youth Science Fund Project (YSFP) of the National Natural Science Foundation of China.[114] The YSFP "supports the young researchers to independently select topics within the scope of the scientific funding and carry out basic research."[115] This project, selected by Ben Hu, was titled, "Pathogenicity of two new bat SARS-related coronaviruses to transgenic mice expressing human ACE2."[116] To date, the two novel SARS-related coronaviruses have not been identified, and the grant money has only been cited in papers published about SARS-CoV-2.

WIV researchers confirmed to the WHO investigative team that they were conducting experimentations testing chimeric coronaviruses in 2018 and 2019.[117] **According to an interview with Shi published by *Science*, all coronavirus experimentation, including infecting hACE2 mice and civets, was done at the BSL-2 and BSL-3 levels – "the coronavirus research in our laboratory is conducted in BSL-2 or BSL-3 laboratories."** [118]

This ongoing work appears to coincide with Peter Daszak's stated goal of developing a broad-spectrum coronavirus vaccine. In a May 19, 2020, interview with "This Week in Virology," Daszak discussed the goal of the gain-of-function work he funded on coronaviruses with the WIV (emphasis added):

> Coronaviruses are pretty good – I mean you're a virologist, you know all this stuff – but the… you can... um manipulate them in the lab pretty easily. The spike protein drives a lot of what happens with the coronavirus – zoonotic risk. So, you can get the sequence, you can build the protein, and we work with Ralph Baric at UNC to do this, insert it into a backbone of another virus, and do some work in the lab. So, you can get more predictive when you find a sequence – you've got this diversity. Now, the logical progression for vaccines is, if you're going to develop a vaccine for SARS, people are going to use pandemic SARS, **but let's try to insert some of these other related [viruses] and get a better vaccine.**

113 "Catalogue and introduction of the 2018 National Natural Science Award winning projects." *Ministry of Science and Technology,* 8 Jan. 2019, https://archive.is/jKq7B#selection-187.0-187.86

114 "Pathogenicity of two new bat SARS-related coronaviruses to transgenic mice expressing human ACE2." *MedSci*, https://archive.is/shrM2#selection-1545.0-1558.0

115 "[Good News] 100% winning bid! All applications of the National Natural Science Foundation of China(NSFC) were approved." F*aculty of Economics and Management, ECNU Academy of Statistics and Interdisciplinary Sciences*, 11 May 2020, http://asis.ecnu.edu.cn/asisenglish/64/ba/c23635a287930/page.htm

116 "Pathogenicity of two new bat SARS-related coronaviruses to transgenic mice expressing human ACE2." *MedSci*, https://archive.is/shrM2#selection-1545.0-1558.0

117 Joint Report – ANNEXES.

118 Shi, Zheng-li. "Reply to Science Magazine." *Science Magazine*, https://www.sciencemag.org/sites/default/files/Shi%20Zhengli%20Q%26A.pdf

119 Racaniello, Vincent. "TWiV 615: Peter Daszak of EcoHealth Alliance." YouTube, interview by Vincent Racaniello,19 May 2020, https://www.youtube.com/watch?v=IdYDL_RK--w

Shi, Hu, and others at the WIV were the ones collecting, identifying, genetically modifying, and testing these novel coronaviruses against human immune systems for Peter Daszak.

In sum, in the years leading up to the emergence of SARS-CoV-2, there was:

- **Research by Shi and others at the WIV on how to alter the spike protein of non-infectious SARS-like coronaviruses so that they can bind to human ACE2 receptors;**
- **Repeated collaboration between Shi, Hu, Daszak, Wang, and other researchers on genetically manipulating coronaviruses to increase their infectiousness in humans;**
- **A new PRC Strategic Priority Research Program, run by Shi, that was actively manufacturing chimeric viruses in BSL-2 and BSL-3 conditions and seeking out novel viruses;**
- **Evidence of ongoing collaboration between Shi and the other scientists who first isolated a live coronavirus in 2013;**
- **A second grant awarded to Hu to test novel coronaviruses against human immune systems in BSL-2 and BSL-3 conditions;**
- **A stated effort to develop a broad-spectrum coronavirus vaccine.**

Given the above, it is self-evident that Shi and her colleagues, with funding and support from Daszak, were actively genetically manipulating coronaviruses and testing them against human immune systems in 2018 and 2019, before the beginning of the pandemic.

Unusual Features of SARS-CoV-2

Committee Minority Staff interviews with scientists and current and former U.S. government officials raised several questions about the natural origins of SARS-CoV-2, including:

1. The highly infectious nature of SARS-CoV-2, which they consider as infectious as measles;

2. The lack of an identified intermediate host (found 4 months after the outbreak of SARS and 9 months after MERS); and

3. The highly efficient binding to human ACE2.

The highly contagious nature of SARS-CoV-2 has been a hot topic of conversation since the virus began to spread around the world. Some scientists and other experts point to the incredibly high case numbers as evidence that SARS-CoV-2 is inherently different from known natural betacoronaviruses. For example, MERS first appeared in 2012 and has infected less than 4,000 people. SARS first appeared in 2002 and infected less than 10,000. At the time of writing, less than two years from when it has first appeared, SARS-CoV-2 has infected more than 196.4 million people.

SARS-CoV-2 also has a highly unusual affinity for binding to human ACE2 receptors over other hosts. In February 2020, American researchers examined this issue closely. They found that SARS-CoV-2's spike protein "binds at least 10 times more tightly than the corresponding spike protein of severe acute respiratory syndrome (SARS)–CoV to their common host cell receptor."[120] In other words, SARS-CoV-2 binds more than 10 times more tightly to human ACE2 than the virus that causes SARS. The researchers found this likely explains why the virus is so contagious.[121]

120 Wrapp, Daniel et al. "Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation." *Science*, 13 March 2020, 367(6483): 1260-1263. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164637/

121 *Ibid.*

Australian and British researchers also examined how SARS-CoV-2 binds to the ACE2 of various animals, publishing their research in *Scientific Reports* on June 24, 2021. The scientists found that SARS-CoV-2's spike protein binds the strongest to human ACE2. They reported (emphasis added):

> This finding was surprising as a **zoonotic virus typically exhibits the highest affinity initially for its original host species,** with lower initial affinity to receptors of new host species until it adapts. As the virus adapts to its new host, mutations are acquired that increase the binding affinity for the new host receptor. Since **our binding calculations were based on SARS-CoV-2 samples isolated in China from December 2019,** at the very onset of the outbreak, the extremely high affinity of S protein for human ACE2 was unexpected.[122]

The first preprint version of this paper went further, concluding, "the data indicates that SARS-CoV-2 is uniquely adapted to infect humans, **raising important questions as to whether it arose in nature by a rare chance event or whether its origins might lie elsewhere**" emphasis added.[123] **This research provides evidence that SARS-CoV-2 is uniquely well adapted to humans, suggesting a non-zoonotic source of the outbreak.**

The Furin Cleavage Site

One of the most discussed questions centers around the furin cleavage site (FCS) of SARS-CoV-2. The FCS is part of the virus' spike protein, which enables it to bind to and enter human cells. In February 2020, French and Canadian scientists reported SARS-CoV-2 contains an FCS that is absent in other coronaviruses of the same clade, or branch of viruses believed to have a similar common ancestor. The scientists also reported that when a bronchitis virus was modified by inserting a similar cleavage site, the virus' pathogenicity was increased.[124] While some scientists have noted that other coronaviruses contain furin cleavage sites, phylogenetic analysis shows that SARS-CoV-2 is the only identified sarbecovirus (a subsection of *betacoronaviruses*) with this feature.[125]

In January 2021 a group of American researchers published "Loss of furin cleavage site attenuates SARS-CoV-2 pathogenesis" in *Nature*. In the article, researchers reported the FCS "may have facilitated the emergence of SARS-CoV-2 in humans."[126] Using a reverse genetic system, they created a mutant strain of SARS-CoV-2 which lacked the FCS. The result was a virus that was weakened in human respiratory cells and that exhibited reduced development in hACE2 expressing mice. This demonstrates the importance of the FCS in the rapid spread of COVID-19.

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122 Piplani, S., et. al. "In silico comparison of SARS-CoV-2 spike protein-ACE2 binding affinities across species and implications for virus origin." *Scientific Reports,* 24 June 2021, 11(13063) https://www.nature.com/articles/s41598-021-92388-5

123 Piplani, S., et. al. Preprint of "In silico comparison of SARS-CoV-2 spike protein-ACE2 binding affinities across species and implications for virus origin." *ArXiv*, 13 May 2020, https://arxiv.org/abs/2005.06199v1

124 Coutard, B et al. "The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade." *Antiviral Research,* Feb. 2020, 176: 104742 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7114094/

125 Wu, Yiran, and Suwen Zhao. "Furin cleavage sites naturally occur in coronaviruses." *Stem Cell Research,* 9 Dec. 2020, 50:102115. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7836551/

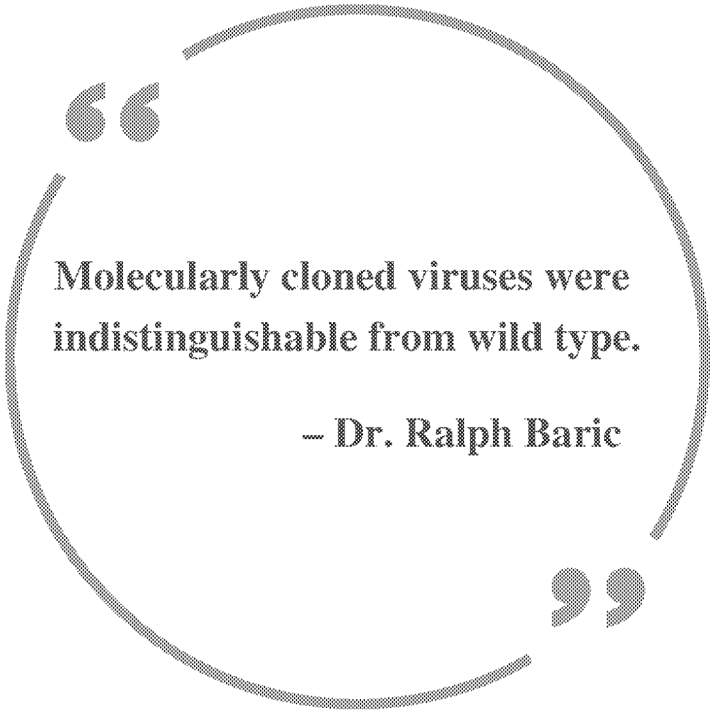
126 Johnson, B.A., et. al. "Loss of furin cleavage site attenuates SARS-CoV-2 pathogenesis." *Nature*, 25 Jan. 2021, 591: 293-299. https://www.nature.com/articles/s41586-021-03237-4

In other words, did the FCS develop naturally, or was it added in via genetic manipulation? Part of the genetic sequence for the FCS includes a CGG double codon (CGG-CGG). This group of six nucleotides (a group of three nucleotides is also known as a codon) is half of the 12 nucleotides that create the FCS. SARS-CoV-2 is the only identified coronavirus within its class to feature this combination. Some believe this is evidence of genetic manipulation, arguing this double codon is a telltale sign of the FCS being artificially inserted into the virus.[127]

The "No-See-Um" Method

Critics of the theory that the virus was genetically modified or man-made have repeatedly pointed to the apparent lack of telltale signs of genetic manipulation in the SARS-CoV-2 genome. They claim this is "proof" the virus was not only naturally occurring, but that the COVID-19 pandemic could only be the result of a zoonotic spillover event. Such arguments ignore key pieces of evidence to the contrary.

In 2005, Ralph Baric, one of the researchers at UNC Chapel Hill with whom Shi would later collaborate with between 2014 and 2016, published a paper entitled, "Development of mouse hepatitis virus and SARS-CoV infectious cDNA constructs."[128] In this paper, Baric references using a novel genetic engineering system he developed with other UNC colleagues to engineer full-length SARS-CoV genomes via a "no-see-um" method. This method allows for the assembly of various partial genomic sequences into a full-length genome, creating a new and infectious coronavirus.[129] The publication includes the below figure, which is titled, "Systemic Assembly Strategy for the SARS-CoV infectious clone." It clearly shows the various SARS fragments and how they were used to create a full-length, custom genomic sequence.



127 Quay, Steven, and Richard Muller. "The Science Suggests a Wuhan Lab Leak." *The Wall Street Journal*, 6 June 2021, www.wsj.com/articles/the-science-suggests-a-wuhan-lab-leak-11622995184.

128 Baric R.S., Sims A.C. "Development of Mouse Hepatitis Virus and SARS-CoV Infectious cDNA Constructs." *Curr Top Microbiol Immunol,* 2005; 287:229-52. https://doi.org/10.1007/3-540-26765-4_8

129 *Ibid.*

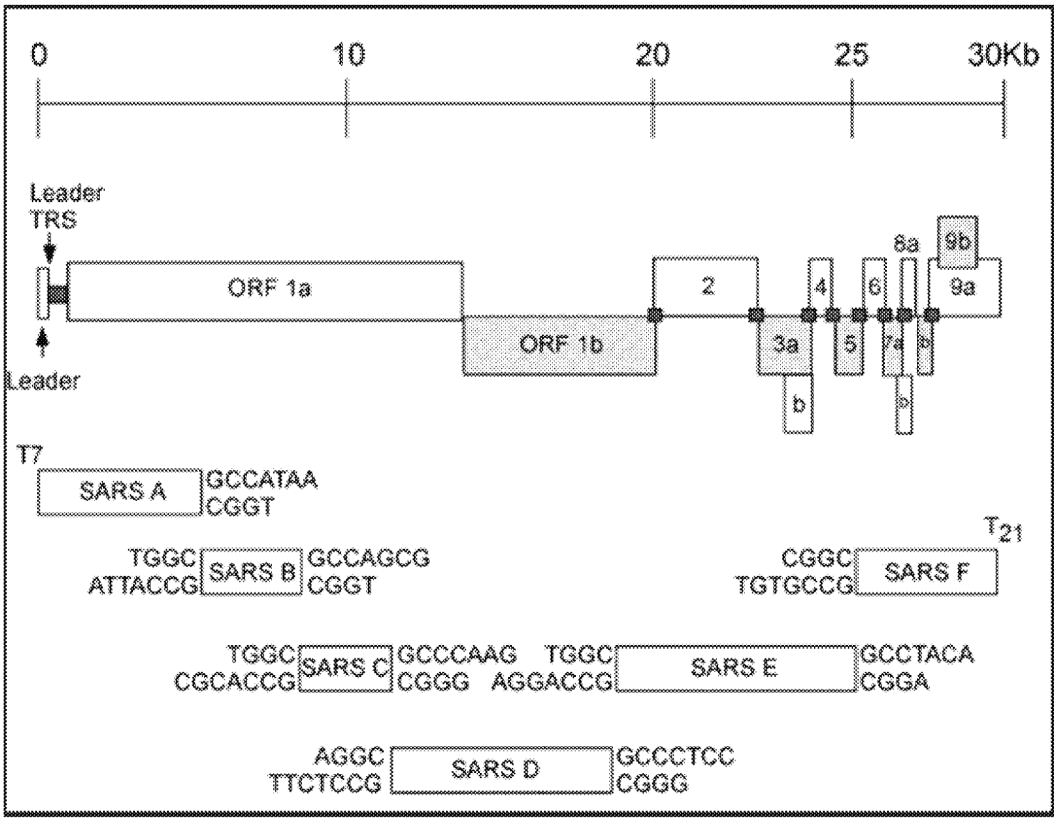


Fig. 5: Baric's "No-See-Um" System

The paper stated these viruses were "indistinguishable from wild type," [130] meaning that it is impossible to tell they were synthetically created.

Baric himself confirmed this interpretation in a September 2020 interview, where he stated, "You can engineer a virus without leaving any trace. The answers you are looking for, however, can only be found in the archives of the Wuhan laboratory." [131] Referring to chimeric viruses he generated in 2015 with WIV researchers, Baric said his team intentionally left signature mutations to show that it was genetically engineered. "Otherwise there is no way to distinguish a natural virus from one made in the laboratory." [132]

Shi and Baric have collaborated on multiple papers regarding coronaviruses. The most recent of which was in May 2020, when they joined other researchers in publishing "Pathogenesis of SARS-CoV-2 in Transgenic Mice Expressing Human Angiotensin-Converting Enzyme 2." [133] **One year later, Baric signed onto a May 14, 2021, letter published in *Science* which argued that the lab leak theory must be taken seriously and should be fully evaluated.**[134]

130 *Ibid.*

131 Renda, Silvia. "Possibile Creare Un Virus in Laboratorio Senza Lasciare Traccia? La Risposta Dell'autore Della Chimera Del 2015 Di Cui Parlò Tg Leonardo." *L'HuffPost,* 14 Sept. 2020, www.huffingtonpost.it/entry/e-possibile-creare-un-virus-in-laboratorio-senza-lasciare-traccia-la-risposta-dellesperto_it_5f5f3993c5b62874bc1f7339.

132 *Ibid.*

133 Jiang, Ren-Di et al. "Pathogenesis of SARS-CoV-2 in Transgenic Mice Expressing Human Angiotensin-Converting Enzyme 2." *Cell*, 21 May 202, 182(1): 50-58.e8, https://dx.doi.org/10.1016%2Fj.cell.2020.05.027

134 Bloom, Jesse D., et. al. "Investigate the origins of COVID-19." *Science*, 14 May 2021; 372(6543): 694. https://science.sciencemag.org/content/372/6543/694.1

In 2017, a dissertation was submitted to the University of Chinese Academy of Sciences by Zeng Leiping, a doctoral student working at the WIV, entitled "Reverse Genetic System of Bat SARS-like Coronaviruses and Function of ORFX."[135] The referenced reverse genetic system is the same that was used by the WIV in 2016 to create genetically modified viruses and conduct experiments with live viruses under BSL-2 conditions. In his dissertation, Zeng stated the he and other WIV researchers used this system to "construct an S gene chimeric recombinant viral infectious BAC clone with WIV1 as the backbone and without leaving any trace sequences (e.g. incorporated enzymatic sites) in the recombinant viral genome" (emphasis added).

In an end-of-chapter discussion in the dissertation, Zeng reiterates this lack of evidence of genetic manipulation, stating:

> We established a reverse genetics system for coronaviruses, and based on the genomic backbone of WIV1, we **established a scheme to replace the S gene without traces,** constructed infectious BAC clones of 12 S-gene chimeric recombinant viruses, and successfully rescued. Four of these recombinant viral strains (including Rs4231, Rs4874, Rs7327, and SHC014) were tested for ACE2 utilization by these strains in humans, civets, and bats.

Zeng was employed at the WIV when he submitted his dissertation, and Shi was his advisor. **As such, it is clear that Shi and others at the WIV not only possessed the capability to genetically modify coronaviruses "without traces," but were actively doing so in the years leading up to the current pandemic.** It appears Zeng Leiping is currently a postdoctoral research fellow in bioengineering at Stanford University.

IV. EVIDENCE OF A LAB LEAK COVER-UP

In addition to the events previously discussed (sequence database taken offline, road closures during the MWG, etc.), there are several additional incidents that suggest the PRC, WIV researchers, and others were actively working to suppress and discredit early conversations that the virus could have been man-made or that it could have leaked from a WIV facility.

In April 2012, six miners working in a copper mine located in Yunnan province of the PRC fell ill. Between the ages of 30 and 63, the workers presented to a hospital in Kunming with "persistent coughs, fevers, head and chest pains and breathing difficulties."[139] Three of the six eventually died. Researchers from the WIV were asked to investigate and test samples from the sick miners. They also began collecting samples from bats in the cave that housed the mine, which led to the discovery of several new coronaviruses. As a result, the WIV began a long-term study of the mine, collecting samples each year. Despite this, Shi maintains the miners were killed by a fungus growing on bat feces not from a virus.[140]

135 Leiping, Zeng. *Reverse Genetic System of Bat SARS-like Coronaviruses and Function of ORFX.* 2017. The University of Chinese Academy of Sciences, PhD dissertation. English translation first made available by @TheSeeker268 on Twitter, https://twitter.com/TheSeeker268/status/1392575597772107776?s=20

136 *Ibid.*

137 *Ibid.*

138 "Leiping Zeng." *Stanford*, https://profiles.stanford.edu/leiping-zeng

139 Stanway, David. "Explainer: China's Mojiang Mine and Its Role in the Origins of COVID-19." *Reuters*, 9 June 2021, www.reuters.com/business/healthcare-pharmaceuticals/chinas-mojiang-mine-its-role-origins-covid-19-2021-06-09/.

140 Qiu, Jane. "How China's 'Bat Woman' Hunted Down Viruses from SARS to the New Coronavirus." *Scientific American*, 1 June 2020, www.scientificamerican.com/article/how-chinas-bat-woman-hunted-down-viruses-from-sars-to-the-new-coronavirus1/

ID4991 vs. RaTG13: SARS-CoV-2's "Closest Relative"

A 2016 paper published by PRC researchers (most of whom are affiliated with the WIV) describes these efforts as researchers conducting "surveillance of coronaviruses in bats in an abandoned mineshaft in Mojiang County, Yunnan Province, China, from 2012–2013."[141] Shi and Hu are listed as coauthors. WIV researchers identified two new betacoronaviruses – HiBtCoV/3740-2 and RaBtCoV/4991. The study concluded, "RaBtCoV/4991 showed more divergence from human SARS-CoV than other bat SL-CoVs and could be considered as a new strain of this virus lineage."[142] Shi designed and coordinated the study, drafted the manuscript, and is listed as the corresponding author.

Four years later and after the initial reports of an unknown SARS-like coronavirus in Wuhan, Shi and 28 other PRC scientists submitted an article to *Nature* for publication entitled, "A pneumonia outbreak associated with a new coronavirus of probably bat origin,"[143] on January 20, 2020. It was published in early February. It should be noted that this manuscript was submitted on the same day the PRC's National Health Commission first issued a statement confirming human-to-human transmission – one month after local health officials warned the CCP human-to-human transmissions were occurring.[144] It is highly unlikely Shi and her coauthors would have written this paper the same day they submitted it, meaning they were aware for days or perhaps weeks that the virus was spreading via from human-to-human transmission and did not alert the world. According to a study by researchers at the University of Southampton, implementing appropriate restrictions based on human-to-human transmission just one week before this paper was published would have reduced the number of cases in Wuhan by 66%.[145] This would have made a significant difference in the spread of the virus, especially in conjunction with the significant travel that occurred during the Spring Festival, which ran from January 10 to January 23, 2020, when the city of Wuhan was locked down.

Shi is listed as the corresponding author for the article, which states that COVID-19 "has now progressed to be transmitted by human-to-human contact."[146] The researchers conclude that RaTG13, an allegedly naturally occurring bat coronavirus, is the closest relative to SARS-CoV-2 (emphasis added):

> **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. **We carried out full-length sequencing** on this RNA sample (GISAID accession number EPI_ISL_402131). Simplot analysis showed that 2019-nCoV was highly similar throughout the genome to RaTG13 (Fig. 1c), with an overall genome sequence identity of 96.2%. Using the aligned genome sequences of 2019-nCoV, RaTG13, SARS-CoV and previously reported bat SARSr-CoVs, no evidence for recombination events was detected

141 Ge, Xing-Yi et al. "Coexistence of multiple coronaviruses in several bat colonies in an abandoned mineshaft." *Virologica Sinica,* 3 Feb. 2016; 31(1): 31-40. https://dx.doi.org/10.1007%2Fs12250-016-3713-9

142 Ibid.

143 Zhou, P., et al. "A pneumonia outbreak associated with a new coronavirus of probable bat origin." *Nature*, 3 Feb 2020, 579: 270–273. https://doi.org/10.1038/s41586-020-2012-7

144 Wang, Yanan. "Human-to-Human Transmission Confirmed in China Coronavirus." *AP NEWS*, 20 Jan. 2020. https://apnews.com/14d7dcffa205d9022fa9ea593bb2a8c5

145 Lai, Shengjie, et al. "Effect of Non-Pharmaceutical Interventions for Containing the COVID-19 Outbreak in China." *MedRxiv*, 2020, https://www.medrxiv.org/content/10.1101/2020.03.03.20029843v3.

146 Zhou (2020).

> in the genome of 2019-nCoV. Phylogenetic analysis of the full-length genome and the gene sequences of RdRp and spike (S) showed that—for all sequences—**RaTG13 is the closest relative of 2019-nCoV and they form a distinct lineage from other SARSr-CoVs** (Fig. 1d and Extended Data Fig. 2)…**The close phylogenetic relationship to RaTG13 provides evidence that 2019-nCoV may have originated in bats.**[147]

A close examination of the paper, and the corrections published months later, reveal inconsistences in the researchers' claims. Several of the statements made in the above quotation are simply false. After months of criticism and questioning about RaTG13, Shi and the other researchers were forced to publish an addendum on November 17, 2020. **That addendum reveals that RaTG13 was actually ID4991, the sample collected years prior in 2012 or 2013, and that the full-length genomic sequence was obtained in 2018, not in January 2020 as the paper originally stated.**[148]

Unfortunately, no other labs can confirm the genomic sequence of RaTG13 – Shi said in an interview published in *Science Magazine* that the entire sample was used up after genomic sequencing.[149] The inability of outside researchers to verify the genome of RaTG13, and the above efforts to obfuscate when the WIV collected and sequenced RaTG13, raises multiple questions:

- Why leave out of the February 2020 article that the virus sequence was renamed?
- Why lie about when the full-length sequence was obtained?
- Why only issue a correction almost ten months later?
- Why was this sample destroyed via testing when others weren't?

In December 2020, reporters from *BBC News* attempted to visit the cave in Yunnan where RaTG13 was collected. They found themselves followed by plain-clothes police officers and stopped at checkpoints where they were told to stay out of the area.[150] A French publication, *Envoye Special*, produced a video in which they reported conversations with villagers who lived near the mine. According to one of those villagers, the mine was closed and monitored via surveillance cameras. That villager also alleged several people were arrested for venturing too close to the mine.[151]

It is important to note that in March 2020, American, British, and Australian researchers published "The proximal origin of SARS-CoV-2" in *Nature Magazine*.[152] Regarding RaTG13, they found, "Although RaTG13, sampled from a Rhinolophus affinis bat, is ~96% identical overall to SARS-CoV-2, its spike diverges in the RBD, which suggests that it may not bind efficiently to human ACE2."[153] "RBD" is an abbreviation for receptor-binding domain, part of the virus' spike protein. **This is the same part of the virus' genome that Shi, Hu, and other WIV researchers were genetically modifying and replacing as far back as 2015.**

147 *Ibid.*

148 Zhou, P., et. al. "Addendum: A pneumonia outbreak associated with a new coronavirus of probable bat origin." *Nature*, 17 Nov. 2020, 588: E6. https://doi.org/10.1038/s41586-020-2951-z

149 Shi, Zheng-li. "Reply to Science Magazine." *Science Magazine,* https://www.sciencemag.org/sites/default/files/Shi%20Zhengli%20Q%26A.pdf

150 Sudworth, John. "Covid: Wuhan Scientist Would 'Welcome' Visit Probing Lab Leak Theory." *BBC News,* 21 Dec. 2020, www.bbc.com/news/world-asia-china-55364445.

151 Asis, Francisco de. "Quite Important the Conversation with Danaoshan Inhabitant.- He Pointed towards the Location We Already Knew for the Mine.- The Roadblocks Are Probably the Diverted Traffic We Already Observed Too.Rest of the Story Is Just Incredible! Pic.twitter.com/kzHz7v5rSg." *Twitter,* Twitter, 12 Mar. 2021, https://twitter.com/franciscodeasis/status/1370183826731888641?s=20.

152 Andersen, Kristian G et al. "The proximal origin of SARS-CoV-2." *Nature Medicine,* 17 March 2002, 26(4):450-452. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7095063/

153 I*bid.*

If SARS-CoV-2 was genetically modified, this could represent a viable model for how. RaTG13's RBD, or full spike protein, could be replaced using the WIV's reverse genetic system. If one of the many unpublished coronaviruses in the WIV's possession was modified, and the resulting chimeric virus was then exposed to hACE2 expressing mice or civets, the resulting virus could become better adapted to infecting humans – just like SARS-CoV-2.

According to scientists – including those working at the WIV – ID4991/RaTG13 is more closely related to SARS-CoV-2 than any other publicly identified virus. It's now clear WIV researchers had this virus as early as 2013, several years before the WIV began genetically modifying other coronaviruses found in the wild. **Given the largest difference between RaTG13 and SARS-CoV-2 is at the spike protein – precisely where the WIV modified various coronaviruses for years – and that WIV researchers renamed the virus and lied about when they sequenced, ID4991/RaTG13 could be a source of genetic material if SARS-CoV-2 was indeed genetically modified.**

According to emails obtained by *Buzzfeed News,* it appears Kristian G. Andersen, the lead and corresponding author of the abovementioned article, initially considered this a viable theory. In a January 31, 2020 email to Dr. Anthony Fauci, the director of NIAID, Andersen stated that parts of the virus were possibly engineered and inconsistent with evolutionary theory:

From: Kristian G. Andersen <[redacted]>
Sent: Friday, January 31, 2020 10:32 PM
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 [154]

Fig. 8: Andersen Email Suggesting SARS-CoV-2 was Genetically Modified

The WIV's intentionally misleading February 2020 paper regarding RaTG13 was uploaded as a preprint on January 23rd[155]. Given that Andersen and his coauthors cited it in their March 2020 paper, it is all but certain that Andersen, Dr. Fauci, and the others would have seen it before Andersen sent this email. The day after Anderson emailed Dr. Fauci on February 1, 2020, Dr. Fauci, Andersen, and others debated this issue via teleconference. Previously, they had agreed to keep the debate confidential. Following this discussion, Andersen abandoned his claims that the virus was genetically modified.[156] It is unclear what was said on this call that led to Anderson doing so.

154 Andersen, Kristian G. Email to Anthony Facui and Jeremy Farrar. 31 Jan. 2020. https://s3.documentcloud.org/documents/20793561/leopold-nih-foia-anthony-fauci-emails.pdf

155 Zhou, Peng, et. al. Preprint of "Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin." 23 Jan. 2020, *bioRxiv*, https://www.biorxiv.org/content/10.1101/2020.01.22.914952v2

156 Young, Alison. "'I Remember It Very Well': Dr. Fauci Describes a Secret 2020 Meeting to Talk about COVID Origins." *USA Today*, 18 June 2021, www.usatoday.com/story/opinion/2021/06/17/covid-19-fauci-lab-leaks-wuhan-china-origins/7737494002/.

Additional Cover-Up Activities by Scientists at the WIV

As more investigative work continues on the type of research being conducted at the WIV, CCP censors and WIV researchers have been deleting or scrubbing references to coronavirus research that could be related to the origins of the COVID-19 pandemic. As previously discussed, Ben Hu received a Youth Science Fund Project award to test the pathogenicity of two novel SARS-related coronaviruses beginning in 2019. In some publicly facing PRC websites, Hu's name has now been struck from the grant.

Fig. 9: Ben Hu's Name Removed From 2019 Grant [157]

Of the almost 80 WIV grants listed in the database, the one awarded to Ben Hu is the only one that does not identify the principal investigator.

A December 12, 2017, interview with Hu was pulled offline after it began circulating on Twitter. In the article, Hu discusses monitoring and collecting samples from the bat cave in Yunnan and his work using the reverse genetic system to insert spike proteins into live coronaviruses. Interestingly, he discusses how Shi Zheng-li "often personally leads the team to take samples."[158] It is likely that this article was pulled down for drawing attention to the cave where RaTG13 was collected.

Similarly, a 2018 article written by Hu and published on the website for the Wuhan Branch of the Chinese Academy of Sciences has also been removed.[159] While the article broadly discusses the work of Shi and other researchers at the WIV, it does not offer any unique insight or evidence of dangerous research. So why was it removed?

157 2019 Natural Science Foundation Query and Analysis System. https://journal.medsci.cn/m/nsfc.do?u=%E4%B8%AD%E5%9B%BD%E7%A7%91%E5%AD%A6%E9%99%A2%E6%AD%A6%E6%B1%89%E7%97%85%E6%AF%92%E7%A0%94%E7%A9%B6%E6%89%80

158 "Hunting bat viruses, tracking the origin of SARS, an interview with Dr. Hu Ben, Wuhan Institute of Virology, Chinese Academy of Sciences." *First Author,* 12 Dec. 2017, https://archive.vn/sVHmq#selection-45.79-45.215

159 Hu, Ben. "The Wuhan Institute of Virology's "Research on Chinese Bats Carrying Important Viruses" won the first prize of the 2018 Hubei Provincial Natural Science Award." *Wuhan Branch, Chinese Academy of Sciences, 13* April 2018, archived: https://web.archive.org/web/20210107222832/http://whb.ac.cn/xw/kyjz/201811/t20181122_5191050.html

Perhaps most incriminating are Shi's repeated lies about activities taking place at the WIV. In August 2020, after the publication of the Committee Minority Staff's interim report, the China Global Television Network interviewed Shi about our work. In the resulting article, Shi denied that Major General Chen Wei took over the BSL-4 lab:

> Liu Xin: The report actually went further and said that the lab has been taken over by the Chinese military. It says that Major General Chen Wei has succeeded Yuan Zhiming as the Director of the WIV and Chen Wei is a Chinese military medical sciences expert.
> Shi Zhengli: This is a rumor; there is no such thing.
> Liu Xin: You absolutely deny that the Chinese military has taken over the WIV.
> Shi Zhengli: Yes, it is a rumor.[160]

This is demonstrably false. As previously discussed, posts made on CCP-controlled forums announcing Chen's arrival acknowledged her takeover of the lab. The report stated, "PLA Maj. Gen. Chen Wei has been in Wuhan for more than 10 days. She took over the P4 lab as if it were a 'reassurance pill.'"[161]

During the same interview, and in response to Committee Minority Staff raising questions about a possible lab leak, Shi again lied, claiming that all of the WIV's research has been published and their samples available for review:

> Another piece of evidence that I can give you is that our lab has been doing research for 15 years, and all our work has been published. We also have a library of our own genetic sequences, and we have experimental records of all our work related to the virus, which are accessible for people to check.[162]

This, again, is demonstrably false. The WIV's sequence library was taken offline in September 2019 and is not "accessible for people to check." Given the previously discussed undisclosed coronavirus research and military activities at the WIV, it is obvious that not "all" of the WIV's work has been published. Daszak confirmed this in an interview with *Nature*: "we have data that we've gathered over 15 years of working in China — 5 years under a previous grant from the NIH — which haven't been published yet."[163]

In a June 2021 interview, Shi told the *New York Times*, "my lab has never conducted or cooperated in conducting GOF experiments that enhance the virulence of viruses."[164] This is a bizarre claim given the years of published research, often designed and led by Shi, that explicitly sought to make coronaviruses more infectious to humans. In the same interview, Shi lied about WIV researchers falling ill in the fall of 2019 – "The Wuhan Institute of Virology has not come across such cases." This is despite the State Department's January 15th 2021 fact sheet and confirmation from a Dutch virologist on the WHO's investigative team that several researchers were sick.[165]

160 Xin, Liu. "Exclusive Interview: CGTN's Liu Xin Talks to China's 'Bat Woman'." *CGTN*, 26 Aug. 2020, https://news.cgtn.com/news/2020-08-22/Can-politics-be-put-aside-while-looking-for-origins-of-coronavirus--T9HgctyKv6/index.html.

161 Guli.

162 Xin.

163 Subbaraman, Nidhi. "'Heinous!': Coronavirus Researcher Shut down for Wuhan-Lab Link Slams New Funding Restrictions." *Nature News*, 21 Aug. 2020, www.nature.com/articles/d41586-020-02473-4.

164 Qin, Amy, and Chris Buckley. "A Top Virologist in China, at Center of a Pandemic Storm, Speaks Out." *The New York Times*, 14 June 2021, www.nytimes.com/2021/06/14/world/asia/china-covid-wuhan-lab-leak.html

165 Gordon, Michael R., et al. "WSJ News Exclusive | Intelligence on Sick Staff at Wuhan Lab Fuels Debate on Covid-19 Origin." *The Wall Street Journal*, 23 May 2021, www.wsj.com/articles/intelligence-on-sick-staff-at-wuhan-lab-fuels-debate-on-covid-19-origin-11621796228.

Cover-Up Activities by the Chinese Communist Party

According to a WHO internal document from August 2020, the PRC put little effort into determining the source of the SARS-CoV-2 after January 2020:

> Following extensive discussions with and presentation from Chinese counterparts, it appears that little had been done in terms of epidemiological investigations around Wuhan since January 2020. The data presented orally gave a few more details than what was presented at the emergency committee meetings in January 2020. No PowerPoint presentations were made and no documents were shared.[166]

Given the large amount of financial resources devoted by the PRC in the years prior for locating, sampling, identifying, and experimenting with coronaviruses, it is odd that little effort would be put into determining the source of the virus, if the source was unknown. In mid-February 2020, the PRC's Ministry of Science and Technology issued new guidelines for laboratory research in the PRC. Official PRC sources stressed:

> The mention of biosafety at labs by the ministry has nothing to do with some saying that the coronavirus leaked from the Wuhan Institute of Virology of the Chinese Academy of Sciences.[167]

Experts interviewed in February 2020 by *The Global Times* stated that PRC labs paid "insufficient attention to biological disposal."[168] This included disposing of lab materials into sewage systems.[169] Given that these new guidelines were issued after the PRC stopped searching for the source of the outbreak, it raises questions as to what prompted the PRC to stop its search.

Shortly thereafter, on February 25, 2020, the Chinese Center for Disease Control and Prevention issued supplementary regulations affecting how PRC scientists work on research related to COVID-19. The guidelines prohibit researchers from sharing data or samples and requires them to receive permission prior to conducting research or publishing the results.

> 3. No one can, under their own name or in the name of their research team, provide other institutions and individuals with information related to the COVID-19 epidemic on their own, including data, biological specimens, pathogens, culture, etc.
>
> 4. Before publishing papers and research results related to the COVID-19 epidemic, you must first report them to the Science and Technology Group/Department for preliminary review, and if necessary, submit it to the Emergency Leading Group or the Department of Science and Education of the National Health Commission for approval.
>
> Papers that have been submitted but not yet reviewed by the Science and Technology Group/Department should be withdrawn as soon as possible and redone according to these regulations.

Fig. 10: Excerpt from China CDC Regulations Issued on February 25th[170]

166 Kirchgaessner, Stephanie. "China Did 'Little' to Hunt for Covid Origins in Early Months, Says WHO Document." *The Guardian,* 23 Feb. 2021, www.theguardian.com/world/2021/feb/23/china-did-little-hunt-covid-origins-early-months-says-who-document

167 Caiyu, Liu, and Leng Shumei. "Biosafety Guideline Issued to Fix Chronic Management Loopholes at Virus Labs." *Global Times,* 16 Feb. 2020, www.globaltimes.cn/content/1179747.shtml.

168 *Ibid.*

169 *Ibid.*

A full copy of the regulations is included in the Appendix.

On February 27, 2020, *Health Times,* published remarks from an interview with Yu Chuanhua, who referenced health data from February 25th. Yu is the Vice President of the Hubei Health Statistics and Information Society and Professor of Epidemiology and Health Statistics at Wuhan University, and was running a database of confirmed COVID-19 cases in early 2020. In the interview, Yu stated he had evidence of COVID-19 cases as early as September 2019:

> Professor Yu Chuanhua said, "For example, there is data on a patient who became ill on September 29. The data shows that the patient has not undergone nucleic acid testing. The clinical diagnosis (CT diagnosis) is a suspected case. The patient has died. This data has not been confirmed and there is no time to death. It may also be wrong data." With the research of the database, Professor Yu Chuanhua found more and more case data before December 8. There were two cases in November, and the onset time was November 14 and November 21, 2019. Before December 8, there were also five or six cases. Among them, one patient who became ill at the end of November was hospitalized on December 2 and was clinically diagnosed with pneumonia.[171]

Before the interview was published on February 27th, Yu called the reporter and tried to retract the information regarding the two sick patients in November.[172] It is likely that this was done to comply with the China CDC gag order that was issued two days prior.

Nine days later, on March 5, 2020, the Joint Prevention and Control Mechanism (JPCM) of the State Council Novel Coronavirus Pneumonia Scientific Research Group issued a confidential memo, obtained by the *Associated Press*, entitled, "Notice on the Standardization of the Management and Publication of Novel Coronavirus Scientific Research."[173] The notice announced the research group was taking control of all publication work related to the pandemic for "coordinated deployment."[174] It also required units publishing research to notify the JPCM's propaganda team, which was tasked to work with a special public opinion team to coordinate publication of research with public opinion and "social concerns."[175]

170 Chinese Center for Disease Control and Prevention. "On the Supplementary Regulations on Strengthening the Management of Science and Technology During the Emergency Response to the Novel Coronavirus." 25 Feb. 2020. https://www.documentcloud.org/documents/7340336-China-CDC-Sup-Regs.html

171 Wang, Zhenya. "Experts Judge the Source of the New Crown: December 8 Last Year May Not Be the Earliest Time of Onset." *Health Times,* 27 Feb. 2020, www.jksb.com.cn/index.php?m=wap&a=show&catid=629&id=160018.

172 *Ibid.*

173 Joint Prevention and Control Mechanism of the State Council Novel Coronavirus Pneumonia Scientific Research Group. "Notice on the Standardization of the Management and Publication of Novel Coronavirus Scientific Research." 3 Mar. 2020. https://www.documentcloud.org/documents/7340337-State-Research-regulations.html

174 *Ibid.*

175 *Ibid.*

Each member work unit of the scientific research team will gather scientific research information within their own unit and systems, review and check the content and form of its publication, and report it to the scientific research team for approval in a timely manner. The scientific research group's dedicated teams of professionals and various experts are responsible for reviewing the publication's content and format and giving expert opinions, and when necessary, arranging expert assessment. After the scientific research group approves, the publishing work unit should, according to work requirements, arrange publication via press conferences, official websites, state social media, news media and other platforms, and notify the propaganda and scientific research teams of the Joint Prevention and Control Mechanism of the State Council. In principle, COVID-19 scientific research should be published first in the form of an official authoritative publication. The special group on public opinion should strengthen communication with the propaganda team, take into account the trend of public opinion and social concerns, and strengthen guidance of the publication of scientific research and information.

Fig. 11: Excerpt from JPCM Memo

The memo concludes with a warning: "Those who fail to apply for approval in accordance with the prescribed procedures and publish unconfirmed false information on scientific research, thereby causing serious adverse social impacts, shall be held accountable."[176] A full copy of the memo is included in the Appendix. These documents are clear evidence of the CCP's effort to restrict research on SARS-CoV-2, so that the only research published supports the Party's official story on the origins and emergence of COVID-19.

After the release of the Committee Minority Staff's interim report on the origins of COVID-19, *China Global Television Network*, a PRC state-owned media outlet, released a propaganda video aimed at undermining this investigation. Entitled, "Clearing up confusion in McCaul report on COVID-19," the approximately 45-minute video labels the report "misinformation."[177] It also discusses what they call the "tired old theory that the virus could have leaked from a lab"[178] and reveals that Shi Zheng-li was interviewed about our report. The piece also claims the BSL-4 lab space at the WIV was never taken over by Maj. Gen. Chen Wei.[180] As discussed earlier, this statement is demonstrably untrue.

In June 2021, Jesse Bloom published a preprint entitled, "Recovery of deleted deep sequencing data sheds more light on the early Wuhan SARS-CoV-2 epidemic." Bloom is a Principal Investigator and Associate Professor for Basic Sciences and the Herbold Computational Biology Program at Fred Hutch, a cancer research center. Bloom was able to recover multiple deleted viral sequences collected from patients in Wuhan in early December 2020. These sequences were originally uploaded to the NIH's Sequence Read Archive by researchers in Wuhan, but later deleted at their request.

176 *Ibid.*

177 "The Point: Clearing up Confusion in the McCaul Report On Covid-19." *CCTV News*, 25 July 2020, www.youtube.com/watch?v=n5qYogMTZOw.

178 *Ibid.*

179 *Ibid.*

180 *Ibid.*

Oddly, these samples more greatly diverge from SARS-CoV-2's bat coronavirus ancestor – "the earliest SARSCoV-2 sequences were collected in Wuhan in December, but these sequences are more distant from RaTG13 than sequences collected in January from other locations in China or even other countries."[181] Bloom concludes (emphasis added):

> **The fact that this informative data set was deleted suggests implications beyond those gleaned directly from the recovered sequences.** Samples from early outpatients in Wuhan are a gold mine for anyone seeking to understand spread of the virus. Even my analysis of 13 partial sequences is revealing, and it clearly would have been more scientifically informative to fully sequence all 34 samples rather than delete the partial sequence data. **There is no obvious scientific reason for the deletion:** the sequences are concordant with the samples described in Wang et al. (2020a,b), there are no corrections to the paper, the paper states human subjects approval was obtained, and the sequencing shows no evidence of plasmid or sample-to-sample contamination…. Even though the sequencing data were on the Google Cloud (as described above) and the mutations were listed in a table in the Small paper by Wang et al. (2020b), **the practical consequence of removing the data from the SRA was that nobody was aware these sequences existed.** Particularly in light of the directive that labs destroy early samples (Pingui 2020) and multiple orders requiring approval of publications on COVID-19 (China CDC 2020; Kang et al. 2020a), **this suggests a less than wholehearted effort to maximize information about viral sequences from early in the Wuhan epidemic.**[182]

The PRC's efforts to obfuscate the origins of COVID-19 were not limited to destroying samples and silencing doctors, but featured a sustained disinformation campaign as well. As discussed in our previous report, Lijian Zhao, an official within the PRC's Foreign Ministry, shared an article on Twitter that claimed the virus was brought to the PRC by the U.S. military.[183] The article was from the *Global Times* research.ca, a website that pushes pro-Putin propaganda and has reported ties to Russian state media.[184] His tweet was amplified by the Chinese Embassy in South Africa.[185]

181 Bloom, Jesse D. Preprint: "Recovery of deleted deep sequencing data sheds more light on the early Wuhan SARS-CoV-2 epidemic." *bioRxiv*, 29 June 2021, https://www.biorxiv.org/content/10.1101/2021.06.18.449051v2

182 *Ibid.*

183 Zhao, Lijian. "This Article Is Very Much Important to Each and Every One of Us. Please Read and Retweet It. COVID-19: Further Evidence That the Virus Originated in the US. Https://T.co/LPanIo40MR." *Twitter*, 13 Mar. 2020, www.twitter.com/zlj517/status/1238269193427906560

184 Thomas, Elise, and Aspi. "Chinese Diplomats and Western Fringe Media Outlets Push the Same Coronavirus Conspiracies." *The Strategist,* 30 Mar. 2020, www.aspistrategist.org.au/chinese-diplomats-and-western-fringe-media-outlets-push-the-same-coronavirus-conspiracies/.

185 Chinese Embassy in South Africa. "More Evidence Suggests That the Virus Was Not Originated at the Seafood Market in Wuhan at All, Not to Mention the so Called 'Made in China'. Https://T.co/8cRxkSZB3z." *Twitter*, 16 Mar. 2020, www.twitter.com/ChineseEmbSA/status/1239453193689587712

Fig. 12: PRC Spokesman Tweet Suggesting COVID-19 Arrived in Wuhan via the Military World Games

To further drive this narrative, CCP-controlled media outlets accused Maatje Benassi, a member of the U.S. Army Reserve, as being "patient zero." Benassi competed at the Military World Games without becoming ill, yet has been repeatedly targeted for harassment. Videos pushing the theory have been uploaded to WeChat, Weibo, and Xigua – PRC based sites. Two weeks after Zhao tweeted that the U.S. army brought the virus to Wuhan, the *Global Times* amplified the narrative, urging the U.S. government to release athletes' health info and repeated the claim about Benassi. [186]

Another tweet by Zhao actually suggests the pandemic did start in September, as is suggested in this addendum, but that it began in the United States.[187]

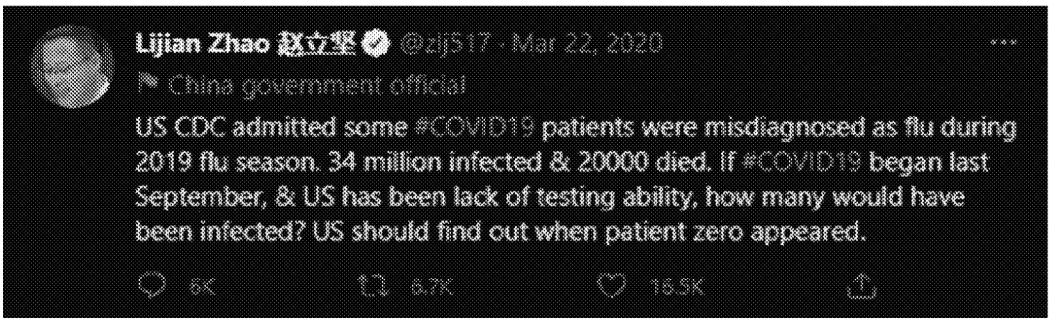


Fig. 13: PRC Spokesman Tweet Suggesting the COVID-19 Pandemic Started in September 2019.

186 Shumei, Leng, and Wan Lin. "US Urged to Release Health Info of Military Athletes Who Came to Wuhan in October 2019." *Global Times*, 25 Mar. 2020, www.globaltimes.cn/content/1183658.shtml.

187 Zhao, Lijian. *US CDC Admitted Some #COVID19 Patients Were Misdiagnosed as Flu during 2019 Flu Season. 34 Million Infected & 20000 Died. If #COVID19 Began Last September, & US Has Been Lack of Testing Ability, How Many Would Have Been Infected? US Should Find out When Patient Zero Appeared.* Twitter, 22 Mar. 2020, https://twitter.com/zlj517/status/1241723635964039168?s=20.

It is important to note that this tweet was sent in March 2020. The previously discussed Harvard study suggesting the pandemic began in September was not published until the second half of 2020. This accusation came ten days after Zhao repeated his theory that the U.S. military brought COVID-19 to Wuhan. If the CCP realized an investigation would show an uptick in visits of patients with symptoms similar to COVID-19 in September, October, and November of 2019, this would likely be the actions they would take to coverup the source of those illnesses.

WIV Disinformation Campaign Involving Peter Daszak

As we have previously explained, Peter Daszak was heavily involved in the gain-of-function research taking place at the WIV, including research that was done at BSL-2 levels and that was done while the United States had a moratorium in place on funding gain-of-function research. In addition, we have uncovered strong evidence that suggests Peter Daszak is the public face of a CCP disinformation campaign designed to suppress public discussion about a potential lab leak. Emails obtained by a third-party organization show that Daszak organized a February 19, 2020, statement in the *Lancet* "condemn[ing] conspiracy theories suggesting that COVID-19 does not have a natural origin."[188] The statement continued, "Conspiracy theories do nothing but create fear, rumours, and prejudice that jeopardise our global collaboration in the fight against this virus."[189] The emails show Daszak's effort to organize a large group of scientists to sign onto a statement that he personally drafted. One email concludes with Daszak stating, "Please note that this statement will not have EcoHealth Alliance logo on it and will not be identifiable as coming from any one organization or person, the idea is to have this as a community supporting our colleagues."[190]

The emails, sent from Daszak's EcoHealth Alliance email account, also reveal the statement was drafted in response to a request by WIV researchers with whom Daszak had worked (emphasis added):

> You should know that the conspiracy theorists have been very active, targeting our collaborators with some extremely unpleasant web pages in China, and some have now received death threats to themselves and their families. **They have asked for any show of support we can give them.**[191]

In a separate email, Daszak states that Linfa Wang (who did not sign the statement) pushed for Daszak and Baric to not sign the statement, effectively hiding their involvement. As previously discussed, Linfa Wang, who is copied on several other emails about the statement, was a coauthor of multiple Daszak/Shi/Hu papers. Wang is currently the Director and Professor of the Program in Emerging Infectious Diseases at the Duke-NUS Graduate Medical School in Singapore. He is a PRC national who received his B.S. in biochemistry from the East China Normal University in Shanghai, PRC[192] before completing a Ph.D. in molecular biology at the University of California, Davis in the United States.

188 Calisher, Charles et al. "Statement in support of the scientists, public health professionals, and medical professionals of China combatting COVID-19." *Lancet*, 7 Mar. 2020, 395(10226): e42-e43. https://pubmed.ncbi.nlm.nih.gov/32087122/

189 *Ibid.*

190 Daszak, Peter. Email to Linda Saif, Hume Field, JM Hughe, Rita Colweel, Alison Andrew, Aleksei Chmura, Hongying Li, William B. Karesh, and Robert Kessler. 6 Feb. 2020. https://usrtk.org/wp-content/uploads/2020/11/The_Lancet_Emails_Daszak-2.6.20.pdf

191 Daszak, Peter. Email to Rita Colwell. 8 Feb. 2020. https://usrtk.org/wp-content/uploads/2020/11/The_Lancet_Emails_Daszak-2.8.20.pdf

192 Wang, Linfa. "Curicullum Vitae." https://globalhealth.duke.edu/sites/default/files/cv/cv-linfa_wang-jan2017.pdf

In January 2020, Wang was at the WIV in Wuhan, visiting researchers he worked with. Given his previous publications, this likely included a vsiit with Hu and Shi, with whom he has authored dozens of papers. He departed the city on January 18th,[192] less than three weeks before Daszak externally circulated his draft *Lancet* statement. Wang is included on the email soliciting cosigners.[193]

In the email, Daszak states, (emphasis added):

> I spoke with Linfa last night about the statement we sent round. He thinks, and I agree with him, that **you, me and him should not sign this statement, so it has some distance from us** and therefore doesn't work in a counterproductive way... **We'll then put it out in a way that doesn't link it back to our collaboration so we maximize an independent voice.**[194]

Copies of these emails are included in the Appendix.

While pushing for Daszak and Baric, the WIV's most prominent American collaborators, to hide their efforts to organize this statement, Wang was serving as the Chair of the Scientific Advisory Board for the Center for Emerging Diseases at the Wuhan Institute of Virology, of which Shi Zheng-li is the Director.[195]

Baric agreed and chose not to sign. It is unclear why Daszak ultimately changed his mind and signed the statement. Despite Daszak's role as the organizer of the *Lancet* statement, Charles Calisher is listed as the corresponding author. Oddly, the email address listed for Calisher is a generic one (COVID19statement@gmail.com[196]) that appears to have been created specifically for this statement, an unusual practice for scientific publications.

The February 2021 Lancet statement declared the authors had "no competing interest," despite Daszak organizing the letter on behalf of WIV researchers who he funded and with whom he collaborated. In June 2020, after public concerns regarding Daszak's connection to the WIV, "the *Lancet* invited the 27 authors of the letter to re-evaluate their competing interests."[197] **Daszak submitted a revised disclosure statement which, while transparent about his prior work with PRC researchers, fails to reference the WIV or disclose that he drafted the statement at the request of PRC researchers.**[198]

The emails also reveal that Daszak helped edit a letter sent on February 6, 2020 by the Presidents of the U.S. National Academies of Sciences, Engineering, and Medicine to the White House Office of Science and Technology Policy regarding the origins of COVID-19.

192 Kupferschmidt, Kai. "This Biologist Helped Trace SARS to Bats. Now, He's Working to Uncover the Origins of COVID-19." Science, 9 Sept. 2020, www.sciencemag.org/news/2020/09/biologist-helped-trace-sars-bats-now-hes-working-uncover-origins-covid-19.

193 Daszak (6 Feb.)

194 Daszak, Peter. Email to Ralph Baric, Toni Baric, Alison Andre, and Aleksei Chmura. 6 Feb. 2020. https://usrtk.org/wp-content/uploads/2021/02/Baric_Daszak_email.pdf

195 Wang.

196 Calisher.

197 Editors of The Lancet. "Addendum: competing interests and the origins of SARS-CoV-2." *The Lancet,* 26 June 2021, 397: 2449-50. https://www.thelancet.com/action/showPdf?pii=S0140-6736%2821%2901377-5

198 *Ibid.*

199 McNutt, Marcia, et al. "NASEM Response to OSTP Re Coronavirus_February 6, 2020." Received by Kelvin Droegemeier , National Academies of Science, Engineering, and Medicine, 6 Feb. 2020, Washington, District of Columbia. https://www.nationalacademies.org/documents/link/LDA8FF8BAB7F1D4A98AC250C7916649E610A15AD51C6/fileview/DA215521A660F40FD8D752FFB82A8E21FA8D3C29976D/NASEM%20Response%20to%20OSTP%20re%20Coronavirus_February%206%2C%202020.pdf?hide=thumbs+breadcrumbs+favs+props+nextprev+sidebar+pin+actions&scheme=light&fitwidth

While not included in the final version, the last draft edited by Daszak and the other experts who were consulted included a line stating, "The initial views of the experts is that the available genomic data are consistent with natural evolution and that there is currently no evidence that the virus was engineered to spread more quickly among humans." Daszak actually pushed for broader language, as he believed "this is a bit too specific, because there are other conspiracy theories out there." It is unclear why the sentence was removed by the Presidents of the U.S. National Academies before the letter was sent to the White House. Daszak specifically sought to time the publication of his statement in The Lancet for after this letter was released. And the statement references the letter as proof of the virus' natural origin, without disclosing that Daszak helped edit it. It is highly likely that senior government officials, including Dr. Fauci, would have seen both the letter from the U.S. National Academies of Sciences, Engineering, and Medicine and the statement published in The Lancet, shaping their opinion and stifling debate within the U.S. federal government regarding the origins of COVID-19.

Sixteen months after sending this initial letter, the Presidents of the U.S. National Academies of Sciences, Engineering, and Medicine released an updated statement on June 15, 2021, titled, "Let Scientific Evidence Determine Origin of SARS-CoV-2, Urge Presidents of the National Academies." [199] This updated statement acknowledges there are scenarios that the origin of the pandemic could have resulted from a lab leak, stating (emphasis added):

> However, misinformation, unsubstantiated claims, and personal attacks on scientists surrounding the different theories of how the virus emerged are unacceptable, and are sowing public confusion and risk undermining the public's trust in science and scientists, including those still leading efforts to bring the pandemic under control… In the case of SARS-CoV-2, there are multiple scenarios that could, in principle, explain its origin with varying degrees of plausibility based on our current understanding. **These scenarios range from natural zoonotic spillover (when a virus spreads from non-human animals to humans) to those that are associated with laboratory work.**[200]

Unlike the letter to the White House, this statement does not state which, if any, outside experts were consulted when drafting the statement.

Interestingly, three weeks later, in July 2021, Daszak and his colleagues released an update to their February 2020 statement with a very similar title: "Science, not speculation, is essential to determine how SARS-CoV-2 reached humans." The second statement was signed by 24 of the original 27 authors and reflects a major step back from those authors' original position (emphasis added):

200 *Ibid.*

Interestingly, three weeks later, in July 2021, Daszak and his colleagues released an update to their February 2020 statement with a very similar title: "Science, not speculation, is essential to determine how SARS-CoV-2 reached humans." The second statement was signed by 24 of the original 27 authors and reflects a major step back from those authors' original position (emphasis added):

> **The second intent of our original Correspondence was to express our working view that SARS-CoV-2 most likely originated in nature and not in a laboratory,** on the basis of early genetic analysis of the new virus and well-established evidence from previous emerging infectious diseases, including the coronaviruses that cause the common cold as well as the original SARS-CoV and MERS-CoV. **Opinions, however, are neither data nor conclusions.** Evidence obtained using the scientific method must inform our understanding and be the basis for interpretation of the available information.[201]

This is quite different from Daszak's words in the first border-line propaganda statement "condemn[ing] conspiracy theories suggesting that COVID-19 does not have a natural origin."[202] Despite this softening, the authors continue to accuse those who seek to investigate the lab leak hypothesis of being the source of the PRC's unwillingness to cooperate with an international investigation:

> Allegations and conjecture are of no help, as they do not facilitate access to information and objective assessment of the pathway from a bat virus to a human pathogen that might help to prevent a future pandemic. Recrimination has not, and will not, encourage international cooperation and collaboration.[203]

Whereas the first statement cited the letter from the Presidents of the U.S. National Academies of Sciences, Engineering, and Medicine (which Daszak helped edit), the second cites the Presidents' statement released just weeks prior. This raises the question of whether Daszak, or any of the authors, assisted in drafting or editing the June 15th statement issues by the National Academies.

It should also be noted that Daszak was the only representative of the United States on the WHO-China Joint Study team in early 2021. The United States put forth a list of experts to be considered, none of whom were chosen. Daszak was not on that list but was nevertheless selected and approved by the CCP.[204] The annexes of the WHO's report on the origins of COVID-19, issued in March 2021, include multiple examples of CCP disinformation that have been repeated by Daszak. This include a discussion of "conspiracy theories,"[205] which include the lab leak hypothesis and questions regarding the possible genetically modified nature of SARS-CoV-2. It also refers to the WIV's sequence database that was taken offline as a "rumour about missing data."[206] This is similar language to that which Daszak used during his Chatham House interview – despite the database remaining offline.[207] Committee Minority Staff was unable to determine whether Daszak assisted in the drafting or editing of the WHO report.

201 Calisher, Charles H et al. "Science, not speculation, is essential to determine how SARS-CoV-2 reached humans." *Lancet*, 5 July 2021, 398:209-211. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8257054/

202 Calisher (Feb.)

203 Calisher (July)

204 Testimony from former senior U.S. official received by Committee Minority Staff.

205 Joint Report - ANNEXES.

206 *Ibid.*

207 *Ibid.*

Peter Daszak has taken several additional concerning actions in regard to the origins of COVID-19, including inexplicably lying about the work conducted by EcoHealth Alliance in the months following the emergence of SARS-CoV-2. In an August 21, 2020, interview with *Nature,* after the NIH suspended the grants he was using to fund research at the WIV, Daszak claimed "The grant isn't used to fund work on SARS-CoV-2. Our organization has not actually published any data on SARS-CoV-2."[208] This is despite the fact that four days later Nature Communications published "Origin and cross-species transmission of bat coronaviruses in China."[209] Daszak, Shi, Hu, and Wang are all listed as authors, with Shi and Daszak both being listed as corresponding authors. The preprint for the article was uploaded on May 31, 2020, almost three months before Daszak's interview with *Nature*. The paper includes a phylogenetic analysis "suggesting a likely origin for SARS-CoV-2 in Rhinolophus spp. bats."[210] Daszak, Shi, three EcoHealth Alliance affiliated researchers, and Linfa Wang are credited with designing the study, conducting fieldwork, and establishing collection and testing protocols.

The research was funded by the NIH (grant no. R01AI110964) and USAID's PREDICT project (cooperative agreement number GHN-A-OO-09-00010-00), as well as the Strategic Priority Research Program of the Chinese Academy of Sciences (grant no. XDB29010101) that Shi was directing. It also received support from the National Natural Science Foundation of China (grants no. 31770175 and 31830096). The paper notes:

> All work conducted by EcoHealth Alliance staff after April 24th 2020 was supported by generous funding from The Samuel Freeman Charitable Trust, Pamela Thye, The Wallace Fund, & an Anonymous Donor c/o Schwab Charitable.[211]

April 24th was the day the NIH terminated the project Understanding the Risk of Bat Coronavirus Emergence, which was funded under grant R01AI110964,[212] which is cited in the paper as funding this work.[213] The grant Daszak told Nature was not being used to fund work on SARS-CoV-2 is cited in a paper presenting research on SARS-CoV-2.

Earlier, in March 2020, Peter Daszak and two other EcoHealth Alliance affiliated researchers published "A strategy to prevent future epidemics similar to the 2019-nCoV outbreak."[214] While the paper lacked lab experimentation, it discussed SARS-CoV-2 and claimed that "wildlife trade has clearly played a role in the emergence of"[215] the virus. This work was also funded by the same NIH grant (grant no. R01AI110964), as well as the same cooperative agreement with USAID's PREDICT Project.

In December 2020, Daszak stated in a tweet that the suspension of the aforementioned NIH grant directly prevented him from accessing samples at the WIV. If the grant did not support EcoHealth Alliance's work on SARS-CoV-2, how could it be related to their inability to access SARS-CoV-2 samples?

208 Subbaraman.

209 Latinne, Alice et al. "Origin and cross-species transmission of bat coronaviruses in China." *Nature Communications,* 25 Aug. 2020, 11(1):4235, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7447761/

210 *Ibid.*

211 *Ibid.*

212 Lauer, Michael. Email to Peter Daszak. 24 April 2020. https://www.sciencemag.org/sites/default/files/Lauer.Daszak.NIH%20grant%20killed.partial%20email%20transcripts.April%202020.pdf

213 Latinne

214 Daszak, Peter et al. "A strategy to prevent future epidemics similar to the 2019-nCoV outbreak." *Biosafety and Health,* March 2020, 2(1): 6-8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7144510/

215 *Ibid.*

Why did Daszak claim the NIH grant "isn't used to fund work on SARS-CoV-2"[216] when his own published research and statements show that it was?

Another concerning example of Daszak's behavior comes from a March 10, 2021 discussion with Chatham House. In response to a question about the WIV taking down its viral sequence and sample database in September 2019 and whether the WHO investigative team requested to see the data, Peter Daszak stated (emphasis added):

> I asked the question in front of the whole team, both sides, while we were at the Wuhan Institute of Virology, about the **so-called missing database.** And what we were told, by Shi Zheng-li, was that there had been hacking attempts on it, about 3,000 hacking attempts, and they took down this excel spreadsheet-based database. Absolutely reasonable. **We did not ask to see the data,** and as you know, a lot of this work is work that has been conducted with EcoHealth Alliance, and I'm also part of those data, and **we do basically know what's in those databanks.** And I shared, **I gave a talk to both sides about the work we've done with the Wuhan Institute of Virology and explained what's there. There is no evidence of viruses closer to SARS-CoV-2 than RaTG13 in those databases. It's as simple as that.**[217]

This is a stunning claim given the database contained more than 22,000 samples and was inaccessible by anyone outside of the WIV after September 2019. It was physically impossible for Daszak to remotely access the database after the SARS-CoV-2 genome was released in January 2020 in order to compare the genome to samples in the database. **If not, given that no one outside of the WIV knew RaTG13 was closely related to SARS-CoV-2 prior to publication in February 2020, how could Daszak claim to know there is not a closer match in one of the 22,000 plus samples when he could not access the data? This raises the question of whether he has copy of the database.**

Daszak has also been, at best, incorrect about how the WIV handed RaTG13. In an April 21, 2020 interview with the *New York Times,* he stated (emphasis added):

> We found the closest relative to the current SARS-CoV-2 in a bat in China in 2013. **We sequenced a bit of the genome, and then it went in the freezer;** because it didn't look like SARS, we thought it was at a lower risk of emerging. With the Virome project, we could have sequenced the whole genome, discovered that it binds to human cells and upgraded the risk. And maybe then when we were designing vaccines for SARS, those could have targeted this one too, and we would have had something in the freezer ready to go if it emerged.[218]

This is, of course, untrue. Researchers at the WIV fully sequenced RaTG13's genome in 2018.[219] Either Daszak knew this was untrue, and lied to the *New York Times,* or he was being kept in the dark about the work being conducted at the WIV. If the later is true, it raises more questions about Daszak's March 2021 claim to know everything in the WIV's database that was taken offline.

216 Subbaraman.

217 "Sustaining the Response: Inside the WHO-China Mission." *Chatham House,* 10 March 2021, https://www.youtube.com/watch?v=GMllEF58944&t=3249s.

218 Kahn, Jennifer. "How Scientists Could Stop the Next Pandemic Before It Starts." *The New York Times,* 21 Apr. 2020, www.nytimes.com/2020/04/21/magazine/pandemic-vaccine.html.

219 Zhou, (Nov. 2020).

V. HYPOTHESIS: A LAB LEAK THAT CAUSED A PANDEMIC

Having examined the evidenced discussed in this addendum, Committee Minority Staff has put together the following hypothesis that could reasonably represent what could have occurred in the early months of the COVID-19 pandemic.

In the months leading up to an accidental release of SARS-CoV-2, the hazardous waste treatment system at the WNBL was undergoing renovation. The central air conditioning system at one of the facilities needed to be renovated, which likely resulted in lower than ideal air circulation and enabling viral particles to remain suspended in the air longer. After the July 4, 2019 notice from the Ministry of Science and Technology, and prior to the September 30th deadline, researchers at the WIV were reviewing samples collected under grant 2013FY113500, held by Yuan Zhiming, the Director of the WNBL BSL-4.[220]

This is the same grant which funded:

- The 2013 paper reporting the first isolation of a live SARS-like coronavirus after sampling at the cave in Kunming.[221]
- The 2014 paper, which was the result of collecting 986 samples from 39 species of small mammals in Guangxi and Yunnan provinces.
- The 2016 paper, where a second live coronavirus was successfully isolated.
- The 2017 paper, where a third live SARS-like coronavirus was isolated and WIV researchers created eight chimeric coronaviruses with altered spike proteins.

Hu, Shi, and others at the WIV were actively testing novel and genetically manipulated coronaviruses against hACE2 expressing mice and civets at BSL-2 and BSL-3 conditions, including viruses collected from the cave in Yunnan where the miners fell ill. A defective hazardous waste treatment system and central air conditioning system would increase the likelihood of a lab employee (or several) becoming infected with SARS-CoV-2, as viral particles would be more likely to remain in the air for longer periods of time. As previously discussed, the WIV provides a shuttle for employees, transporting individuals from near the old WIV facility in Wuchang to the WNBL and back. The infected employees (whether from the WNBL or the WIV Headquarters) then traveled throughout central Wuhan, likely by the metro, spreading the virus.

In early September, it became known that an accidental release occurred. Initially, not knowing SARS-CoV-2 spreads via human-to-human transmission or that asymptotic people are responsible for a large number of new cases, concern was low. Concern was additionally tempered by the knowledge that previous accidental releases from labs resulted in only a small number of infections. Still, measures are ordered in response. At midnight local time on the morning of September 12th, the Wuhan University, which sits less than a mile from the WIV Headquarters and whose medical school houses a BSL-3 lab accredited to experiment on animals,[222] issues a notice for laboratory inspections in late September.[223] It is likely that officials issued similar orders to other labs in the area. Between two and three hours later, the WIV's viral sequence database is taken offline in the middle of the night.[224] Roughly 17 hours later, at 7:09 p.m. local time, the WIV publishes a procurement announcement for "security services" at the WNBL, to include gatekeepers, guards, video surveillance, security patrols, and people to handle the "registration and reception of foreign personnel."[225] The budget provided was in excess of $1.2 million.[226]

In order to prevent national embarrassment, the decision was made to allow the 2019 Military World Games to continue. No spectators were allowed to attend the games, but international athletes and some of the 236,000 volunteers still become infected, spreading the virus in the city. Dozens of athletes fall ill with symptoms. Since COVID-19 can infect humans without causing symptoms, an untold number of athletes and volunteers become infected, but are asymptomatic and unaware they are infectious.

The athletes return to their home countries in late October, carrying SARS-CoV-2 across the world. Just as was the case in 2002 with SARS,[227] the CCP sought to hide the outbreak, wasting precious time that could have been used to prevent the global pandemic. By the time the world was alerted to the virus spreading in Wuhan, it had already begun to spread around the world.

In December, as cases begin to overload local hospitals, it became impossible to hide the outbreak. At some point in late 2019, Major General Chen Wei is brought in to take over the BSL-4 lab at the WNBL and lead the response efforts. The Wuhan Branch of the China CDC set a case definition for COVID-19 that only included those who have visited the Huanan Seafood Market, meaning that only people who had a link to the market were identified as having COVID-19. This further obscured the true origins of the virus.

Linfa Wang, a scientist with ties to the WIV and who has worked with Shi, Hu, and Daszak on the genetic modification of coronaviruses, was in Wuhan in early January 2020. While there he visited the WIV and likely met with Shi, Hu, and others. Sometime after his departure on Januarty 18th and before February 6th, WIV researchers asked Peter Daszak to organize a public statement suppressing debate regarding the lab as the origin of SARS-CoV-2. On January 20th, WIV researchers submitted the February 2020 article where ID4991 was renamed as RaTG13 and which contained false information about when the genomic sequence for the virus was obtained.

At 12:43am on February 6th, Daszak sent the draft statement to Wang, Baric, and others asking them to join as cosigners. Sometime before Daszak went to bed that night, Wang called him and requested that he, Daszak, and Baric not sign the statement in order to obfuscate their connections to the WIV. Baric agreed, and neither him nor Wang signed the statement. The statement was published on February 19th, declaring discussion of a lab leak a conspiracy theory, and suppressing public debate on the origins of COVID-19.

220 "Notice of the Resource Allocation and Management Department of the Basic Research Department of the Ministry of Science and Technology on the Comprehensive Performance Evaluation of Special Projects of Basic Science and Technology Work." *Ministry of Science and Technology,* 4 July 2019. https://archive.is/pIwh4#selection-703.7-711.34

221 Ge.

222 "About Wuhan University School of Medicine (WUSM)." *Wuhan University School of Medicine,* 23 Apr. 2013, https://wsm70.whu.edu.cn/English_Site/About.htm

223 "Notice on the implementation of laboratory safety inspections in 2019." *Wuhan University,* http://simlab.whu.edu.cn/info/1107/1018.htm

224 "Status breakdown of the database of characteristic wild animals carrying virus pathogens (September 2019)." *Scientific Database Service Monitoring & Statistics System.* https://archive.is/AGtFv#selection-1553.0-1567.2

225 "Competitive consultation on the procurement project of security services in Zhengdian Science Park, Wuhan Institute of Virology, Chinese Academy of Sciences." China Government Procurement Network, 12 Sept. 2019, https://web.archive.org/web/20210716170719/http://www.ccgp.gov.cn/cggg/dfgg/jzxcs/201909/t20190912_12900712.htm

226 *Ibid.*

227 Epstein, Gady A. "Chinese Admit to SARS Mistakes." *Baltimoresun.com*, Baltimore Sun, 1 Apr. 2003, www.baltimoresun.com/bal-te.sars21apr21-story.html.

V. RECOMMENDATIONS

In the previously issued report, Committee Minority Staff provided several recommendations for actions to be taken by the United States in response to COVID-19, including seeking new leadership at the WHO, pursuing Taiwan's re-admittance to the WHO as an observer, engaging in an international investigation with likeminded WHO Member States regarding the early stages of COVID-19, and supporting concrete reforms to the International Health Regulations. These recommendations remain relevant.

In response to the new information laid out in this addendum, there are additional steps that can be taken by the Committee, Congress more broadly, and the Executive Branch on this issue. Given the previously detailed inconsistences and CCP disinformation campaign regarding a possible lab leak, Peter Daszak must be subpoenaed to appear before the House Foreign Affairs Committee and Senate Foreign Relations Committee as material witness to this investigation. Committee Minority Staff attempted, on multiple occasions, to contact Daszak with a list of questions relevant to this report. He never responded. In contrast, Ralph Baric provided answers to a list of questions from Committee Minority Staff. His assistance was appreciated, and we believe his testimony would also be useful. Daszak and Baric should provide expert testimony, including but not limited to the following questions:

- What was the extent of genetic manipulation of coronaviruses and their testing against human immune systems at the WIV in 2018 and 2019?
- Who requested the statement of support published in the *Lancet*?
- Did this request include labeling discussion of a possible lab leak as a conspiracy theory?
- What was the nature and content of Wang's call to Daszak in the early hours of February 6th, 2020?
- Why did Daszak make conflicting, and apparently false, statements regarding the NIH grant terminated in 2020?
- How could Daszak confirm RaTG13 is the closet match to SARS-CoV-2 in the WIV's database if it was taken offline in September 2019?
- Does Daszak have a copy of the WIV's database that was taken offline?
- Who put forth Daszak's name to join the joint WHO-China investigative team?
- Was Daszak aware the funding he was providing directly supported gain-of-function research by paying for the collection of viruses the WIV later experimented with, even though the federal government had a moratorium on such research from 2014 through 2017?
- Do they believe SARS-CoV-2 could possibly be a genetically modified virus created via a system similar toBaric's "no-see-um" method and the system used by WIV researchers in 2016, thus leaving no evidence of manipulation?

Committee Minority Staff also recommends Congress pursue legislation to implement the following restrictions and sanctions in response to the pandemic:

- Institute a ban on conducting and funding any work that includes gain-of-function research until an international and legally binding standard is set, and only where that standard is verifiably being followed.
- Authorize and fund a public-private partnership for pandemic prevention, warning, and early detection.

- Sanction the Chinese Academy of Sciences and affiliated entities.
- List the Wuhan Institute of Virology and its leadership on the Specially Designated Nationals and Blocked Persons List and apply additional, appropriate secondary sanctions.
- Expand statutory and administrative sanctions regimes to curb the abuse of dual-use technology.
- Authorize new sanctions for academic, governmental, and military bioresearch facilities that fail to ensure the appropriate levels of safety and information sharing.
- Review all H-2B visas of Chinese nationals engaged in biological, chemical, or related research in the United States for possible revocation.
- Review all student visas of Chinese nationals studying at U.S. academic institutions for possible revocation.

Additionally, the Executive Branch should engage in international negotiations to establish a legally binding international standard for laboratory biosafety, to include certification and inspections by an international organization similar to the International Atomic Energy Agency.

Foreign governments facing economic contraction that have entered into agreements under the PRC's Belt and Road Initiative are encouraged to examine bilateral agreement terms. In particular, agreements or memoranda of understanding that promote joint scientific and academic research wherein the Chinese government has access to natural resources, minerals, plant life, and animals unique to the nation state. Agreements that promote adaptation of governing structures that centralize control over all local, municipal, or provincial levels increase the risk of creating national governing structures that manipulate, misinform, misdirect and gaslight their own citizens to protect centralized governing structures.

Foreign governments considering entering into bilateral agreements with the PRC are advised to be aware that based on the information presented within this report, the PRC conducts scientific research without regard for adequate safety protocols in place, in a manner that does not comport with international safety standards, and without adequate assessment of the risks scientific research may pose to the environment, test subjects, or humanity. It is the recommendation of the Committee Minority Staff that such agreements be avoided.

VII. CONCLUSION

The Intelligence Community 90-day review report on the origins of COVID-19, ordered by President Biden, is due no later than August 24, 2021. While based on open source information, it is the hope of Committee Minority Staff that the collection and analysis contained within this addendum, produced at the direction of Ranking Member Michael T. McCaul, will help inform the public debate about the viability of a laboratory accident being the source of SARS-CoV-2. It is vital the public discourse surround the Wuhan Institute of Virology is transparent, honest, and detailed.

It is the opinion of Committee Minority Staff, based on the preponderance of available information; the documented efforts to obfuscate, hide, and destroy evidence; and the lack of physical evidence to the contrary; that SARS-CoV-2 was accidentally released from a Wuhan Institute of Virology laboratory sometime prior to September 12, 2019. The virus, which may be natural in origin or the result of genetic manipulation, was likely collected in the identified cave in Yunnan province, PRC, sometime between 2012 and 2015. Its release was due to poor lab safety standards and practices, exacerbated by dangerous gain-of-function research being conducted at inadequate biosafety levels, including BSL-2. The virus was then spread throughout central Wuhan, likely via the Wuhan Metro, in the weeks prior to the Military World Games. Those games became an international vector, spreading the virus to multiple continents around the world.

It is incumbent on the parties identified in this report to respond to the issues raised herein and provide clarity and any new or additional evidence as soon as possible. As always, Committee Minority Staff stands ready to receive such evidence or testimony that supports or contradicts this report. Until such time as the Chinese Communist Party lifts its self-imposed veil of secrecy, explains its lies regarding the early stages of the pandemic, and provides access to the WIV's archives and sample database, questions will remain as to the origins of SARS-CoV-2 and the COVID-19 pandemic. Until that day, it is incumbent upon the United States and likeminded countries around the world to ensure accountability, and implement the reforms necessary to prevent the CCP's malfeasance from giving rise to a third pandemic during the 21st century.

VII. APPENDIX

Timeline of the WIV Lab Leak and the Start of the COVID-19 Pandemic

April 2012: Six miners working in a copper mine located in a cave in Yunnan province of the PRC fall ill. Between the ages of 30 and 63, the workers presented to a hospital in Kunming with persistent coughs, fevers, head and chest pains, and breathing difficulties." Three of the six died.

Late 2012 – 2015: Researchers from the WIV collect samples from bats in the cave.

2015 - 2017: Shi Zheng-li, Ben Hu, Peter Daszak, and Linfa Wang jointly publish research on the isolation of novel coronaviruses. They conduct gain-on-function research, testing novel and genetically manipulated coronaviruses against mice and other animals expressing human immune systems. At times they collaborate with Ralph Baric.

2018 – 2019: Shi, Hu, and other researchers at the WIV infect transgenic mice and civets expressing human immune systems with unpublished novel and genetically modified coronaviruses.

July 4, 2019: The PRC's Ministry of Science and Technology orders a review of several grants, including grant no. 2013FY113500. This is the grant which funded the collection of hundreds of coronaviruses and bat samples from the cave in Yunnan province.

July 16, 2019: The WIV publishes a tender requesting bids to conduct renovation on the hazardous waste treatment system at the Wuhan National Biosafety Lab (WNBL). The closing date was July 31st.

Late August/Early September 2019: One or more researchers become accidently infected with SARS-CoV-2, which was either collected in the Yunnan cave, or the result of gain-of-function research at the WIV. They travel by metro in central Wuhan, spreading the virus.

September 12, 2019: At 12:00am local time, the Wuhan University issues a statement announcing lab inspections. Between 2:00am and 3:00am, the WIV's viral sequence and sample database is taken offline. At 7:09pm, the WIV publishes a tender requesting bids to provide security services at the WNBL.

September – October 2019: Car traffic at hospitals surrounding the WIV Headquarters, as well as the shuttle stop for the WNBL, show a stead increase before hitting its highest levels in 2.5 years. Baidu search terms for COVID-19 related symptoms increase in a corresponding manner.

Late October – Early November 2019: The international athletes return home, carrying SARS-CoV-2 around the world.

November 21, 2019: A 4-year-old boy from Milan, Italy develops a cough. His samples will later test positive for COVID-19.

November 27, 2019: Samples of wastewater are collected in Brazil that will later test positive for the presence of SARS-CoV-2 RNA.

December 1, 2019: The CCP's first "official" case of COVID-19 become infected.

Late 2019: Major General Chen Wei arrives in Wuhan, taking over the WNBL BSL-4 lab.

Dec. 27, 2019: A Chinese genomic company reportedly sequenced most of the virus in Wuhan and results showed a similarity to SARS. Zhang Jixian, a doctor from Hubei Provincial Hospital of Integrated Chinese and Western Medicine, tells PRC health authorities that a novel disease affecting some 180 patients was caused by a new coronavirus.

Dec. 29, 2019: Wuhan Municipal CDC organized an expert team to investigate after the Hubei Provincial Hospital of Integrated Chinese and Western Medicine and other hospitals find additional cases.

Dec. 30, 2019: Doctors in Wuhan report positive tests for "SARS Coronavirus" to local health officials. Under the 2005 International Health Regulations, the PRC is required to report these results to the WHO within 24 hours. They do not.

Dec. 31, 2019: WHO officials in Geneva become aware of media reports regarding an outbreak in Wuhan and direct the WHO China Country Office to investigate.

Jan. 2020: Linfa Wang meets with collaborators at the WIV, likely including Shi and Hu.

Jan. 1, 2020: Hubei Provincial Health Commission official orders gene sequencing companies and labs who had already determined the novel virus was similar to SARS to stop testing and to destroy existing samples. Dr. Li Wenliang is detained for "rumor mongering."

Jan. 2, 2020: The Wuhan Institute of Virology (WIV) completes gene sequencing of the virus, but the CCP does not share the sequence or inform the WHO. PRC aggressively highlights the detentions of the Wuhan doctors.

Jan. 3, 2020: China's National Health Commission ordered institutions not to publish any information related to the "unknown disease" and ordered labs to transfer samples to CCP controlled national institutions or destroy them.

Jan. 11-12, 2020: After a researcher in Shanghai leaks the gene sequence online, the CCP transmits the WIV's gene sequencing information to the WHO that was completed 10 days earlier. The Shanghai lab where the researcher works is ordered to close.

Jan. 14, 2020: Xi Jinping is warned by a top Chinese health official that a pandemic is occurring.

Jan. 18, 2020: Linfa Wang departs Wuhan.

Jan. 20, 2020: WIV researchers submitted an article claiming that SARS-CoV-2 is natural in origin. The article renames ID4991 as RaTG13 and contained false information about when the genomic sequence for the virus was obtained.

Jan. 23, 2020: The CCP institutes a city-wide lockdown of Wuhan. However, before the lockdown goes into effect, an estimated 5 million people leave the city.

Last Week of January 2020: Daszak and other outside experts edit a letter to be sent by the Presidents of the National Academies of Sciences, Engineering, and Medicine to the White House Office of Science and Technology Policy. Daszak pushes for language to address "conspiracy theories."

Jan. 30, 2020: One week after declining to do so, Tedros declares a Public Health Emergency of International Concern.

Late Jan. – Early Feb. 2020: PRC researchers, likely those at the WIV, request Peter Daszak's assistance in responding to suggestions of a lab leak or genetic manipulation of SARS-CoV-2. Daszak helps edit the National Academies of Sciences, Engineering, and Medicine's response to the White House Office of Science and Technology Policy on the origins of COVID-19.

Feb. 3, 2020: The WIV researchers' paper submitted on January 20th is published by *Nature* online.

Feb. 6, 2020 at 12:43:40 am: Daszak sends the draft Lancet statement, which cites the Feb. 3 WIV paper, to Wang, Baric, and others asking them to join as cosigners. Within hours, Wang calls him, informs Daszak that he will not sign, and requests that neither Daszak or Baric sign.

Feb. 6, 2020 (Afternoon): At 3:16pm, Daszak send a High Important email to Baric, forwarding Wang's request, and informing Baric the statement will be "put out in a way that doesn't link it back to our collaboration." At 4:01:22 pm, Baric agrees to not sign the statement.

Feb. 7, 2020: Dr. Li, who first shared the positive SARS test results with his classmates via WeChat, dies from COVID-19.

Feb. 9, 2020: The death toll for COVID-19 surpasses that of SARS.

Feb. 15, 2020: First death from COVID-19 outside of Asia occurs, in France.

Feb. 16, 2020: WHO and PRC officials begin a nine-day "WHO-China Joint Mission on Coronavirus Disease 2019" and travel to the PRC to examine the outbreak and origin of COVID-19. Many team members, including at least one American, were not allowed to visit Wuhan.

Feb. 18, 2020: Daszak statement is published by the *Lancet* online, which references the letter from the U.S. National Academies of Sciences, Engineering, and Medicine he helped write and the WIV's February 3rd paper on the origins of COVID-19. Despite drafting the letter, Daszak is not listed as the corresponding author.

Feb. 25, 2020: For the first time, more new cases are reported outside of PRC than within.

Feb. 26, 2020: The WHO-China Joint Mission issues its findings, praising the PRC for its handling of the outbreak.

Feb. 29, 2020: The first reported COVID-19 death in the United States occurs.

March 11, 2020: The WHO officially declares the COVID-19 outbreak a pandemic after 114 countries had already reported 118,000 cases including more than 1,000 in the United States.

Nov. 17, 2020: As a result of public pressure, Shi, Hu, and other WIV researchers publish an addendum to their February 3rd paper, confirming that RaTG13 was ID4991 collected from the cave in Yunnan, and revealing they collected 293 coronaviruses from the cave between 2012 and 2015.

June 15, 2021: The Presidents of the U.S. National Academies of Sciences, Engineering, and Medicine release a statement saying, "let scientific evidence determine origin of SARS-CoV-2."

June 21, 2021: After public pressure, Daszak updates his public disclosure form for the *Lancet* statement. He does not mention the WIV or that the statement was drafted at the request of PRC researchers.

July 5, 2021: Daszak and 23 of the original 27 authors release an update to their February 2021 statement, walking back their labeling of public debate around the source of the virus as "conspiracy theories."

China Center for Disease and Control Memo on Supplementary Regulations

中国疾控中心处(室)便函

科技处便函〔2020〕16号

关于加强新型冠状病毒肺炎应急响应期间有关科技管理的补充规定

中心直属各单位，机关各处室：

为进一步加强我中心新型冠状病毒肺炎应急响应期间科研管理，根据上级有关文件精神，特制定《加强新型冠状病毒肺炎应急响应期间有关科技管理的补充规定》，请各单位和各处室负责人务必高度重视，层层传达，必须通知到每个人。如有违反有关规定者，将追究单位和违规者的责任。

附件：加强新型冠状病毒肺炎应急响应期间有关科技管理的补充规定

中国疾控中心科技处

2020年2月25日

抄送：高福、李新华、刘剑君、冯子健。

附件

加强新型冠状病毒肺炎应急响应期间有关科技管理的补充规定

根据《国家卫生健康委办公厅关于在重大突发传染病防控工作中加强生物样本资源及相关科研活动管理工作的通知》(国卫办科教函〔2020〕3号)、《科技部办公厅关于加强新型冠状病毒肺炎科技攻关项目管理有关事项的通知》等文件精神，为有力抗击新型冠状病毒肺炎(简称“新冠肺炎”)疫情，严格规范科研管理，进一步加强科研管理制度的落实，现对《加强新型冠状病毒感染的肺炎应急响应期间有关科技管理规定》(中疾控科技便函〔2020〕128号)制定本补充规定。

一、坚持国家和人民利益至上，以做好新冠肺炎疫情防控为首要任务。疫情应急响应期间，要集中优势力量，分清轻重缓急，将主要精力放在疫情防控中，把论文“写在祖国大地上”，把研究成果应用到战胜疫情中，在疫情防控任务完成之前不应将精力放在论文发表上。

二、开展新冠肺炎疫情相关科研项目，必须经科技组/科技处进行初审，根据研究内容组织专家进行科学论证和伦理审查，必要时提请应急领导小组或国家卫生健康委科教司审批。上级委托的科研项目必须经科技组/科技处请示应急领导小组审定并备案。

三、任何人不能以个人或研究团队名义擅自向其他机构和个人提供新冠肺炎疫情相关信息，包括数据、生物标本、病原体、培养物等。

四、在发表与新冠肺炎疫情相关的论文和成果前，必须先报科技组/科技处初审，必要时提请应急领导小组或国家卫生健康委科教司审批。

未经科技组/科技处审核的已投稿的论文，尽快撤稿并执行本规定。

五、科研项目进展报告原则上按月报科技组/科技处，或根据上级要求的时限进行报告。

六、要严格遵循医学伦理、科研诚信和学风建设等相关规定。

七、有违反上述规定者，依纪依法依规进行严肃处理。

八、本规定发布之日执行，由科技组/科技处解释。

中国疾控中心科技处

2020 年 2 月 25 日

Memo to the Offices of the Chinese Center for Disease Control and Prevention

Memo (2020) No. 16 of the Science and Technology Department

On the Supplementary Regulations on Strengthening the Management of Science and Technology During the Emergency Response to the Novel Coronavirus Pneumonia

All units and offices directly under the center:

In order to further strengthen scientific research management in our center during the emergency response to the novel coronavirus pneumonia, and in accordance with the spirit of relevant documents issued by the higher authorities, the "Supplementary Regulations on Strengthening the Management of Science and Technology During the Emergency Response to the Novel Coronavirus Pneumonia" has been formulated. Every unit and office, please attach great importance to it and spread it through all levels - everyone must be notified. In case of any violation of relevant regulations, the offender and their unit will be held accountable.

Attachment: Supplementary Regulations on Strengthening the Management of Science and Technology During the Emergency Response to the Novel Coronavirus Pneumonia

Chinese Center for Disease Control and Prevention

February 25, 2020

CC: Gao Fu, Li Xinhua, Liu Jianjun, Feng Zijian.

Annex

Supplementary Regulations on Strengthening the Management of Science and Technology During the Emergency Response to the Novel Coronavirus Pneumonia

According to the spirit of the "Notice of the General Office of the National Health Commission on Strengthening the Management of Biological Sample Resources and Related Scientific Research Activities during the Prevention and Control of Major Infectious Diseases" (National Health Commission Science and Technology Memo [2020] No. 3), the "Notice of the General Office of the Ministry of Science and Technology on Strengthening the Management of New Coronavirus Pneumonia Science and Technology Research Projects" and other documents, and in order to effectively combat the new coronavirus pneumonia ("COVID-19") epidemic, to strictly standardize scientific research management, and to further strengthen the implementation of scientific research management systems, these supplementary "Regulations on Strengthening the Management of Science and Technology During the Emergency Response to the Novel Coronavirus Pneumonia" (Chinese Center for Disease Control Science and Technology Memo [2020] No. 128) have been formulated.

1. Prioritize the interests of the country and the people and take the prevention and control of the COVID-19 epidemic as the primary task. During the emergency response against the epidemic, we must concentrate our forces, distinguish our priorities, focus our main energies on controlling the epidemic, write papers "on the land of the motherland", apply research results to the fight against the epidemic, and not focus on publishing papers until the epidemic is under control.

2. The launch of scientific research projects related to the COVID-19 epidemic must undergo preliminary review by the Science and Technology Group/Department. According to the research subject, experts should be organized to conduct scientific and ethical reviews, and, if necessary, the project must be submitted to the emergency

leading group or the Department of Science and Education of the National Health Commission for approval. The research projects authorized by higher authorities must be examined and approved by the emergency leading group via the Science and Technology Group/Department and be kept on record.

3. No one can, under their own name or in the name of their research team, provide other institutions and individuals with information related to the COVID-19 epidemic on their own, including data, biological specimens, pathogens, culture, etc.

4. Before publishing papers and research results related to the COVID-19 epidemic, you must first report them to the Science and Technology Group/Department for preliminary review, and if necessary, submit it to the Emergency Leading Group or the Department of Science and Education of the National Health Commission for approval.

Papers that have been submitted but not yet reviewed by the Science and Technology Group/Department should be withdrawn as soon as possible and redone according to these regulations.

5. In principle, progress reports on scientific research projects should be reported to the Science and Technology Group/Department on a monthly basis, or according to the time period stipulated by higher authorities.

6. Strictly follow relevant regulations on medical ethics, scientific research integrity and academic spirit.

7. Anyone who violates the above regulations shall be dealt with severely in accordance with discipline, laws and regulations.

8. The date of the implementation of this regulation will be explained by the Science and Technology Group/Department.

Chinese Center for Disease Control and Prevention

February 25, 2020

JCPM Confidential Notice on the Standardization of the Management of Publication of Novel Coronavirus Pneumonia Scientific Research

国务院应对新型冠状病毒肺炎疫情联防联控机制科研攻关组

关于规范新冠肺炎科研攻关成果信息发布管理的通知

国务院应对新型冠状病毒肺炎疫情联防联控机制科研攻关组成员单位办公厅(室)，有关单位：

为深入贯彻国务院应对新型冠状病毒肺炎疫情联防联控机制(以下简称国务院联防联控机制)会议的有关要求，切实规范科研攻关成果信息发布管理，现就有关事项通知如下。

一、全面加强科研攻关成果信息发布管理

按照“依法依规、科学客观、归口管理、精准发布”的原则，把新冠肺炎治疗药物、疫苗、病毒溯源、病毒传播途径、检测试剂等各类疫情防控科研成果信息的发布工作，纳入国务院应对新型冠状病毒肺炎疫情联防联控机制科研攻关组(以下简称科研攻关组)的统一部署。科研攻关组统筹协调科研应急攻关成果信息发布，指导、协调各地各单位科研成果信息发布。

二、建立规范的科研攻关成果信息发布机制

科研攻关组各成员单位及时汇总本单位、本系统科研攻关成果信息，就发布内容、发布形式进行审核把关，并及时报科研攻关组批准。科研攻关组按业务归口组织各专班负责对发布内容、发布形式提出专业性审核意见，必要时组织专家论证。科研攻关组同意后，发布单位应根据工作需要选择新闻发布会、官方网站、政务新媒体、新闻媒体等平台发布，并通报国务院联防联控机制宣传组、科研攻关组。原则上，新冠肺炎科研成果信息首发采用官方权威发布形式。舆论专班加强与宣传组沟通，结合舆情动态和社会关切，强化对科研成果信息发布的指导。

三、严格要求各科研单位做好科研成果信息发布

联防联控机制科研攻关组各成员单位要按照归口管理原则，严格本单位本系统相关科研成果信息的发布审批程序，加强对本单位本系统归口管理的高等院校、研究机构、企业的管理，将本通知要求传达至从事新冠肺炎研究的各相关单位。各成果信息发布单位是发布内容的第一责任人，要综合考虑实际工作进展、疫情防治态势、社会关切问题、预期发布成效等方面，精准确定发布内容，合理引导社会预期。各高等院校、研究机构、医疗机构、企业及其人员在疫情防控期间，未经审批不得擅自发布疫情防控相关科研成果信息。在中华医学会平台交流的论文仍按原备案机制办理。

四、加强科研攻关成果信息发布工作统筹

疫情防控期间，各地各单位要认真贯彻落实习近平总书记关于疫情防控工作的一系列重要指示精神，进一步强化大局意识、责任意识，加强审核把关，主动沟通协调，形成新冠肺炎科研成果信息发布全国“一盘棋”格局。重要敏感科研成果信息要反复核实，把握不准的要及时按程序向科研攻关组及相关部门请示。

五、强化监督问责

对未按规定程序报批，发布未经证实的虚假科研成果信息，造成严重不良社会影响的，要追究责任。

联系人：赵 婧，[redacted]、[redacted]

吴远高，[redacted]、[redacted]

传真：[redacted]，联系邮箱：[redacted]

国务院应对新型冠状病毒肺炎
疫情联防联控机制科研攻关组
（代章）
2020 年 3 月 3 日

(此件不公开)

抄送：国务院联防联控机制宣传组。

科学技术部办公厅　　2020 年 3 月 3 日印发

Joint Prevention and Control Mechanism of the State Council in Response to the Novel Coronavirus Pneumonia Scientific Research Group

Notice on the Standardization of the Management of Publication of Novel Coronavirus Pneumonia Scientific Research

To the Joint Prevention and Control Mechanism of the State Council in Response to the Novel Coronavirus Pneumonia member work units and offices, and other relevant work units:

In order to thoroughly implement relevant requirements from the meeting of the Joint Prevention and Control Mechanism of the State Council in Response to the Novel Coronavirus Pneumonia (hereinafter referred to as the "Joint Prevention and Control Mechanism of the State Council"), and to effectively standardize the management of the publication of scientific research, the following is issued below.

1. Comprehensively strengthen the management of publication of scientific research

In accordance with the principles of "following laws and regulations, being scientific and objective, centralized management, and precise publications", all publication work on epidemic prevention research and information related to COVID-19, including medication, vaccines, virus origins, virus transmission routes, testing reagents, etc. will be taken over by the Joint Prevention and Control Mechanism of the State Council's scientific research group (hereinafter referred to as "the scientific research group") for coordinated deployment. The scientific research group will coordinate the publication of information on emergency scientific research, and guide and coordinate the publication of information on scientific research by all work units in all locations.

2. Establish a standardized publication mechanism for scientific research

Each member work unit of the scientific research team will gather scientific research information within their own unit and systems, review and check the content and form of its publication, and report it to the scientific research team for approval in a timely manner. The scientific research group's dedicated teams of professionals and various experts are responsible for reviewing the publication's content and format and giving expert opinions, and when necessary, arranging expert assessment. After the scientific research group approves, the publishing work unit should, according to work requirements, arrange publication via press conferences, official websites, state social media, news media and other platforms, and notify the propaganda and scientific research teams of the Joint Prevention and Control Mechanism of the State Council. In principle, COVID-19 scientific research should be published first in the form of an official authoritative publication. The special group on public opinion should strengthen communication with the propaganda team, take into account the trend of public opinion and social concerns, and strengthen guidance of the publication of scientific research and information.

3. Strictly require all scientific research units to do a good job on the publication of scientific research

The member work units of the scientific research team of the Joint Prevention and Control Mechanism shall follow the principle of centralized management, strictly enforce their own system's publication approval procedures for relevant scientific research, strengthen the management of universities, research institutions, and enterprises under the centralized management of their work unit systems, and communicate the requirements of this notice to all relevant units engaged in research on COVID-19. The publishing work unit is the one primarily responsible for the research content they publish, and they must consider, in a comprehensive manner, the research progress, the epidemic prevention and control situation, societal concerns, the consequences of publication, and various other issues. They must ensure the accuracy of the published content and guide societal expectations in a reasonable manner. During the period of epidemic prevention and control, all universities, research institutions, medical institutions, enterprises and their staff shall not publish information on scientific research related to epidemic prevention and control without approval. Papers exchanged on the Chinese Medical Association

四、加强科研攻关成果信息发布工作统筹

疫情防控期间，各地各单位要认真贯彻落实习近平总书记关于疫情防控工作的一系列重要指示精神，进一步强化大局意识、责任意识，加强审核把关，主动沟通协调，形成新冠肺炎科研成果信息发布全国“一盘棋”格局。重要敏感科研成果信息要反复核实，把握不准的要及时按程序向科研攻关组及相关部门请示。

五、强化监督问责

对未按规定程序报批，发布未经证实的虚假科研成果信息，造成严重不良社会影响的，要追究责任。

联系人：赵 婧，[redacted]、[redacted]

吴运高，[redacted]、[redacted]

传真：[redacted]、联系邮箱：[redacted]

国务院应对新型冠状病毒肺炎
疫情联防联控机制科研攻关组
（代章）
2020 年 3 月 3 日

(此件不公开)

抄送：国务院联防联控机制宣传组。

科学技术部办公厅　　2020 年 3 月 3 日印发

February 6, 2020, Email at 12:43am from Peter Daszak to Ralph Baric, Linfa Wang, and Others Inviting Them to Sign the Statement

A Statement in support of the scientists, public health and medical professionals of China — Feb 6, 2020 12:43:40 AM EST

A Statement in support of the scientists, public health and medical professionals of China

Subject: A Statement in support of the scientists, public health and medical professionals of China
From: Peter Daszak [redacted]
To: Ralph Baric [redacted]
Cc: [redacted]
Sent: February 6, 2020 12:43:40 AM EST
Attachments: Statement of support_2019nCoV China_Final.docx

A Statement in support of the scientists, public health and medical professionals of China

Feb 6, 2020 12:43:40 AM EST

Dear Ralph, Linda, Jim, Rita, Linfa and Hume,

I've been following the events around the novel coronavirus emergence in China very closely and have been dismayed by the recent spreading of rumors, misinformation and conspiracy theories on its origins. These are now specifically targeting scientists with whom we've collaborated for many years, and who have been working heroically to fight this outbreak and share data with unprecedented speed, openness and transparency. These conspiracy theories threaten to undermine the very global collaborations that we need to deal with a disease that has already spread across continents.

We have drafted a simple statement of solidarity and support for scientists, public health and medical professionals of China, and would like to invite you to join us as the first signatories. If you agree, we will send this letter to a group of around half-a-dozen other leaders in the field and then disseminate this widely with a sign-up webpage for others to show their support by signing up to its language. I will then personally present this at my plenary during the ICID 2020 conference in Malaysia in two weeks, with the goal of also getting widespread attention in SE Asia to our support for the work that our colleagues in China are undertaking.

I sincerely hope you can join us. Please review the letter, and let me know if you are willing to join Billy Karesh and myself as co-signatories. Also, please confirm your title and affiliation that will be shown in the letter. We plan to make circulate this widely to coincide with a letter from the Presidents of the US National Academies of Science, Engineering, and Medicine, which will likely be released tomorrow or Friday.

Thank you for your consideration and support of the scientific and public health community around the world!

Cheers,

Peter

Peter Daszak
President

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EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science we develop solutions that prevent pandemics and promote conservation.

Statement in Support of the Scientists, Public Health, and Medical Professionals of China Combating the Novel Coronavirus Outbreak

We, the undersigned, are scientists who have followed the emergence of 2019-nCoV, and are deeply concerned about its global impact on people's health and well-being. We have watched as the scientists, public health and medical professionals of China have worked heroically to rapidly identify the pathogen behind this outbreak, put in place significant measures to reduce its impact, and share their results transparently with the global health community. We sign this statement in solidarity with all scientists, public health, and medical professionals in China who continue to save lives and protect global health during the challenge of this novel coronavirus outbreak. We want you to know that we are all in this together, with you in front of us on the battlefield against the novel coronavirus.

The rapid, open and transparent sharing of data on 2019-nCoV is now being threatened by rumors and misinformation around the origins of this outbreak. We stand together to strongly condemn conspiracy theories suggesting that 2019-nCoV does not have a natural origin. Scientific evidence overwhelmingly suggests that this virus originated in wildlife, as have so many other emerging diseases (*1-4*). This is further supported by a letter from the Presidents of the US National Academies of Science, Engineering, and Medicine, and by the scientific communities they represent (INSERT REF). Conspiracy theories will do nothing but create fear, rumors, and prejudice that jeopardize our global collaboration in the fight against this virus. We need to prioritize scientific evidence and unity over misinformation and conjecture now. We want you all to know that **we stand with you**, the science and health professionals of China, in your fight against this virus.

We invite others to join us in supporting the scientists, public health, and medical professionals of Wuhan and across China. Stand with our colleagues on the front-line!

Please add your name in an act of support by going to (INSERT LINK HERE).

A Statement in support of the scientists, public health and medical professionals of China

Feb 6, 2020 12:43:40 AM EST

Signatories

Dr. Peter Daszak, President, EcoHealth Alliance
Dr. Jim Hughes, Professor Emeritus, Emory University
Dr. Rita Colwell, former Director of National Science Foundation
Dr. Ralph Baric, Professor, The University of North Carolina, Chapel Hill
Dr. Linda Saif, Distinguished University Professor, The Ohio State University
Dr. Billy Karesh, Executive Vice President, EcoHealth Alliance
Dr. Linfa Wang, Professor, Duke-NUS Medical School
Dr. Hume Field, Honorary Professor, The University of Queensland

References

1. P. Zhou *et al.*, A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, (2020).
2. R. Lu *et al.*, Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet*, (2020).
3. N. Zhu *et al.*, A Novel Coronavirus from Patients with Pneumonia in China, 2019. *New England Journal of Medicine*, (2020).
4. L. Ren *et al.*, Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. *Chin Med J Epub ahead of print*, (2020).

February 6, 2020, Email at 3:16pm from Peter Daszak to Ralph Baric Relaying Wang's Request Not to Sign the Statement

To: Peter Daszak [redacted]
Cc: [redacted]
From: Baric, Ralph [redacted]
Sent: Thur 2/6/2020 4:01:22 PM (UTC-05:00)
Subject: RE: No need for you to sign the "Statement" Ralph!!

I also think this is a good decision. Otherwise it looks self-serving and we lose impact. ralph

From: Peter Daszak [redacted]
Sent: Thursday, February 6, 2020 3:16 PM
To: Baric, Ralph S [redacted]
Cc: [redacted]
Subject: No need for you to sign the "Statement" Ralph!!
Importance: High

I spoke with Linda last night about the statement we sent round. He thinks, and I agree with him, that you, me and him should not sign this statement, so it has some distance from us and therefore doesn't work in a counterproductive way.

Jim Hughes, Linda Saif, Hume Field, and I believe Rita Colwell will sign it, then I'll send it round some other key people tonight. We'll then put it out in a way that doesn't link it back to our collaboration so we maximize an independent voice.

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance
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Twitter: @PeterDaszak

EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science we develop solutions that prevent pandemics and promote conservation.

February 8, 2020, Email at 8:52pm from Peter Daszak to Rita Colwell Alleging WIV Researchers Requested the Statement

From: Peter Daszak [redacted]
Sent: Saturday, February 08, 2020 8:52 PM
To: Rita Colwell [redacted]
Cc: Rita Colwell [redacted]
Subject: RE: coronavirus statement
Importance: High

Hi Rita,

I appreciate your comments and I think at this point, that work has already been done, with >50 genomes published from 12 countries, and phylogenetic analyses published by authors from multiple countries. I've tried to make this a bit more clear, and have edited the letter as follows, so it hopefully addresses your comments:

1) I've inserted a reference to the GISAID webpage where 57 (to date) full genome sequences of 2019-nCoV from 12 countries are published and analyzed

2) I've inserted a reference to the CDC webpage on 2019-nCoV which makes the following statement, completely in concurrence with our letter:
"2019-nCoV is a betacoronavirus, like MERS and SARs, both of which have their origins in bats. The sequences from U.S. patients are similar to the one that China initially posted, suggesting a likely single, recent emergence of this virus from an animal reservoir."

In addition, please note that we will not be referring to this as a 'petition' but as a 'statement in support of' – this is in the title and will be in all materials we send out. This is to avoid the appearance of a political statement – this is simply a letter from leading scientists in support of other scientists and health professionals who are under serious pressure right now.

I hope you are willing to sign on to this - your voice will be very influential, particularly in keeping these critical bridges open between the USA and China. You should know that the conspiracy theorists have been very active, targeting our collaborators with some extremely unpleasant web pages in China, and some have now received death threats to themselves and their families. They have asked for any show of support we can give them.

As soon as we hear back from you we'll get ready to send this to our larger list (attached), but of course if you don't feel comfortable, I'll make sure your name is not associated with this.

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance
460 West 34th Street – 17th Floor
New York, NY 10001

From: Morens, David (NIH/NIAID) [E] [b6] ([b6])
Sent: 6/29/2021 1:27:22 PM
To: Peter Daszak ([b6]) [[b6]]; Keusch, Jerry ([b6]) [[b6]]; Rich Roberts ([b6]) [[b6]]; Peter Hotez ([b6]) [[b6]]
Subject: FW: Global Times, China -- Suspect No.1: Why Fort Detrick lab should be investigated for global COVID-19 origins tracing

You can't make this stuff up…. Oops…. I guess you CAN…

David

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
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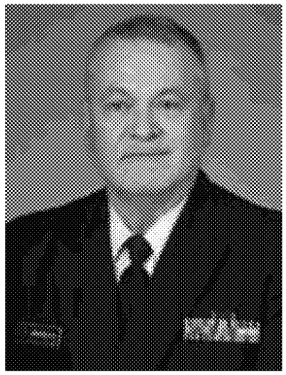
301 496 4409
[b6]



From: Folkers, Greg (NIH/NIAID) [E] b6
Sent: Monday, June 28, 2021 7:13 PM
Subject: Global Times, China -- Suspect No.1: Why Fort Detrick lab should be investigated for global COVID-19 origins tracing

Suspect No.1: Why Fort Detrick lab should be investigated for global COVID-19 origins tracing

Why US labs need to be investigated for COVID-19 origins

By Fan Lingzhi, Huang Lanlan and Zhang Hui Published: 2021/06/28 01:30:00

The lab-leak theory, that COVID-19 was leaked from a laboratory, has once again caused a clamor since the beginning of this year, months after the argument was thrown into the trash can of conspiracy theories by an overwhelming number of scientists.

Observers found that things only get more complicated when the origins of the coronavirus - an already difficult scientific issue - is entangled in political manipulation tricks. Combing through more than 8,000 pieces of news reports related to the lab-leak theory, the Global Times found that as many as 60 percent of the coverage was from the US alone.

It is worth noting that many media outlets in the US-led Western world, which hyped the lab-leak theory, are only willing to focus on the Chinese labs though they have been thoroughly investigated by the World Health Organization (WHO), while turning a blind eye to the more suspicious American biological research institutions, such as the infamous US Army Medical Research Institute of Infectious Diseases (USAMRIID) at Fort Detrick, Maryland.

The USAMRIID was temporarily shut down in 2019 after a Centers for Disease Control and Prevention (CDC) inspection. Although this mysterious lab reported the reason for the closure as "ongoing infrastructure issues with wastewater decontamination," the explanation was not persuasive enough. The Global Times found that the lab's failure to control toxins seemed to have alarmed the Countering Weapons of Mass Destruction related institutions in the US.

Resurgence of lab-leak theory

A joint study into the origins of COVID-19 by Chinese experts and the WHO in March dismissed the "lab-leak" conspiracy theory. More evidence pointed to the fact that the virus had probably jumped from bats to humans via another intermediary animal, and it was "extremely unlikely" that it leaked from a lab, the study report said.

Nonetheless, the lab-leak theory has not disappeared; instead, especially from the beginning of May, it has been largely promoted by some US politicians and media outlets as a "plausible science." In an article published on Bulletin of the Atomic Scientists on May 5, without any evidence, science writer Nicholas Wade claimed that "proponents of lab escape can explain all the available facts about SARS2 considerably more easily than can those who favor natural emergence."

Days later, The Wall Street Journal reported on May 23 that three researchers at Wuhan Institute of Virology (WIV) "became sick enough in November 2019 that they sought hospital care," and they had "symptoms consistent with both Covid-19 and common seasonal illness." The WSJ report quoted a "previously undisclosed US intelligence report."

On May 26, President Biden stated that he had ordered the US intelligence community to "redouble" its efforts to investigate the origins of COVID-19. The US national security adviser Jake Sullivan even claimed on June 20 that China

will face "isolation in the international community" if it doesn't cooperate with a further probe into the origin of the COVID-19 pandemic, Bloomberg reported that day.

Research personnel work inside the bio-level 4 lab at the USAMRIID at Fort Detrick on September 26, 2002. Photo: AFP

Pressure from politicians and the media seems to have affected some authoritative medical scientists in the US, including Director of the US National Institute of Allergy and Infectious Diseases (NIAID), Anthony Fauci. On May 11, after Rand Paul, a Republican to the Senate, accused Fauci of helping the Wuhan lab "create" the virus, Fauci strongly denied the accusation but said he is "fully in favor of any further investigation of what went on in China."

This sudden change in attitude of some US experts is due to the political pressure they have received, a Chinese virologist told the Global Times. "Western media like to ask the experts misguiding questions, like, 'is (lab leak) absolutely impossible?'" said the virologist who requested anonymity.

It's very difficult for experts to answer a question like that, as the possibility, although very little, still exists, the virologist said. "All they can say is, 'it's possible,'" he told the Global Times. Actually, most experts usually add "but it's highly unlikely" after "it's possible," but the media only presents the part which confirms their own bias, he said.

Big data shows the US is pushing the narrative of the COVID-19 lab-leak theory. Among the 8,594 pieces of news report related to "lab leak" that database GDELT collected since 2020, 5,079 were from the US, accounting for 59 percent. Following the US was the UK (611 pieces) and Australia (597 pieces). Almost all the coverage targeted the WIV lab.

While the US is solely focused on Chinese labs, the US seldom pays attention to the fault in its own domestic labs, some of which have even triggered virus-related accidents before. According to an August 2020 article by ProPublica, an independent newsroom that produces investigative journalism, the University of North Carolina at Chapel Hill reported 28 lab incidents involving genetically engineered organisms to safety officials at the National Institutes of Health between January 2015 and June 2020. "Six of the incidents involved various types of lab-created coronaviruses," ProPublica said in the article. "Many were engineered to allow the study of the virus in mice."

Weirdly, very few US mainstream media outlets have raised the question whether there is the possibility that COVID-19 was leaked from US labs, said the Chinese virologist. "They dare not ask that," he said.

In an article published on the independent political blog site Moon of Alabama on May 27, the author pointed out that some Westerners' hyping of the Wuhan lab leak conspiracy is similar to the trick the US played in pushing the Iraq War in 2002 - the US claimed "Saddam Hussein will soon have nuclear weapon," which was "obvious nonsense," the author said.

"The 'lab leak' theory is similar to the WMD claim - evidence-free speculation long promoted by a neoconservative leaning administration that was extremely hostile to the 'guilty' country in question," said the author.

The lab-leak theory, therefore, "isn't just about an implausible, evidence free tale of a SARS-CoV-2 lab escape," the author noted. "It is a campaign launched to depict China as an enemy of humankind."

Intl concerns on US bio-labs

The US has many bio-labs in 25 countries and regions across the Middle East, Africa, Southeast Asia and the former Soviet Union states, with 16 in Ukraine alone. Some of these labs have seen large-scale outbreaks of measles and other dangerous infectious diseases, according to media reports.

Outside view of the bio-level 3 and 4 lab at the USAMRIID at Fort Detrick on September 26, 2002. Photo: AFP

The international community has frequently expressed concern over US' biological militarization activities in other countries.

In October 2020, Deputy Chairman of the Security Council of Russia, Dmitry Medvedev, said that the US research activities in bio-labs in members of the Commonwealth of the Independent States have caused grave concern. The US not only builds bio-labs in these countries, but also tries to do so in other places across the world. However, its research lacks transparency and runs counter to the rules of the international community and international organizations.

Anatoly Tsyganok, a corresponding member of the Russian Academy of Military Sciences and associate professor of Faculty of World Politics at Lomonosov Moscow State University, told the Global Times that biological and bacteriological weapons tests on US territory are prohibited by the US Congress. He said that the US military has been and is still carrying out tests of biological and bacteriological weapons in Georgia.

This is done under the guise of providing sick people with various therapeutic vaccines conducted by the US military and American private contractors at the Richard Lugar Center for Public Health Research, Tsyganok said. Related tests have been exposed by various media outlets.

In December 2015, 30 patients at the research center who were being treated for hepatitis C died. Twenty-four of them died on the same day, and their cause of death was listed as "unknown," according to Tsyganok and Russia news outlet.

Residents of neighborhoods around these labs often complain about health problems.

Bulgarian journalist Dilyana Gaytandzhieva published a story about the Lugar center in early 2018. In her interviews for the report, most residents who lived nearby the labs complained of headaches, nausea and high blood pressure. They also said there was black smoke coming from the lab.

USA Today reported that since 2003, hundreds of incidents involving accidental contact with deadly pathogens occurred in US bio-labs at home and abroad. This may cause the direct contacts to be infected, who can then spread the virus to communities and start an epidemic.

A member of the Russian Academy of Sciences, Armais Kamalov said in an interview with TASS in early June that development of genetically-engineered viruses as biological weapons should be subject to the same worldwide ban as the testing of nuclear weapons. He mentioned US labs in Georgia and Armenia as reference.

"There are a lot of labs, which are bankrolled today by the United States Department of Defense. It's no secret that they are in Georgia, Armenia and other republics. It's surprising that access to such labs is off-limits, and we don't understand what they are doing there," he said.

What had happened in July 2019?

The terrible safety records of American biological labs around the world shows a possibility of a virus escaping from an American lab. Many point to the shutdown of Fort Detrick lab in July 2019.

In July 2019, six months before the US reported its first COVID-19 case, Army laboratory at Fort Detrick that studies deadly infectious material like Ebola and smallpox was shut down after the US Centers for Disease Control and Prevention issued a cease-and-desist order. CDC officials refused to release further information after citing "national security reasons."

The USAMRIID in Fort Detrick said in August 2019 that the shutdown was because the center did not have "sufficient systems in place to decontaminate wastewater" from its highest-security labs, the New York Times reported.

What exactly happened at Fort Detrick in the summer of 2019? Some US media previously turned to CDC to get answers, but many key contents in the report had been redacted.

In early June, a Virginia-based Twitter user got the CDC documents on the inspection of the Fort Detrick under The Freedom of Information Act (FOIA). Global Times found that most of the documents were emails between CDC officials at various departments and USAMRIID from 2018 to 2019. Although some of the emails were covered by an ABC-affiliated television station in Washington, the report did not catch much attention.

The emails revealed several violations at the Fort Detrick lab during CDC's inspections in 2019. Four of which were labeled serious violations.

One of these serious violations, the CDC said, was one inspector who entered a room multiple times without the required respiratory protection while other people in that room were performing procedures with a non-human primate on a necropsy table.

This deviation from entity procedures resulted in a respiratory occupational exposure to select agent aerosols, the CDC said.

In another serious violation, the CDC said the USAMRIID had "systematically failed to ensure implementation of biosafety and containment procedures commensurate with the risks associated with working with select agents and toxins."

Other violations included lack of proper waste management where waste wasn't transported in a durable leak proof container, which creates the potential for spills or leaks.

The CDC documents show that it sent a letter of concern to USAMRIID, which resulted in a temporary shutdown of the Fort Detrick lab in 2019.

In an email on July 12, 2019, the CDC said the USAMRIID reported two breaches of containment on July 1 and July 11, 2019, and this demonstrated a "failure of USAMRIID to implement and maintain containment procedures sufficient to contain select agents or toxin generated by BSL-3 and BSL-4 laboratory operations."

"Effective immediately, USAMRIID must cease all work involving select agents and toxins in registered laboratory areas until the root cause investigation has been conducted for each incident and the results have been submitted to FSAP for review," the CDC said.

The FSAP (Federal Select Agent Program) is jointly comprised of the Centers for Disease Control and Prevention's Division of Select Agents and Toxins and the Animal and Plant Health Inspection Service's Division of Agricultural Select Agents and Toxins. The program oversees the possession, use and transfer of biological select agents and toxins, which have the potential to cause a severe threat to the public, animal or plant health or to animal or plant products. Common examples of select agents and toxins include the organisms that cause anthrax, smallpox, and the bubonic plague.

Three days later, the Fort Detrick replied the email by saying that it had submitted messages in response to the immediate action, but the messages were deliberately blotted out.

The message was submitted by a director for Strategic Studies (Countering Weapons of Mass Destruction) at the USAMRIID whose name was also blotted out.

The Fort Detrick's public statement released in August 2019 said the shutdown was due to problems in decontaminating wastewater. But it's not clear whether the statement was consistent with CDC's inspection results.

The management of such high-level labs in general must be very strict with regular inspections. Various systems should be able to ensure that no potential risks can occur, and equipment failure and wastewater leakage certainly should not occur, a Chinese scientist from the WHO-China virus origins tracing team who requested anonymity told the Global Times.

The wastewater problems revealed major loopholes in the management at the Fort Detrick lab, and one has to wonder what else was leaked with the mismanaged wastewater.

"Some highly pathogenic pathogens in the laboratory were likely released. And the US military never told the public about what they were doing," the scientist said.

It is highly likely that researchers at Fort Detrick may have been infected accidentally but showed no obvious symptoms. In this way they could have brought the virus to the outside world, the scientist said.

"Under the circumstances of no obvious symptoms, 9 of the 10 individuals may not have known that they were infected and it's possible that more than 90 percent of the transmission routes had been lost when the virus was finally detected. This is also why the tracing of virus origins is difficult to conduct," he said, noting only serological survey on a large scale could find some of the early infections.

Why not open Fort Detrick lab

Several virologists and analysts interviewed by the Global Times urged the Fort Detrick lab to open its doors for an international investigation, since international experts have already visited the Wuhan Institute of Virology.

Many Western politicians and media outlets pinned the blame of the pandemic on Wuhan, saying that Wuhan was where the virus was first detected and where the virus came from despite mounting evidence that it's not the case.

In a recent example in June, a research study run by the National Institutes of Health's All of Us Research Program found evidence of COVID-19 infections in the US as early as December 2019, weeks before the first documented infection in the country.

Wuhan recorded the earliest COVID-19 symptoms from a patient on December 8, 2019.

When asked to give more details on the study, a media person with the All of Us Research Program told the Global Times that the program "has nothing further to add" from the information it had already released.

As for why the virus was first detected in Wuhan, the anonymous scientist said that the virus was difficult to be detected at an early stage, especially in autumn and winter with more cold cases. And it would not attract attention until a large number of people were infected. That's what happened in densely populated Wuhan, the scientist said.

China's public health system is very sensitive especially after the SARS outbreak in 2003, but this is not always the case abroad, especially when the population density is low and the virus does not spread so fast, the expert said.

"The novel coronavirus was first discovered by three Chinese companies at the same time. It is very simple to detect these things, and China has lots of such third-party companies with strong medical detection ability," he said.

Without going back to earlier serum samples elsewhere now, it is going to be difficult to find the source of the virus. The retrospective studies that have been done in China have not found any evidence. It's important for the world to work together now to sort through the evidence and do early serological investigations where necessary, he said.

Zeng Guang, former chief epidemiologist of the Chinese Center for Disease Control and Prevention, told the Global Times that laboratory leak is easy to identify, as infections are bound to show signs, whether it is an operational problem or an infection of a lab staff.

The WHO experts assessed the lab-leak hypothesis when they visited Wuhan and found no evidence, and the speculation on its possibility in a Wuhan lab should have ended by now. In the meantime, we should put a question mark on other hypotheses, such as other labs around the world, Zeng said.

Zeng said the US is afraid of WHO's inspection in the same way it was done in China, Zeng said.

The US, the only country obstructing the establishment of a Biological Weapons Convention (BWC) verification mechanism, has systematic problems, Zeng said, adding that the US is afraid that the investigation into its labs would lead to more of its dirt being dug out.

Xia Wenxin contributed to this story
CHINA

From: Morens, David (NIH/NIAID) [E] [b6] ([b6])
Sent: 9/22/2021 5:46:46 PM
To: Peter Daszak ([b6]) [b6]; Kessler, Robert [b6] [[b6]]; Keusch, Jerry ([b6]) [b6]
Subject: FW: Newsweek: DARPA Denies Funding Wuhan Institute of Virology Amid Alleged Document Leak

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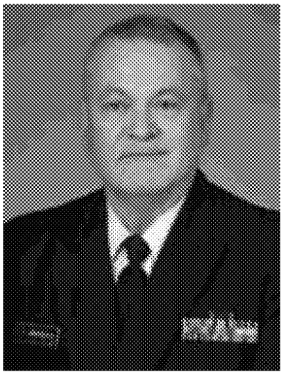

From: Folkers, Greg (NIH/NIAID) [E] [b6]
Sent: Wednesday, September 22, 2021 1:24 PM
Subject: Newsweek: DARPA Denies Funding Wuhan Institute of Virology Amid Alleged Document Leak

DARPA Denies Funding Wuhan Institute of Virology Amid Alleged Document Leak

By Ed Browne On 9/22/21 at 11:46 AM EDT

DARPA, the U.S. advanced research projects agency, has denied funding research activity at the Wuhan Institute of Virology (WIV) after a group released documents allegedly detailing a coronavirus research proposal.

Newsweek cannot confirm the veracity of the DRASTIC group or the existence of the Project DEFUSE documents described. The group says the documents were provided anonymously.

DRASTIC is a group of activists who say they are working towards solving the "riddle" of the origins of the SARS-CoV-2 virus that is behind the COVID pandemic. They say they were given documents by an anonymous source which detail something called "Project DEFUSE."

According to what appear to be funding proposal excerpts published by DRASTIC, Project DEFUSE aimed to reduce the threat of bat-borne coronaviruses through research and was headed by Peter Daszak, president of the U.S.-based research organization EcoHealth Alliance (EHA). It would have run between 2018 and 2022.

DRASTIC states the research proposal would have involved "advanced and dangerous" research into bat coronaviruses in cooperation with the WIV and other facilities, and said the research would qualify as Gain of Function (GoF)—a process that can be used to make viruses more dangerous so that humans can investigate them and improve understanding.

However, DRASTIC said the documents showed that DARPA rejected the DEFUSE proposal in part because of GoF concerns. DRASTIC did not publicly release the actual document it said it had seen.

In a statement to *Newsweek*, DARPA denied funding any activity associated with EHA or the WIV. A spokesman said: "In accordance with U.S. Federal Acquisition Regulations, we are not at liberty to divulge who may have or may not have not submitted a proposal in response to any of the agency's solicitations. Further, information contained within bids is considered proprietary and can only be released by the bidder.

"That being said, DARPA has never funded directly, nor indirectly as a subcontractor, any activity or researcher associated with the EcoHealth Alliance or Wuhan Institute of Virology."

Newsweek has contacted Peter Daszak and EHA for comment. *Newsweek* has also contacted UNC-Chapel Hill, Duke-National University in Singapore, the USGS National Wildlife Health Center (NWHC) and Palo Alto Research Center (PARC), which DRASTIC says are also mentioned in the documents, for comment. *Newsweek* was unable to contact the WIV.

GoF research into coronaviruses has been a hot topic recently, since many are concerned that SARS-CoV-2 could have been accidentally leaked from a lab, sparking the pandemic.

The National Institutes of Health (NIH), for instance, has already denied approving grants that would have supported GoF research on coronaviruses.

Investigation into the origin of SARS-CoV-2 is ongoing. In August, President Joe Biden received a report from the intelligence community into the matter that came back inconclusive. He had ordered the report back in May in the hope of getting closer to a conclusion.

Earlier this year, after the World Health Organization (WHO) completed its initial investigation into the origins of COVID by visiting Wuhan, several nations jointly expressed concerns that the study was "significantly delayed and lacked access to complete, original data and samples."

The study had concluded that the lab leak theory was "extremely unlikely" at the time.

The Wuhan Institute of Virology (WIV), a virus research center in Wuhan, China, seen in February 2021 as a World Health Organization (WHO) investigation team arrive. The facility has become a hot topic amid unconfirmed theories that COVID may have leaked from a lab. Hector Retamal/AFP / Getty

From: Morens, David (NIH/NIAID) [E] [b6]
Sent: 10/21/2021 6:33:08 PM
To: Peter Daszak ([b6]) [b6]; Keusch, Jerry [b6]) [b6]; Kessler, Robert ([b6]) [b6]
Subject: FW: New letter to F Collins

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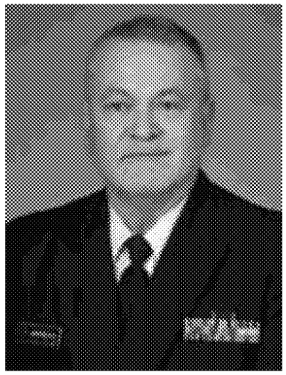

From: Folkers, Greg (NIH/NIAID) [E] b6
Sent: Thursday, October 21, 2021 2:17 PM

To: NIAID OD AM <NIAIDODAM@niaid.nih.gov>
Subject: New letter to F Collins

https://twitter.com/GOPoversight/status/1451249202714054657?s=20

From: Morens, David (NIH/NIAID) [E] [b6 b6]
Sent: 10/6/2021 4:22:36 PM
To: Peter Daszak ([b6]) [b6]; Keusch, Jerry ([b6]) [b6]; Kessler, Robert ([b6]) [b6]
Subject: FW: National Review: Leaked Grant Proposal Confirms Chinese and American Scientists Planned to Create Novel Coronavirus

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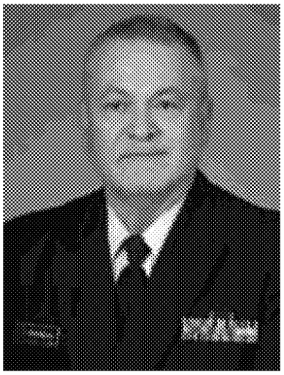

From: Folkers, Greg (NIH/NIAID) [E] b6
Sent: Wednesday, October 6, 2021 11:57 AM

To: NIAID COGCORE <COGCORE@mail.nih.gov>; NIAID OCGR Leg <NIAIDOCGRLeg@mail.nih.gov>; NIAID OD AM <NIAIDODAM@niaid.nih.gov>
Subject: National Review: Leaked Grant Proposal Confirms Chinese and American Scientists Planned to Create Novel Coronavirus

Leaked Grant Proposal Confirms Chinese and American Scientists Planned to Create Novel Coronavirus

By CAROLINE DOWNEY

- October 6, 2021 9:54 AM


Security personnel stand outside Wuhan Institute of Virology in Wuhan, China, February 3, 2021. *(Thomas Peter/Reuters)*

A World Health Organization (WHO) collaborator, who reviewed a coronavirus research grant application unearthed last month, confirmed that the language of the documents suggests American and Chinese scientists planned to collaborate on the creation of a new coronavirus not found in nature.

The grant proposal, obtained by the analysis group DRASTIC last month, was submitted to the U.S. Defense Advanced Research Projects Agency (DARPA) in 2018 by the EcoHealth Alliance, an American research non-profit that planned to collaborate with Chinese scientists at the Wuhan Institute of Virology to create a new virus using the funding.

"We will compile sequence/RNAseq data from a panel of closely related strains and compare full length genomes, scanning for unique SNPs representing sequencing errors," the application states. "Consensus candidate genomes will be synthesised commercially using established techniques and genome-length RNA and electroporation to recover recombinant viruses."

The WHO source explained the procedure and how the brand new virus could still closely resemble the natural viruses it was derived from.

"They would then synthesise the viral genome from the computer sequence, thus creating a virus genome that did not exist in nature but looks natural as it is the average of natural viruses," the individual said. "Then they put that RNA in a cell and recover the virus from it. This creates a virus that has never existed in nature, with a new 'backbone' that didn't exist in nature but is very, very similar as it's the average of natural backbones."

While the grant was never approved, it provides further evidence that American and Chinese scientists were exploring gain-of-function research, in which scientists manipulate existing viruses to make them more transmissible and/or dangerous. Other EcoHealth Alliance grant proposals obtained by the *Intercept* also suggests the group and its Chinese partners were heavily involved in gain-of-function research.

Dr. Anthony Fauci, who leads the NIH's Institute of of Allergies and Infectious Diseases, has repeatedly denied in congressional testimony that any U.S. funding went to gain-of-function research at the Wuhan Institute of Virology.

In an interview with the *Telegraph*, the anonymous WHO source suggested that artificial lab engineering could explain why a close match for Sars-CoV-2 has not yet been identified in nature despite a massive Chinese and international effort to do just that.

"This means that they would take various sequences from similar coronaviruses and create a new sequence that is essentially the average of them. It would be a new virus sequence, not a 100 per cent match to anything," the WHO contact said.

The closest cousin to Sars-CoV-2 that's been found in nature so far is a strain called Banal-52, which shares 96.8 per cent of the genome. However, for a virus to be the direct ancestor of another, the genome should be around a 99.98 percent match, according to the publication.

It was revealed earlier this year that the Wuhan Institute of Virology deleted its main database of samples and viral sequences months before the pandemic erupted. The Chinese government has sequenced the genomes of tens of thousands of animals living in and around Wuhan but has yet to identify the Sars-Cov-2 virus in nature, casting doubt on the natural transmission theory.

"If Sars-CoV-2 comes from an artificial consensus sequence composed of genomes with more than 95 per cent similarity to each other... I would predict that we will never find a really good match in nature and just a bunch of close matches across parts of the sequence, which so far is what we are seeing," the WHO source said.

"The problem is that those opposed to a lab leak scenario will always just say that we need to sample more, and absence of evidence isn't evidence of absence. Scientists overall are afraid of discussing the issue of the origins due to the political situation. This leaves a small and vocal minority of biased scientists free to spread misinformation," he added.

From: Morens, David (NIH/NIAID) [E] [b6 b6]
Sent: 8/11/2021 8:09:41 PM
To: Peter Daszak ([b6]) [b6]; Keusch, Jerry ([b6]) [b6]; Kessler, Robert ([b6]) [b6]
Subject: FW: New Yorker: Fauci Says It Is Safe to Watch YouTube Now That Rand Paul Has Been Suspended

On a lighter note!

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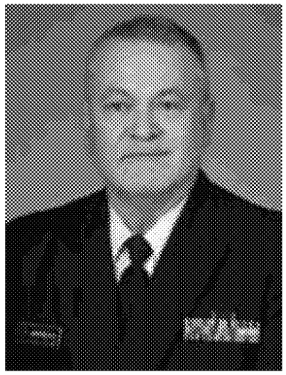
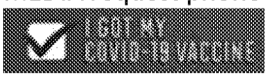


From: Oplinger, Anne (NIH/NIAID) [E] b6
Sent: Wednesday, August 11, 2021 3:54 PM
To: Folkers, Greg (NIH/NIAID) [E] b6; NIAID COGCORE <COGCORE@mail.nih.gov>; NIAID OCGR

Leg <NIAIDOCGRLeg@mail.nih.gov>; NIAID OD AM <NIAIDODAM@niaid.nih.gov>
Subject: RE: New Yorker: Fauci Says It Is Safe to Watch YouTube Now That Rand Paul Has Been Suspended

HAHAHA!
First couple secs of this one funny—didn't watch all—picked at random

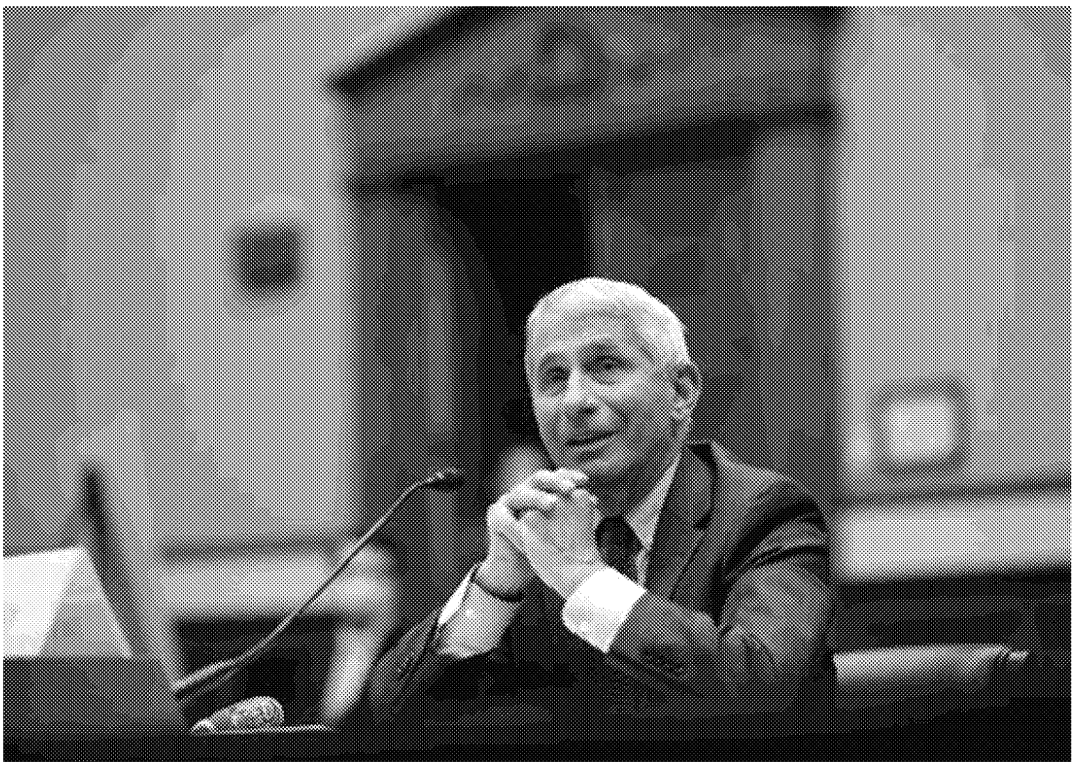
https://www.youtube.com/watch?v=2425wHMiSK0

Anne A. Oplinger
b6
Office of Communications and Government Relations
National Institute of Allergy and Infectious Diseases, NIH
MEDIA request phone 301-402-1663


From: Folkers, Greg (NIH/NIAID) [E] b6
Sent: Wednesday, August 11, 2021 3:15 PM
To: NIAID COGCORE <COGCORE@mail.nih.gov>; NIAID OCGR Leg <NIAIDOCGRLeg@mail.nih.gov>; NIAID OD AM <NIAIDODAM@niaid.nih.gov>
Subject: New Yorker: Fauci Says It Is Safe to Watch YouTube Now That Rand Paul Has Been Suspended

Fauci Says It Is Safe to Watch YouTube Now That Rand Paul Has Been Suspended

By Andy Borowitz



Photograph by Kevin Dietsch / UPI / Alamy

WASHINGTON (The Borowitz Report)—In a new health advisory, the nation's leading epidemiologist, Dr. Anthony Fauci, said that it is "perfectly safe" for Americans to watch YouTube, following news that Senator Rand Paul had been suspended from the platform.

"In the past, I've warned about the health consequences of listening to Rand Paul," he said. "People experience headaches and nausea. Sometimes, they feel like their brain cells are actually leaking straight out of their heads. That's why I've consistently urged people to limit their exposure to this guy."

Fauci said that, given Paul's suspension from the site, previous health advisories regarding YouTube "no longer apply."

"I think that this would be an excellent time for every American to enjoy YouTube," he said. "Watch some funny cat videos, or maybe some kooky skateboard stunts that went awry. Rand Paul's suspended for only seven days, so watch as much YouTube as you can while it's still safe."

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Andy Borowitz is a Times best-selling author and a comedian who has written for The New Yorker since 1998. He writes The Borowitz Report, a satirical column on the news.

From: Morens, David (NIH/NIAID) [E] [b6]
Sent: 8/11/2021 9:38:48 PM
To: Peter Daszak ([b6]) [[b6]]; Kessler, Robert ([b6]) [[b6]]; Keusch, Jerry ([b6]) [[b6]]
Subject: FW: CNN: Intel officials draft classified report as they near finish of 90-day Covid probe https://cnn.it/2Ub2xO7

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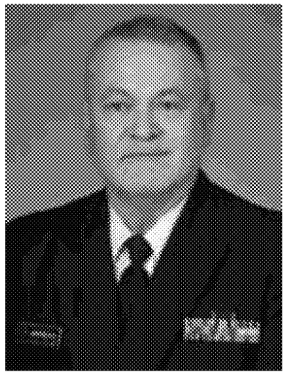

From: Folkers, Greg (NIH/NIAID) [E] [b6]
Sent: Wednesday, August 11, 2021 5:37 PM
Subject: CNN: Intel officials draft classified report as they near finish of 90-day Covid probe https://cnn.it/2Ub2xO7

Intel officials draft classified report as they near finish of 90-day Covid probe

By Kylie Atwood, Natasha Bertrand, Zachary Cohen and Katie Bo Williams, CNN

Updated 4:03 PM ET, Wed August 11, 2021

*Washington (CNN)*Intelligence officials are nearing the end of a 90-day investigation into the origins of Covid-19 that was ordered by President Joe Biden, and have drafted a classified report that is now in the preliminary review process, according to three sources familiar with the probe.

Sources familiar with the initial report say that after three months of poring over data and raw intelligence, the intelligence community is still divided over two theories -- one suggesting the virus originated from a lab in Wuhan, China, and the other suggesting it jumped naturally to humans from animals, the sources said. The report as it stands now contains "nothing too earth shattering," one source explained.

In May, Biden told US intelligence agencies to "redouble" their efforts to investigate how the virus originated, including the possibility that it emerged from a lab accident. Biden ordered the investigation after receiving an earlier report on the origins and asking for follow-up information, he said in a statement. The 90-day clock that Biden set for this investigation will be up in late August.

It's possible that the draft report could undergo significant revisions during the remaining review process. Biden also tasked the intelligence community with declassifying as much of the report as possible, a process now underway as it undergoes initial reviews.

Exclusive: Intel agencies scour reams of genetic data from Wuhan lab in Covid origins hunt,

The intelligence community's inability to present one theory with high confidence after three months of intense work underscores just how hard it is to probe the origins of the Covid-19 pandemic.
"We will not weigh in on the substance of the 90-day review while it is still underway," an ODNI spokesman said in a statement to CNN.

Last week, CNN reported that intelligence agencies had gotten their hands on a trove of genetic data drawn from virus samples at the lab in Wuhan that some officials believe could have been the source of the outbreak. It's unclear whether officials have finished analyzing that data.

Intelligence officials have also taken a fresh look at signals intelligence, like intercepted communications and satellite imagery, that could provide clues.

But ultimately, China's refusal to share information from the early days of the outbreak and the country's lack of transparency has been a major hurdle, and officials had been broadly pessimistic about finding a smoking gun during the 90-day push.
The report -- which was done without any Chinese participation -- is now being reviewed by the intelligence community and outside experts for feedback before it is finalized later this month, the three sources said. Once the classified version is finalized, an unclassified version will also be developed so that the Biden administration can share something with the public, one source explained.

Officials told CNN that the Biden administration has considered whether to launch another investigation if this one proves inconclusive, but it is unclear whether a decision has been made to reopen the probe after the 90-day report is released.
Last month, a bipartisan group of lawmakers made clear they want Biden to continue investigating the origins issue until the intelligence community reaches a high confidence assessment, even if that takes longer than 90 days.

But there are some concerns that the political debate around Covid origins and China's refusal to share pertinent information means that the US may never reach a definitive conclusion on that front, two sources said.

"The failure to get our inspectors on the ground in those early months will always hamper any investigation into the origin of Covid-19," Biden said when he announced that he had launched the investigation, noting that he had previously called for the CDC to get access to China to learn about the virus in order to help fight it more effectively.

Collecting intelligence about the breadth of Chinese actions that may have inhibited the World Health Organization or other origins investigations was one of the two primary objectives of the Biden administration's 90-day review earlier this summer, according to a tasking memo sent to relevant agencies that was obtained by CNN.

Chinese government rejects WHO plan for second phase of Covid-19 origins study

But unlike the question of whether the coronavirus first emerged naturally through human contact with animals in the wild or in markets, or via a lab accident, intelligence officials believe there is enough evidence to make a compelling case that the Chinese government's initial handling of the outbreak and efforts to suppress relevant information in the months since, has significantly constrained all efforts to examine the pandemic's true origins, according to a source familiar with the findings.

Despite a near consensus among those officials about the impact of China's actions, it remains unclear how far the Biden administration will go in calling out Beijing publicly once its ongoing 90-day review is over or how those findings will factor into the version of the report that is publicly released, the source said.

"What they release will be interesting ... but how far is Biden willing to go? If he tries these coercive measures on origins, how will that impact the other issues?" a former US official familiar with intelligence related to the origins investigation told CNN.
Biden's launch of the investigation came after a US intelligence report found several researchers at China's Wuhan Institute of Virology became ill with an unidentified infection or disease in November 2019 and had to be hospitalized -- a new detail that fueled fresh public pressure on Biden to delve deeper into the origin of the virus.

It also came after CNN reported that Biden's team shut down a closely held State Department effort launched late in the Trump administration to prove that Covid-19 originated in a Chinese lab over concerns about the quality of its work. White House officials have said that getting to the bottom of the origin of the pandemic will help prevent another one, and after unsuccessful World Health Organization (WHO) efforts to investigate the matter, the Biden administration orchestrated their own effort.

In July, the White House said it was "deeply disappointed" when China rejected the WHO's plan for a second phase of an investigation into the origin of the coronavirus. And after the WHO's first investigation the White House was critical of their findings due to limited access to "complete, original data and samples."

- P

From: Morens, David (NIH/NIAID) [E] [b6] ([b6])
Sent: 7/7/2021 12:31:24 PM
To: Peter Daszak ([b6]); [b6]
CC: Taubenberger, Jeffery (NIH/NIAID) [E] ([b6]); [b6]
Subject: Peter, I am curious to know what you think of these data and conclusions. TY, David
Attachments: 2021.07.05.451089v1.full.pdf

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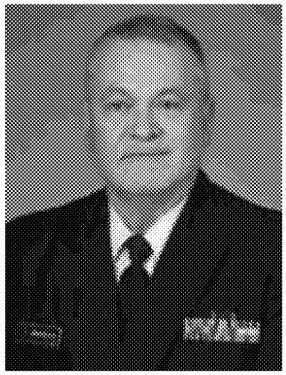

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Mutation signatures inform the natural host of SARS-CoV-2

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Abstract

The before-outbreak evolutionary history of SARS-CoV-2 is enigmatic because it shares only ~96% genomic similarity with RaTG13, the closest relative so far found in wild animals (horseshoe bats). Since mutations on single-stranded viral RNA are heavily shaped by host factors, the viral mutation signatures can in turn inform the host. By comparing publically available viral genomes we here inferred the mutations SARS-CoV-2 accumulated before the outbreak and after the split from RaTG13. We found the mutation spectrum of SARS-CoV-2, which measures the relative rates of 12 mutation types, is 99.9% identical to that of RaTG13. It is also similar to that of two other bat coronaviruses but distinct from that evolved in non-bat hosts. The viral mutation spectrum informed the activities of a variety of mutation-associated host factors, which were found almost identical between SARS-CoV-2 and RaTG13, a pattern

difficult to create in laboratory. All the findings are robust after replacing RaTG13 with RshSTT182, another coronavirus found in horseshoe bats with ~93% similarity to SARS-CoV-2. Our analyses suggest SARS-CoV-2 shared almost the same host environment with RaTG13 and RshSTT182 before the outbreak.

Introduction

Darwin's evolutionary theory has been challenged ever since it was proposed by the unavailability of some key intermediates between extant species[1]. Importantly, the growing understanding of life in the past one and half century, particularly since the time of molecular biology, provided indisputable intermediate-free supports to Darwin's theory. When we examine the genomes of current human and, say, chimpanzee, mouse, fish and fly, it's clear that the delicate principles operating in the non-human species apply to humans as well. There is simply no need to call for a special creator or designer to explain the origin of human beings.

Today we are facing a similar scenario Darwin used to face. The debate on the natural or unnatural origin of SARS-CoV-2, the causative virus of COVID-19, has existed since the beginning of the outbreak[2] and surged lately[3,4]. One of the main reasons is that RaTG13, the closest relative so far found[5] (in horseshoe bats *Rhinolophus affinis*), has only ~96% nucleotide similarities to SARS-CoV-2 (with ~1,200 nucleotide differences). The situation is distinct from the two previous coronavirus outbreaks happened this century (SARS at 2003 and MERS at 2012); in both cases, a closely related virus with over 99% nucleotide similarities to the causative virus was found in wild animals shortly after the start of each outbreak[6,7]. The missing intermediates between RaTG13 and SARS-CoV-2 prevent a better understanding of the

spillover. Fortunately, the signatures left on the available viral genomes would inform the before-outbreak history of SARS-CoV-2.

SARS-CoV-2 belongs to the Betacoronavirus genus, with a single-stranded positive-sense RNA genome of ~30 thousand nucleotides[8]. There are 12 types of substitution mutations on the viral genome: C>U, C>A, C>G, G>U, G>A, G>C, A>U, A>G, A>C, U>A, U>G, and U>C. The genome-wide mutation spectrum, which measures the relative rates of the 12 mutation types, comprises a set of summary statistics with little functional relevance. More importantly, the viral mutation spectrum is expected to be heavily shaped by host factors[9]. For example, the large number of RNA-binding proteins in mammalian cells would necessarily interact with the single-stranded RNA genome[10], which is critical for preventing the hydrolytic deamination of cytosines (leading to C>U) and the reactive oxygen species (ROS) induced oxidation of guanines (leading to G>U)[11]. Also, the two key RNA editing protein families, ADAR[12] (adenosine deaminase acting on RNA) and APOBEC[13] (apolipoprotein B mRNA editing enzyme catalytic polypeptide-like), would cause A>G and C>U mutations, respectively. In addition, when the host immunity failed to prevent high virion production, the cellular supply of dATP, dUTP, dCTP, and dGTP would modulate the viral mutations during genome replication[14]. The activities of the host factors often vary substantially among different species or even among different tissues of the same species[15], and their interplay would be even more complex. Hence, the viral mutation spectrum as a 12-dimension signature vector would be a powerful tool for tracking the hosts.

Results

Evolution of mutation spectrum in the SARS-CoV-2 lineage

We included SARS-CoV-2 and six related viruses in the analysis (Fig. 1a). The six related viruses were chosen because they are evolutionarily close enough for reliable mutation inferences while distant enough for observing plenty of mutations. At least three different hosts, bat, pangolin and human, are involved, highlighting a complex host history of this viral lineage[16,17]. Two separate phylogenetic trees were constructed to avoid the phylogeny confusions caused by recombination (Fig. S1), which results in different genealogical histories at different genomic regions in the ancestor of Bat-Cov-ZXC21 and Bat-Cov-ZC45 (both found in horseshoe bats *Rhinolophus sinicus*[18]). The branch X, which represents the before-outbreak history of SARS-Cov-2, and the B1, which represents the history of RaTG13 after it split from SARS-Cov-2, are present in both phylogenetic trees. Using conventional molecular evolutionary methods[11], we compared the viral genomes to infer the substitution mutations occurred on the evolutionary branches as marked in Fig. 1a (Methods). We considered only the third codon positions such that the obtained mutation spectra are less shaped by selection[19] (Fig. 1b and Table S1). Because the mutations on different evolutionary branches occurred independently, the derived mutation spectra of the branches are independent. To quantify the similarity between two mutation spectra we computed an identity score (i-score), which is the proportion of the total rate variation explained by the x=y dimension in a two-dimensional plot of the two spectra as in Fig. 1c (Methods). An i-score equal to 100% means the two mutation spectra are 100% identical.

The mutation spectra calculated separately in the two phylogenetic trees are nearly identical for the same branches (i-score = 99.9% for X versus X' and 99.4% for B1 versus B1'; Fig. S2), suggesting the results of the two trees comparable. There are three notable features

regarding the obtained spectra (Fig. 1b-c). First, the branch X is nearly identical to B1, with an i-score = 99.9%. Second, the branch X is distinct from the after-outbreak branch of SARS-CoV-2 (i.e, the Human branch), with an i-score = 83.9%. The obtained spectrum of the Human branch is consistent with a previous study[9]. Compared to branch X, the Human branch has a lot more G>U and C>U mutations, suggesting much stronger mutational pressures imposed by ROS and APOBEC family, respectively, to the SARS-CoV-2 genome in infected human cells. Meanwhile, the rates of A>G/U>C mutations reduce substantially, suggesting weaker activity of the ADAR family. Third, the branch X is in general highly similar to the branches with bats as the putative hosts (B1, B6 and B7) while less similar to the branches with non-bat hosts involved. These results, in particular, the 99.9% identify of X and B1, suggest SARS-CoV-2 not be artificially synthesized for gain-of-function research, because mutation spectrum is of little functional relevance and a synthesized genome is unlikely to show such a similar mutation spectrum to a naturally evolved viral genome (RaTG13). Notably, making comparably similar mutation spectra is doable by nature for close sister lineages like B6 and B7 (Fig. S2)

Host signatures inferred from viral mutations

The viral mutations are caused by both replication errors and replication-independent lesions or editing. The former is mostly associated with the viral self-encoded replication-transcription complex (RTC) and the latter would be mostly explained by host factors[20] (Fig. 2a). The coronavirus positive-sense RNA genome is replicated first by forming a negative-sense RNA intermediate, which then serves as template for both transcription and replication[8]. The same replication errors occurred in producing negative-sense strand and in producing positive-sense strand would result in different mutation types. For example, the two steps for replicating a

nucleotide C (C-to-G followed by G-to-C) are the same, but in an opposite order, as the two steps of replicating a G (G-to-C followed by C-to-G). Then, the same replication error of, say, C-to-A, in the C-to-G step would cause a C>U mutation in the replication of C but a G>A mutation in the replication of G (Fig. 2a). Other types of replication errors have the same feature. As a result, the 12 mutation types would form six complementary pairs: C>A/G>U, C>U/G>A, C>G/G>C, A>U/U>A, A>C/U>G, and A>G/U>C; in each pair the two complementary mutation types would have the same rate if all mutations were due to replication errors. Hence, the different mutation rate observed in each complementary pair would be ascribed to replication-independent factors, which are associated in a large part with host. For example, the preferential binding of the host APOBEC family to the single-stranded positive-sense RNA would lead to more C>U mutations than G>A mutations[21]. The host ADAR family would preferentially edit the negative-sense strand that are often in a double-stranded form, resulting in more U>C mutations than A>G mutations[22]. In addition, the damage effects of ROS primarily on single-stranded RNA would cause a higher rate of G>U mutations over C>A mutations[23]. The direction and magnitude of the rate difference in each complementary pair then constitute a signature of host factors, which informs the identity of hosts.

To obtain the host signatures we calculated the rate difference in each complementary pair. The six host signatures (S1-S6), each corresponding to a complementary pair, are indeed informative (Fig. 2b). For example, S1, the rate of C>U minus the rate of G>A, ranges from 0.06 to 0.42 among the different evolutionary branches. This may represent the different activities of the APOBEC family in different hosts. S2, the rate of U>C minus the rate of A>G, ranges from -0.03 to 0.1. This is likely associated with the relative activity of the ADAR family. S3, the rate of G>U minus the rate of C>A, ranges from -0.03 to 0.23 and appeared unusually

strong in the Human branch. This could be related to ROS that may preferentially target the single-stranded positive-sense RNA and have a strong induction in the infected human cells. Notably, the mentioned genes/pathways are just putatively associated with the observed host signatures. We found branch X has nearly identical host signatures to B1, with an i-score = 99.5%, despite substantial deviations from the human or pangolin associated branches (Fig. 2c). A multidimensional scaling plot shows that X is almost perfectly overlapping with B1, close to B6 and B7, and distant from the other branches (Fig. 2d). These results suggest that SARS-CoV-2 shared almost the same host environment with RaTG13 before the outbreak.

To gauge the probability that an arbitrary cell culture condition in laboratory matches the natural host environment of RaTG13, we estimated the size of the space formed by the host signatures, each of which has an empirical range according to the nine branches presented in Fig. 2b. We considered S1, S2 and S3 because their empirical ranges are the largest and their associated genes/pathways (APOBEC, ADAR and ROS) appear independent. As shown in Fig. 2e, the probability of approaching, as closely as SARS-CoV-2, the host environment of RaTG13 is ~2.0%, if S1 and S2 are considered. The number would be 0.02% if S3 is also considered (Fig. 2f). The estimations are conservative because the other three signatures (S4-S6) were not considered and also the real ranges of the signatures would be larger than the empirical ranges based on the nine evolutionary branches. We cautioned that the calculations assumed the associated gene/pathway activities are uniformly distributed within the empirical ranges. Nevertheless, the results are helpful for thinking of the likelihood that an arbitrary cell culture condition set in laboratory happens to duplicate a defined natural host environment.

Robust signals after replacing RaTG13 with RshSTT182

Because there are concerns on the quality of the assembled genome of RaTG13[24], we reproduced the above analyses after replacing RaTG13 with another bat coronavirus RshSTT182. RshSTT182 was isolated from Shamel's horseshoe bats (*Rhinolophus shameli*), being the first close relative of SARS-CoV-2 found in Southeast Asia (Cambodia) and with 92.6% genomic identity to SARS-CoV-2[25]. The whole-genome phylogeny of the involved viruses is (((((SARS-CoV-2, RaTG13), RshSTT182), Pangolin-CoV-GD), Pangolin-CoV-GX), Rc-o319). Hence, replacing RaTG13 with RshSTT182 would affect mainly the branches X, B1, and B2 in our analyses. Using the same procedure we obtained the mutation spectra and derived the host signatures for each of the evolutionary branches. The findings remain qualitatively the same (Fig. S3-S4 and Table S2). In brief, the mutation spectrum of SARS-CoV-2 is 99.3% identical to that of RshSTT182 (99.9% in the case of RaTG13). The slight reduction of the similarity may reflect the fact that the host of RaTG13 is *Rhinolophus affinis* but the host of RshSTT181 is another horseshoe bat species *Rhinolophus shameli*. Taken together, our analyses suggest the host environment of SARS-CoV-2 before the outbreak be fully compatible with horseshoe bats.

Discussion

It should be emphasized that this study is to address the evolution of the SARS-CoV-2 genome but nothing else. Using mutational signatures inferred from the available viral genomes we probed the evolutionary time window (branch X) SARS-CoV-2 spent before the outbreak and after the split from bat coronavirus RaTG13. The missing intermediates within this time window that presumably spans a few tens of years[26] prevents a better understanding of the spillover. Our analyses based on public data provide compelling evidence that during this time window SARS-CoV-2 evolved in a host environment highly similar, if not identical, to RaTG13. The host

environment is also similar to that of the three bat coronaviruses RshSTT182, ZXC21 and ZC45, and difficult to duplicate by an arbitrary cell culture condition set in laboratory. One may argue that, while the branch X as a whole is compatible with natural laws, it may not be at a few key sites. Such an argument presumes that there are intermediates with over 99% similarity to SARS-CoV-2 to be found in nature. Notably, claiming such natural intermediates would leave little room for speculations, as in the cases of SARS[6] and MERS[7]. The mission of the scientific community is then to find them in nature to better understand the spillover.

Methods

Genomic Data

The SARS-CoV-2 related bat and pangolin coronavirus genomic sequences were obtained from NCBI GenBank (https://www.ncbi.nlm.nih.gov/genbank). For genomes without accurate annotations of ORFs, we re-annotated these genomes with CDSs annotated in SARS-CoV-2 by Exonerate2 (–model protein2genome: bestfit –score 5 -g y)[27]. The complete genomic sequences and metadata of SARS-CoV-2 were retrieved from Global Initiative on Sharing All Influenza Data (GISAID; https://www.gisaid.org/; accessed on 19 March 2021)[28]. Gap-containing genomes in examined regions were removed, and only genomes from Dec. 2019 to Dec. 2020 were chosen for analysis. All available genomes submitted to GISAID from Dec. 2019 to Feb. 2020 were included, and, among the too many submitted genomes from Mar. to Dec. 2020, 2,000 genomes were randomly selected for each month. Finally, a total of 214,32 SARS-CoV-2 genomes were included. Following GISAID we used SARS-CoV-2 WIV04 (EPI_ISL_402124)

as the reference genome. The detailed information of SARS-CoV-2 and the related coronaviruses included in this analysis is summarized in Supplementary Dataset I.

Phylogenetic analysis and mutation spectra calculation

The codon alignments of ORFs were performed based on amino acid sequences translated by TranslatorX[29] and MAFFT v7.471[30], and further concatenated by AMAS[31] and refined with visual check. Only ORFs with consistent annotations in the examined viruses were included. Maximum likelihood phylogenetic analysis based on the whole coding regions was conducted by using IQ-TREE v2.0.3[32] with GTR+FO+R10 substitution model and 1,000 bootstrap replicates. The ancestral sequences of the internal nodes were inferred in IQ-TREE with an *-asr* parameter, and mutations on each branch were derived by comparing the ancestral sequence to the descendant sequence. To avoid the confounding effects of potential recombination and convergent evolution, the region covering the receptor binding domain and the furin-like cleavage site (319^{th}-770^{th} codons) of the spike protein was removed from the analysis. Only the third codon positions were considered in calculation of the mutation spectra. The aligned sequences can be found in Supplementary Dataset II-V.

To obtain the after-outbreak mutations of SARS-CoV-2, 59 separate main clades each containing more than 100 sequences and supported by a bootstrap value >90 were selected from the phylogenic tree. Mutations were inferred by comparing each individual sequences to the corresponding common ancestral sequences of each clade, respectively. To avoid redundancy, recurrent mutations within a clade were counted once. Then, the 59 clade-specific ancestral sequences were compared to the earliest common ancestral sequence of SARS-CoV-2.

Mutations obtained from the two steps were pooled to derive the mutation spectrum of the Human branch.

For a specific mutation type, say C>A, the rate was calculated as the number of C>A mutations divided by the total number of C nucleotides in the ancestral sequence of the given branch (third codon positions). The mutation rates of the 12 mutation types were then each divided by their sum to obtain the relative mutation rates (i.e., mutation spectrum). The i-score of two mutation spectra is the proportion of variance explained by the x=y dimension in a two-dimensional plot of the two spectra. Specifically, let $A = [S_1, S_2]^T$, where S_1 and S_2 are the two mutation spectra under examination, and $B = [D_1, D_2]^T$, where D_1 is the projection of A onto the x=y dimension and D_2 onto the x= -y dimension. Then, the i-score = $cov(D_1) / (cov(S_1)+ cov(S_2))$.

To verify the whole-genome-based evolutionary branches at different genomic regions a sliding window analysis through the viral genomes was conducted. Specifically, each window covers 500 codons (or 1500 nucleotides, ~5% of the viral genome) and the step size is a half window. For each window we constructed the phylogeny of the viruses using synonymous sites, and then checked if the whole-genome-based branches exist in the window. Neighbor-Joining phylogeny was obtained in MEGA X[33], which allows such analysis on synonymous sties, with 1,000 bootstrap replicates.

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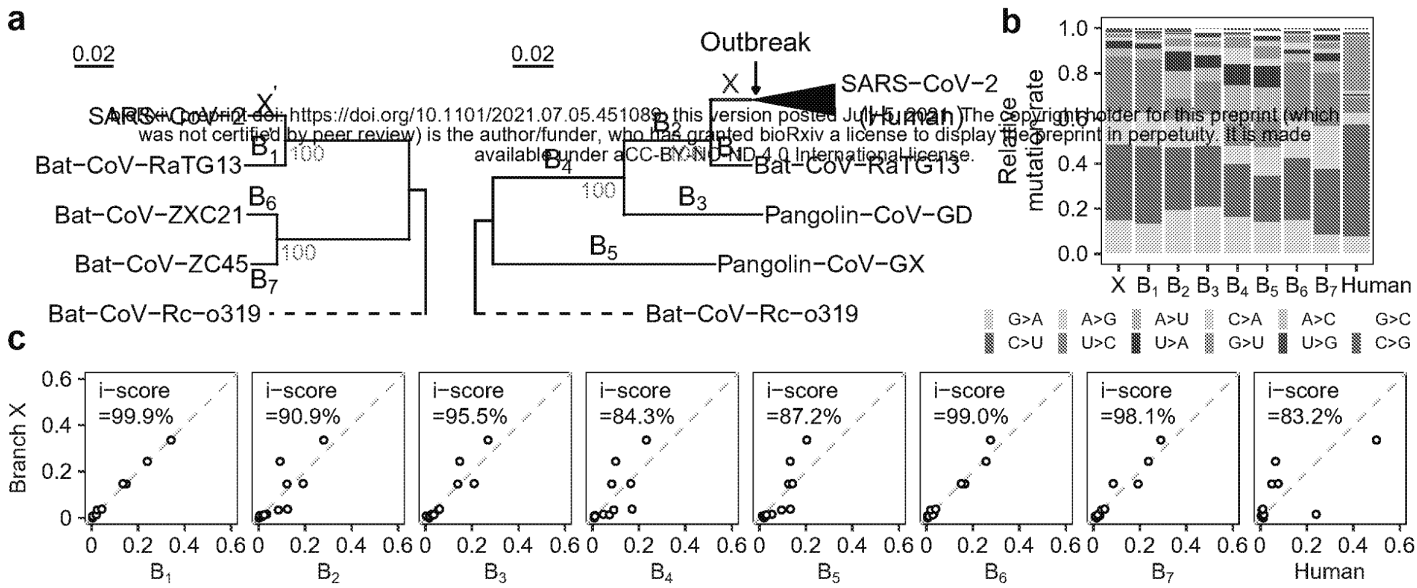
Figure legends

Fig. 1. Evolution of mutation spectrum in the SARS-CoV-2 lineage. a. The phylogenetic relationships of the seven coronaviruses included in the analysis. Two separate phylogenetic trees are considered to resolve the confusions caused by recombination, which results in different genealogical histories at different genomic regions in the ancestral branch of Bat-CoV-ZXC21 and Bat-CoV-ZC45. Nine major evolutionary branches examined in this study, X, B1-B7, and the Human branch, are shown. The branch X and B1 are also present (as X' and B1') in the tree with B6 and B7 to help infer the ancestor of B6 and B7. The Bat-CoV-Rc-o319 is used as outgroup in both trees. **b.** The relative mutation rate of the 12 mutation types on each of the nine evolutionary branches. **c.** The similarity of mutation spectrum between branch X and each of the other eight branches. The similarity of two branches is measured by identity score (i-score), which is the proportion of total rate variation explained by the x=y dimension in the plot of the two spectra.

Fig. 2. Host signatures inferred from viral mutation spectrum. a. A diagram showing the major sources of viral mutations, which include the replication errors (by the viral replication-transcription complex RTC) and the lesions caused by host factors. Because replication processes are the same, despite in the opposite order, for nucleotides G and C (or A and T), replication errors would result in equal rates of complementary mutations such as C>A and G>T. However, host factors would distort the equal-rate pattern of complementary mutation pairs. The positive-sense RNA is often in a single-stranded form, sensitive to ROS and the APOBEC family, while the negative-sense RNA tends to be in a double-stranded form, thus more affected by the ADAR family. **b.** The rate difference of each complementary mutation pair serves as a signature of host factors. There are thus six host signatures, each corresponding to a complementary mutation pair, inferred from the viral mutation spectrum. Among the three major host signatures, S1 is likely associated with the APOBEC family, S2 the ADAR family, and S3 the ROS. **c.** The similarity of host signatures between branch X and each of the other eight branches. Branch X is highly similar to B1, B6 and B7, the three branches of bat coronavirus. **d.** A multidimensional scaling (MDS) plot of the host signatures reveals nearly the same positions of branch X and B1. **e.** Estimation of the likelihood that an arbitrary laboratory condition happens to match the host signatures of B1 (the branch of RaTG13). The grey rectangle area is defined by the empirical ranges of S1 (APOBEC-associated) and S2 (ADAR-associated) that are based on the data of panel b. The probability of approaching B1 as closely as X is the area of the circle divided by the whole rectangle area, which is ~2.0%. The positions of the other seven branches are also shown in the rectangle area. **f.** The probability that an arbitrary condition approaches B1 as closely as X is given, by considering the different combinations of S1, S2, and S3, respectively.



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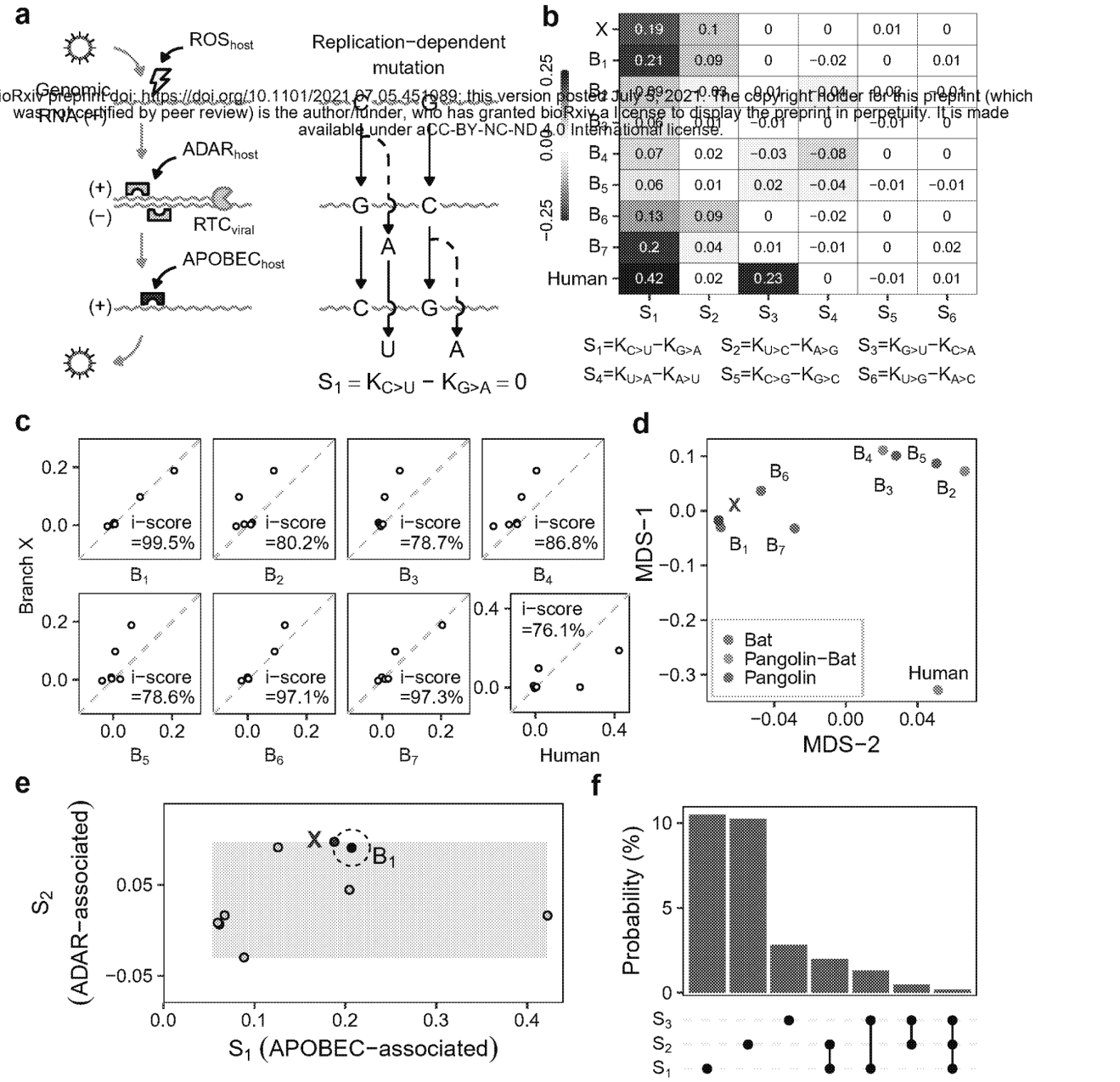

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From: Morens, David (NIH/NIAID) [E] [b6 b6]
Sent: 9/22/2021 4:40:14 PM
To: Jason Gale [j.gale@bloomberg.net]; [b6]; [b6] Garry, Robert F [b6 b6]; [b6]
Subject: RE: (TEL) Wuhan Scientists Planned to Release coronaviruses Into

If I read it correctly, these are inert nanopartricles to which are affixed proteins of interest, like a spike protein, so they wouldn't replicate but might be used as vaccines. The later part of the article describes so-called potential GoF experiments with live viruses.

David

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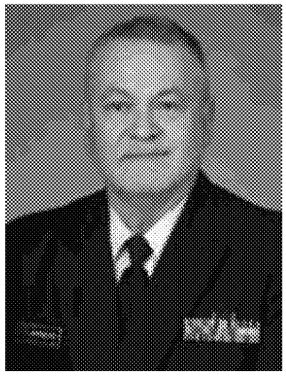

From: Jason Gale (BLOOMBERG/ NEWSROOM:) <j.gale@bloomberg.net>
Sent: Wednesday, September 22, 2021 12:28 PM
To: b6; Morens, David (NIH/NIAID) [E] b6; b6; Garry, Robert F b6; b6
Subject: RE: (TEL) Wuhan Scientists Planned to Release coronaviruses Into

I have no idea, David. It's the first time I've heard of this and it seemed too ridiculous to be true.

----- Original Message -----
From: David Morens b6
To: JASON GALE, b6, b6
At: 09/23/21 00:27:24 UTC+10:00

> Jason et all, these are just inert protein nanoparticles, correct, not live viruses as it might imply at the top?

David M. Morens, M.D.
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b6

From: Jason Gale (BLOOMBERG/ NEWSROOM:) <j.gale@bloomberg.net>
Sent: Wednesday, September 22, 2021 3:09 AM
To: b6; Morens, David (NIH/NIAID) [E]
b6;
Garry, Robert F b6
Subject: (TEL) Wuhan Scientists Planned to Release coronaviruses Into

The latest installment, jfyi

Wuhan Scientists Planned to Release coronaviruses Into Cave Bats 18 Months Before Outbreak
2021-09-21 17:14:22.531 GMT

By Sarah Knapton, Science Editor

(Telegraph) -- Wuhan scientists were planning to release enhanced airborne coronaviruses into Chinese bat populations to inoculate them against diseases that could jump to humans, leaked grant proposals dating from 2018 show.

New documents show that just 18 months before the first Covid-19 cases appeared, researchers had submitted plans to release skin-penetrating nanoparticles containing "novel chimeric spike proteins" of bat coronaviruses into cave bats in Yunnan, China.

They also planned to create chimeric viruses, genetically enhanced to infect humans more easily, and requested $14million from the Defense Advanced Research Projects Agency (Darpa) to fund the work.

Papers, confirmed as genuine by a former member of the Trump administration, show they were hoping to introduce "human-specific cleavage sites" to bat coronaviruses which would make it easier for the virus to enter human cells.

When Covid-19 was first genetically sequenced, scientists were puzzled about how the virus had evolved such a human-specific adaptation at the cleavage site on the spike protein, which is the reason it is so infectious.

The documents were released by Drastic, the web-based investigations team set up by scientists from across the world to look into the origins of Covid-19.

In a statement, Drastic said: "Given that we find in this proposal a discussion of the planned introduction of human-specific cleavage sites, a review by the wider scientific community of the plausibility of artificial insertion is warranted."

The proposal also included plans to mix high-risk natural coronavirus strains with more infectious but less dangerous varieties.

The bid was submitted by British zoologist Peter Daszak of EcoHealth Alliance, the US-based organisation, which has worked closely with the Wuhan Institute of Virology (WIV) researching bat coronaviruses.

Team members included Dr Shi Zhengli, the WIV researcher dubbed "bat woman", pictured below, as well as US researchers from the University of North Carolina and the United States Geological Survey National Wildlife Health Centre.

Darpa refused to fund the work, saying: "It is clear that the proposed project led by Peter Daszak could have put local communities at risk", and warned that the team had not properly considered the dangers of enhancing the virus (gain of function research) or releasing a vaccine by air.

Grant documents show that the team also had some concerns about the vaccine programme and said they would "conduct educational outreach … so that there is a public understanding of what we are doing and why we are doing it, particularly because of the practice of bat-consumption in the region".

Angus Dalgleish, Professor of Oncology at St Georges, University of London, who struggled to get work published showing that the Wuhan Institute of Virology (WIV) had been carrying out "gain of function" work for years before the pandemic, said the research may have gone ahead even without the funding.

"This is clearly a gain of function, engineering the cleavage site and polishing the new viruses to enhance human cell infectibility in more than one cell line," he said.

Daszak was also behind a letter published in The Lancet last year which effectively shut down scientific debate into the origins of Covid-19.

Viscount Ridley, who has co-authored a book on the origin of Covid-19, due for release in November, and who has frequently called for a further investigation into what caused the pandemic in the House of Lords, said: "For more than a year I tried repeatedly to ask questions of Peter Daszak with no response.

"Now it turns out he had authored this vital piece of information about virus work in Wuhan but refused to share it with the world. I am furious. So should the world be.

"Peter Daszak and the EcoHealth Alliance (EHA) proposed injecting deadly

chimeric bat coronaviruses collected by the Wuhan Institute of Virology into humanised and 'batified' mice, and much, much more."

A Covid-19 researcher from the World Health Organisation (WHO), who wished to remain anonymous, said it was alarming that the grant proposal included plans to enhance the more deadly disease of Middle-East Respiratory Syndrome (Mers).

"The scary part is they were making infectious chimeric Mers viruses," the source said.

"These viruses have a fatality rate over 30 per cent, which is at least an order of magnitude more deadly than Sars-CoV-2.

"If one of their receptor replacements made Mers spread similarly, while maintaining its lethality, this pandemic would be nearly apocalyptic."

EcoHealth Alliance and the Wuhan Institute of Virology have been aproached for comment.

-0- Sep/21/2021 17:14 GMT

To view this story in Bloomberg click here:
https://blinks.bloomberg.com/news/stories/QZSNVY33O5C1

From: Morens, David (NIH/NIAID) [E] [b6] ([b6])
Sent: 10/4/2021 3:30:34 PM
To: Peter Daszak ([b6]) [[b6]]; Kessler, Robert ([b6]) [[b6]]; Keusch, Jerry ([b6]) [[b6]]
Subject: FW: Guardian, 2/2020: Coronavirus closures reveal vast scale of China's secretive wildlife farm industry https://bit.ly/3A3ITCj

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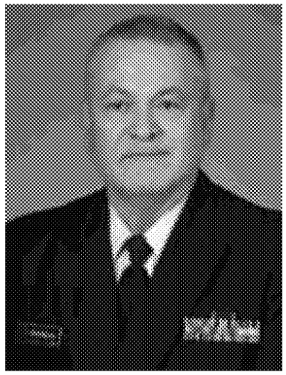

From: Folkers, Greg (NIH/NIAID) [E] [b6]
Sent: Sunday, October 3, 2021 11:00 AM

Subject: Guardian, 2/2020: Coronavirus closures reveal vast scale of China's secretive wildlife farm industry https://bit.ly/3A3ITCj

Animals farmedWildlife

Coronavirus closures reveal vast scale of China's secretive wildlife farm industry

Freshly-slaughtered meat from wildlife and farm animals is preferred over meat that has been slaughtered before being shipped. Photograph: Visual China Group/Getty

Peacocks, porcupines and pangolins among species bred on 20,000 farms closed in wake of virus

Mon 24 Feb 2020 22.01 EST

Last modified on Wed 1 Jul 2020 13.22 EDT

Nearly 20,000 wildlife farms raising species including peacocks, civet cats, porcupines, ostriches, wild geese and boar have been shut down across China in the wake of the coronavirus, in a move that has exposed the hitherto unknown size of the industry.

Until a few weeks ago wildlife farming was still being promoted by government agencies as an easy way for rural Chinese people to get rich.

But the Covid-19 outbreak, which has now led to 2,666 deaths and over 77,700 known infections, is thought to have originated in wildlife sold at a market in Wuhan in early December, prompting a massive rethink by authorities on how to manage the trade.

China issued a temporary ban on wildlife trade to curb the spread of the virus at the end of January and began a widespread crackdown on breeding facilities in early February.

Make ban on Chinese wildlife markets permanent, says environment expert

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The country's top legislative officials are now rushing to amend the country's wildlife protection law and possibly restructure regulations on the use of wildlife for food and traditional Chinese medicine.

The current version of the law is seen as problematic by wildlife conservation groups because it focuses on utilisation of wildlife rather than its protection.

"The coronavirus epidemic is swiftly pushing China to reevaluate its relationship with wildlife," Steve Blake, chief representative of WildAid in Beijing, told the Guardian. "There is a high level of risk from this scale of breeding operations both to human health and to the impacts on populations of these animals in the wild."

The National People's Congress released new measures on Monday restricting wildlife trade, banning consumption of bushmeat and sales of wildlife for meat consumption at wet markets between now and the time the Wildlife Protection Law can be amended and adopted. Untouched however, are breeding operations for traditional Chinese medicine, fur and leather, lucrative markets known to drive illegal poaching of animals including tigers and pangolins.

For the past few years China's leadership has pushed the idea that "wildlife domestication" should be a key part of rural development, eco-tourism and poverty alleviation. A 2017 report by the Chinese Academy of Engineering on the development of the wildlife farming industry valued the wildlife-farming industry those operations at 520bn yuan, or £57bn.

Civet cats – thought to be potential carriers of Sars – are among the animals farmed for meat in China. Photograph: China Photos/Getty

Just weeks before the outbreak, China's State Forestry and Grassland Administration (SFGA) was still actively encouraging citizens to get into farming wildlife such as civet cats – a species pinpointed as a carrier of Sars, a disease similar to Covid-19. The SFGA regulates both farming and trade in terrestrial wildlife, and quotas of wildlife products – such as pangolin scales – allowed to be used by the Chinese medicine industry.

"Why are civet cats still encouraged to [be eaten] after the Sars outbreak in 2003? It's because the hunters, operators, practitioners need that. How can they achieve that? They urged the government to support them under the pretext of economic development," Jinfeng Zhou, secretary-general of the China Biodiversity Conservation and Green Development Foundation (CBCGDF), told the Guardian.

On state TV the popular series Secrets of Getting Rich, which has aired since 2001, often touts these kinds of breeding operations – bamboo rats, snakes, toads, porcupines and squirrels have all had starring roles.

But little was known about the scale of the wildlife farm industry before the coronavirus outbreak, with licensing mainly regulated by provincial and local-level forestry bureaus that do not divulge full information about the breeding operations under their watch. A report from state-run Xinhua news agency on 17 February revealed that from 2005–2013 the forestry administration only issued 3,725 breeding and operation licenses at the national level.

But since the outbreak at least 19,000 farms have been shut down around the country, including about 4,600 in Jilin province, a major centre for traditional Chinese medicine. About 3,900 wildlife-farming operations were shuttered in Hunan province, 2,900 in Sichuan, 2,300 in Yunnan, 2,000 in Liaoning, and 1,000 in Shaanxi.

Breeding of animals such as rats has been seen as central to alleviating poverty in rural areas. Photograph: Zhang Ailin/Alamy

There is little detail available about the animals farmed across China, but local press reports mention civet cats, bamboo rats, ostriches, wild boar, sika deer, foxes, ostriches, blue peacocks, turkeys, quails, guinea fowl, wild geese, mallard ducks, red-billed geese, pigeons, and ring-necked pheasants.

Neither do reports offer much detail about the shutdowns and what is happening to the animals, although Blake said he does not think animals are being culled, due to issues over compensation.

Chen Hong, a peacock farmer in Liuyang, Hunan, said she is concerned about her losses and whether she will get compensation after her operations were suspended on 24 January.

“We now aren’t allowed to sell the animals, transport them, or let anyone near them, and we have to sanitise the facility once every day,” Chen said. “Usually this time of year would see our farm bustling with clients and visitors. We haven’t received notice on what to do yet, and the peacocks are still here, and we probably won’t know what to do with [them] until after the outbreak is contained.

“We’re very worried about the farm’s future,” she added. “The shutdown has resulted in a loss of 400,000–500,000 yuan (£44,000–55,000) in sales, and if they decide to put an outright ban on raising peacocks, we’ll lose even more, at least a million yuan(£110,000).”

Peacock breeders use plastic bags to wrap up the birds in transit to stop their feathers falling off. Photograph: Visual China Group/Getty

On a visit to Shaoguan, Guangdong province, last year, the Guardian and staff from CBCGDF saw a caged facility previously used for attempted breeding of the notoriously hard-to-breed pangolin.

While there were no longer pangolin at the site, several locals near the facility confirmed the species had been raised there, along with monkeys and other wildlife.

Appetite for 'warm meat' drives risk of disease in Hong Kong and China

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Besides being used for Chinese medicine, much of the meat from the wildlife trade is sold through online platforms or to "wet markets" like the one where the Covid-19 outbreak is thought to have started in Wuhan.

"All animals or their body parts for human consumption are supposed to go through food and health checks, but I don't think the sellers ever bothered," said Deborah Cao, a professor at Griffith University in Australia and an expert on animal protection in China. "Most of them [have been] sold without such health checks."

There have been calls for a deep regulatory overhaul to remove the conflicting duties of the forestry administration, and for a shift in government mindset away from promoting the utilisation of wildlife and towards its protection.

Zhangjiakou city has more than 1,500 firms processing furs from animals including foxes and racoons. Photograph: Greg Baker/Getty

"The 'referee-player' combination needs to be addressed and is the toughest [challenge]," Li Shuo, a senior campaigner at Greenpeace East Asia told the Guardian. "This goes back to the institutional identity [of the SFGA] which was established to oversee timber production. Protection was an afterthought."

uProposals include fully banning trade in wildlife that is protected or endangered within and outside of China, plus bans on raising and selling meat from known carriers of diseases that can impact humans such as civets, bats and rodents.

There are concerns that in trying to prevent outbreaks authorities may go too far in the culling of wild animals that can carry disease.

"Some law professors have suggested 'ecological killing' of disease-transmitting wild animals, such as pangolins, hedgehogs, bats, snakes, and some insects," Zhou said. "We believe lawmakers need to learn [more about] biodiversity before advising on the revisions to the law, or they'll bring disaster."

Additional research and reporting assistance provided by Jonathan Zhong.

From: Morens, David (NIH/NIAID) [E] [b6] ([b6])
Sent: 8/2/2021 3:09:24 PM
To: Peter Daszak ([b6]) [b6]; Keusch, Jerry [b6] [b6]
Subject: FW: Republican report says coronavirus leaked from China lab; scientists still probing origins

David

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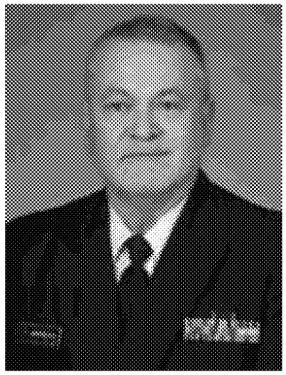

From: Folkers, Greg (NIH/NIAID) [E] [b6]
Sent: Monday, August 2, 2021 11:01 AM
Subject: Republican report says coronavirus leaked from China lab; scientists still probing origins

August 2, 202112:37 AM EDTLast Updated 11 minutes ago

United States

Republican report says coronavirus leaked from China lab; scientists still probing origins

Reuters

-

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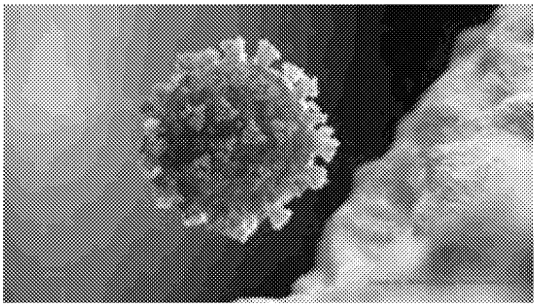

A computer image created by Nexu Science Communication together with Trinity College in Dublin, shows a model structurally representative of a betacoronavirus which is the type of virus linked to COVID-19, shared with Reuters on February 18, 2020. NEXU Science Communication/via REUTERS

WASHINGTON, Aug 2 (Reuters) - A preponderance of evidence proves the virus that caused the COVID-19 pandemic leaked from a Chinese research facility, said a report by U.S. Republicans released on Monday, a conclusion that U.S. intelligence agencies have not reached.

The report also cited "ample evidence" that Wuhan Institute of Virology (WIV) scientists - aided by U.S. experts and Chinese and U.S. government funds - were working to modify coronaviruses to infect humans and such manipulation could be hidden.

Representative Mike McCaul, the top Republican on the House Foreign Affairs Committee, released the report by the panel's Republican staff. It urged a bipartisan investigation into the origins of the COVID-19 coronavirus pandemic that has killed 4.4 million people worldwide.

China denies a genetically modified coronavirus leaked from the facility in Wuhan - where the first COVID-19 cases were detected in 2019 - a leading but unproven theory among some experts. Beijing also denies allegations of a cover-up.

Other experts suspect the pandemic was caused by an animal virus likely transmitted to humans at a seafood market near the WIV.

"We now believe it's time to completely dismiss the wet market as the source," said the report. "We also believe the preponderance of the evidence proves the virus did leak from the WIV and that it did so sometime before September 12, 2019."

The report cited what it called new and under-reported information about safety protocols at the lab, including a July 2019 request for a $1.5 million overhaul of a hazardous waste treatment system for the facility, which was less than two years old.

In April, the top U.S. intelligence agency said it concurred with the scientific consensus that the virus was not man-made or genetically modified.

U.S. President Joe Biden in May ordered U.S. intelligence agencies to accelerate their hunt for the origins of the virus and report back in 90 days.

A source familiar with current intelligence assessments said the U.S. intelligence community has not reached any conclusion whether the virus came from animals or the WIV.

Reporting by Jonathan Landay and Mark Hosenball; Editing by Lisa Shumaker

Our Standards: The Thomson Reuters Trust Principles.

From: Morens, David (NIH/NIAID) [E] [b6 (b6)]
Sent: 10/19/2021 7:24:03 PM
To: Peter Daszak (b6) [b6]; Keusch, Jerry (b6) [b6]; Kessler, Robert (b6) [b6]; Taubenberger, Jeffery (NIH/NIAID) [E] (b6) [b6]
Subject: FW: Sen. Marshall Introduces Legislation to Halt Viral Gain of Function Research
Attachments: Viral GoF-Research Moratorium Act.pdf

David

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From: Folkers, Greg (NIH/NIAID) [E] b6
Sent: Tuesday, October 19, 2021 1:19 PM
To: NIAID COGCORE <COGCORE@mail.nih.gov>; NIAID OCGR Leg <NIAIDOCGRLeg@mail.nih.gov>; NIAID OD AM

<NIAIDODAM@niaid.nih.gov>
Subject: Sen. Marshall Introduces Legislation to Halt Viral Gain of Function Research

Sen. Marshall Introduces Legislation to Halt Viral Gain of Function Research

- October 19, 2021

(Washington, D.C., October 19, 2021) – U.S. Senator Roger Marshall, M.D. led a group of colleagues in introducing the *VIRAL GAIN OF FUNCTION RESEARCH MORATORIUM ACT* to place a moratorium on all federal research grants to universities and other organizations conducting gain-of-function research and risky research on potential pandemic pathogens. This legislation is in response to the congressional inquiries and various MEDIA INVESTIGATIONS revealing national security issues including federal agencies authorizing dangerous research with certain foreign entities that may have contributed to the COVID-19 pandemic.

Original cosigners of this legislation are Senators Rand Paul, M.D. (R-KY), Joni Ernst (R-IA), Tommy Tuberville (R-AL), Marsha Blackburn (R-TN), Bill Hagerty (R-TN), Mike Braun (R-IN), James Lankford (R-OK), Marco Rubio (R-FL), and Tom Cotton (R-AR).

"It's outrageous that a comprehensive global investigation on the origins of COVID-19 has still not been carried out, and with mounting evidence pointing towards the labs in Wuhan, additional guardrails on gain-of-function research must be established to make sure nothing like this ever happens again," **said Senator Marshall.** "For the last decade, Dr. Fauci has funded gain-of-function research on SARS viruses, and until we get to the bottom of the origins of COVID-19, the federal government should not provide another dime in funding for viral gain-of-function research in the name of global health."

"While Communist China continues to keep the American people and the world in the dark about the origins of the COVID-19 pandemic, Wuhan lab-linked organizations like EcoHealth Alliance are failing to tell the truth about U.S. taxpayer money being doled out to fund their dangerous studies on coronaviruses," **said Senator Ernst.** "This important effort will block Iowans' hard-earned tax dollars from funding viral gain-of-function research—and help prevent another pandemic from ever happening again."

"Even as Dr. Fauci denies it, there is strong evidence COVID-19 started in a lab in Wuhan," **said Dr. Paul.** "However, if we have learned anything from this pandemic, it's that risky virus enhancing research – like the type conducted at the Wuhan Institute of Virology, also funded by

the U.S. government – is an unnecessary form of science that could lead to the death of millions of people. The Viral Gain of Function Research Moratorium Act puts a stop to federal research grants to universities and organizations that participate in this type of research, ensuring that taxpayer money will no longer be used to fund deadly manmade viruses."

"Communist China has worked hard to suppress information about COVID-19, including its origins and the role of gain-of-function research in its development," **said Senator Lankford.** "This potentially dangerous research and any US involvement in it needs to be fully exposed. I will continue to advocate for defunding China's Wuhan Institute of Virology and ending US support for any high-risk gain-of-function research. As we put Americans' safety and health first, we must continue to keep a watchful eye on the plans and tasks of the communist Chinese government."

"The Biden administration dropped the ball in determining the origins of COVID-19. Biden's Chief Medical Advisor, Anthony Fauci, has been a leading advocate for deadly gain-of-function (GoF) research, and the Wuhan Institute of Virology received American taxpayer dollars to fund GoF research on his watch. We must halt GoF research until we can determine the necessary safety guardrails," **said Senator Blackburn.**

"I've long said that identifying the origin of the COVID-19 pandemic is vital for preventing future pandemics. The moratorium on gain-of-function research will allow more time to understand how gain-of-function research may have played a role in catalyzing the pandemic, while ensuring that no additional gain-of-function research is being conducted or posing risk of future pandemic. Additionally, this moratorium will ensure that American taxpayers will not be funding foreign research projects, like those conducted in the Wuhan Institute of Virology," **said Senator Braun.**

"More than a year and half after the initial outbreak of COVID-19 in Wuhan, serious questions remain regarding the origins of this deadly virus and its possible connection to federally-funded gain of function research in China," **said Senator Rubio.** "The American people deserve to know the truth, and until a full and transparent investigation is guaranteed and real oversight is imposed on this risky line of research, no taxpayer dollars should be squandered by unelected bureaucrats operating in the dark."

"American lives and livelihoods have been lost due to COVID-19, and we need answers about any link between gain-of-function research and the origins of the pandemic," **said Senator Tuberville.** "The Chinese government won't tell the full story, and Dr. Fauci takes every opportunity to tout the importance of gain-of-function research. Until the truth has been brought to light, Alabamians' hard-earned tax-payer dollars should not be used to fund any research that seeks to threaten the health and safety of our nation."

"Significant evidence suggests that COVID-19 originated in the Wuhan Institute of Virology, which received gain-of-function research grants and funding. Until the origin of this virus can be confirmed, funding for similar research programs should be halted to help prevent another global crisis," **said Senator Cotton.**

Background:

The U.S. National Institutes of Health (NIH) has historically applied a broad and inconsistent definition of gain-of-function (GoF) research – a process that aims to genetically alter a virus or organism to gain (or lose) function on its transmissibility or pathogenicity. However, viral GoF on infectious diseases places great risk to global health as it directly aims to alter viruses deadly to people. Recognizing the threat of GoF research and biosecurity issues in lab facilities, White House officials PLACED A MORATORIUM on this work in 2014. Unfortunately, the National Institute of Allergy and Infectious Diseases, led by Dr. Anthony Fauci, continued funding GoF research UNDER EXCEPTIONS TO THE MORATORIUM. In 2017 – with key cabinet appointments vacant or pending Senate confirmation – NIH successfully advocated for the LIFTING OF THE MORATORIUM.

The majority of the funded research in question involves EcoHealth Alliance. A non-profit organization based in New York, their GoF projects involved researchers at the Wuhan Institute of Virology, Wuhan University, and the China's CDC and Prevention of Guangdong Province. In addition to the NIH, other federal agencies involved in this type of risky research include the U.S. Agency for International Development and the U.S. Department of Defense (DoD). In fact, the DoD PROVIDED OVER $40 MILLION in funding to the EcoHealth Alliance to conduct risky research at China's Wuhan Institute of Virology with no transparency and no accountability.

Senator Marshall has been actively involved in uncovering the origin of COVID-19, but certain agencies have refused to cooperate fully. Last month, Senator Marshall – along with Senators Chuck Grassley (IA) and Marsha Blackburn (TN) – SENT A FOLLOW-UP LETTER demanding answers to questions that may shed light on the origins of COVID-19. Specifically, the Senators requested answers regarding NIH's data retention policies for the Sequence Read Archive, the largest public database for DNA sequencing data. NIH had deleted coronavirus gene sequences data from the database at the request of researchers from Wuhan University. NIH INADEQUATELY ADDRESSED previous congressional oversight inquiries dating back to June. The exchange between the Senators and NIH was REPORTED ON BY THE WALL STREET JOURNAL.

In May, Senator Marshall – along with Senators Rand Paul (KY), Ron Johnson (WI), James Lankford (OK), Rick Scott (FL), Tom Cotton (AR), and Rep. Mike Gallagher (WI) LED A

LETTER highlighting a response to the World Health Organization's study of SARS-CoV-2's origins from a group of eighteen scientists stating that the leak of the virus from a lab is a "viable" theory and should be thoroughly investigated. The letter touched on several high profile biosafety incidents at the labs and GoF research studies that led to a 2014 HHS and NIH pause on funding research for gain of function experiments *"involving influenza, SARS, and MERS viruses."* This pause did not halt ongoing research being conducted or research that received an exception from the head of the USG funding agency.

###

117TH CONGRESS
1ST SESSION

S. _____

To provide a moratorium on all Federal research grants provided to any institution of higher education or other research institute that is conducting gain-of-function research.

IN THE SENATE OF THE UNITED STATES

Mr. MARSHALL introduced the following bill; which was read twice and referred to the Committee on _____

A BILL

To provide a moratorium on all Federal research grants provided to any institution of higher education or other research institute that is conducting gain-of-function research.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "_____ Act of _____".

SEC. 2. PROHIBITION ON FEDERAL RESEARCH GRANTS FOR INSTITUTIONS AND RESEARCH INSTITUTES CONDUCTING GAIN-OF-FUNCTION RESEARCH.

(a) DEFINITION OF GAIN-OF-FUNCTION RESEARCH.—In this section, the term ''gain-of-function research'' means any research that—

(1) may be reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the virus would have enhanced pathogenicity or transmissibility in any organism; or

(2) involves the enhancement of potential pandemic pathogens or related risky research with potentially dangerous pathogens.

(b) PROHIBITION.—Notwithstanding any other provision of law, no research grants supported by Federal funds may be awarded to institutions of higher education, or other research institutes, that are conducting gain-of-function research.

From: Morens, David (NIH/NIAID) [E] [b6 ([b6])]
Sent: 7/22/2021 10:26:06 PM
To: Peter Daszak [b6]; Gerald Keusch [b6]

From Scalise presser: every single expert we have identified tells us the virus was released from the Wuhan lab. This is the BS that 50-100 million Americans hear every day. d

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

From: Morens, David (NIH/NIAID) [E] [b6] ([b6])
Sent: 7/5/2021 4:08:56 PM
To: Peter Daszak ([b6]) [[b6]]; Keusch, Jerry ([b6]) [b6]
Subject: FW: Global Times, China: Western scientists face government probe, death threats for opposing COVID-19 lab-leak theory: source

David

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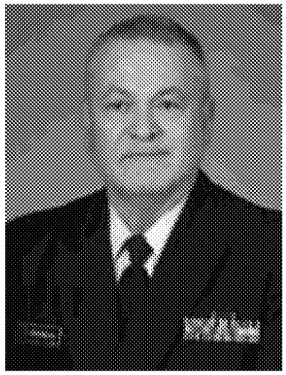

From: Folkers, Greg (NIH/NIAID) [E] [b6]
Sent: Monday, July 5, 2021 11:50 AM

Subject: Global Times, China: Western scientists face government probe, death threats for opposing COVID-19 lab-leak theory: source

Western scientists face government probe, death threats for opposing COVID-19 lab-leak theory: source

By GT staff reporters Published: Jul 05, 2021 02:18 PM

Peter Ben Embarek (center) talks with Liang Wannian (left) and Marion Koopmans (right) after a press conference to wrap up a visit by an international team of experts from the World Health Organization (WHO) in the city of Wuhan, in Central China's Hubei Province on Tuesday. Photo: AFP

Prominent US and Australian scientists focused on the COVID-19 origins tracing are now facing tremendous political pressure, and some have been sidelined for not yielding to politicians-driven conspiracy theory on the matter and received anonymous threatening letters with bullets, the Global Times learned from people familiar with the matter. Chinese experts have urged the US to stop politicizing the origin-tracing research and conduct a comprehensive investigation in the US.

Since the Biden administration ordered in May US intelligence agencies to report on COVID-19 origins within 90 days, several US scientists have been put at the center of the political storm. These scientists have been facing the suppression of Republicans. For example, Anthony Fauci, who advises US President Joe Biden and leads National Institute of Allergy and Infectious Diseases, has been a target of the GOP. Elise Stefanik, the House Republicans conference chair, sent a fundraising email recently with the subject "Fire Fauci" and senator Josh Hawley also tweeted that Fauci's recently released emails and investigative reporting about COVID-19 origins are shocking. The time has come for him to resign and for a full congressional investigation into the origins to take place, according to US media reports.

Under such growing political pressure, Fauci has been increasingly ambiguous on his rhetoric. Another US scientist, who also took part in the WHO-China joint team on the origins research, has also been a target of such attacks, the Global Times learned. After collaborating in the project with China, Peter Daszak, president of EcoHealth Alliance, was recused from the UN-backed commission work on the origins of the epidemic.

A source close to the matter told the Global Times earlier that the US scientist is being personally threatened by emails, phone calls and messages on social media, and people who attacked him generally have far-right and even white supremacism leanings. GOP members of Congress are whipping those extremists up now.

"There is a coordinated political campaign to undermine anyone involved in the origins work if they do not fit the lab leak narrative. This is coming mainly from the right wing circles in the US, Australia, and in Europe, mainly the UK," the

source said.

In the meantime, some so-called "international scientists" seeking attention have been making grandstanding campaigns by issuing open letters to call for an investigation into the COVID-19 origins.

It's revealing that some so-called "international scientists" who recently called for a COVID-19 origins inquiry were politicians with political agendas. But many scientists who truly uphold the spirit of science - objectivity and impartiality - have been attacked by some governments and extremists, or even received death threats, Chinese Foreign Ministry spokesperson Wang Wenbin said at Monday's routine press conference. Wang said that the right idea was to carry out more in-depth and detailed scientific studies in a wider range.

Death threats, unable to continue work

Letting politics to override science is not only prevailing in the US but also in Australia. Evolutionary biologist Edward Holmes at the University of Sydney, who released an open letter back in last April, is being probed by the Australian government. In the letter, Holmes claimed that there was no evidence that SARS-CoV-2, the virus that causes COVID-19 in humans, originated in a lab in Wuhan, Central China's Hubei Province. Like many others who oppose the lab-leak theory, Edward Holmes has received a number of threatening letters with real bullets, the Global Times learned from the people familiar with the matter.

He was threatened that if he continued expressing opinions on the origins of the virus, he may face even further crackdown, a source close to the matter said. Due to the tremendous pressure Holmes faces, he is undergoing psychotherapy and is unable to carry out normal scientific research work, the source said.

According to a Sydney Morning Herald report in October, 2020, Holmes became the target of online harassment after he co-authored a paper in Nature Medicine debunking the pervading conspiracy theory that the virus was engineered in or escaped from a laboratory in Wuhan. He also received "death threats" from conspiracy theorists, the report said.

Though the US government and politicians have been pushing forward their political agenda in bashing China with the lab-leak theory, targeting a number of global scientists and the Wuhan Institute of Virology (WIV), most scientists spoke out and dismissed the theory, reiterating that the most likely scenario is that the virus has a natural origin.

For instance, Danielle Anderson, the only foreign scientist who once worked at the WIV, was quoted as saying in a Bloomberg report on June 28 that no one she knew at the Wuhan institute was ill toward the end of 2019. Recently the Wall Street Journal falsely claimed three researchers from the lab were hospitalized with flu-like symptoms in November 2019. She also described the place as having the highest biosafety designation with very strict procedures.

After she told Health Feedback that it's "simply false" to label the WIV as a bioweapons research lab, she had her name "trashed so viciously by extremists she had to call in police," the Sydney Moring Herald reported on Sunday.

"I really find it hard to think that if something escaped from a laboratory it would be this difficult to prove that concept. Among other things, it is an unknown virus that has no signs of genetic engineering inside," said Massimo Galli, director of Infectious Diseases at Milan's Luigi Sacco Hospital, the Adnkronos reported on June 22.

He said that there is a 99-percentage chance that the spread of the virus is a natural event. "This story of the laboratory virus does not have the slightest basis from a scientific point of view to be carried forward," added Galli.

Next country for tracing virus origins: the US

The US National Institute of Health issued a new antibody testing study that suggested the virus was present in some states in late December 2019, earlier than the first case reported in the country in January 2020. With some US scientists reporting more earlier cases, Chinese scientists have urged that these cases should serve as evidence for the next-stage virus-tracing investigations in the US.

In the All of Us study, by the US institutes released on June 15, researchers analyzed more than 24,000 stored blood samples contributed by program participants across all 50 states between January 2 and March 18, 2020. "In this study, the first positive samples came from participants in Illinois and Massachusetts on January 7 and 8, 2020, respectively, suggesting that the virus was present in those states in late December," it said.

However, the study authors noted several limitations to their study. While the study included samples from across the US, the number of samples from many states was low.

Yang Zhanqiu, a virologist from Wuhan University, told the Global Times on Monday that the research has shown the epidemic in the US probably emerged earlier than in Wuhan. In other words, the epidemic in the US was probably caused by a domestic virus rather than one transmitted from Wuhan.

But more large-scale epidemiological surveys are needed in the US to identify the relationship between these cases and those in other countries and regions, including Wuhan, to determine the origin and transmission route of the virus.

Yang mentioned the outbreaks of flu and pneumonia related to the use of E-cigarette in the US prior to the COVID-19 pandemic, calling for the US to release epidemiological surveys into these outbreaks, if they did any, to find out if they were COVID-19 cases.

The US has nearly all the variants spreading around the world, based on this, the virus most likely originated in the US rather than the Wuhan lab, according to Yang.

From: Morens, David (NIH/NIAID) [E] [b6] ([b6])
Sent: 6/29/2021 8:16:53 PM
To: Peter Daszak ([b6]) [[b6]]; Keusch, Jerry ([b6]) [[b6]]; Rich Roberts ([b6]) [[b6]]
Subject: FW: Wash Examiner: Trump COVID testing czar testifies coronavirus most likely originated in Wuhan lab

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From: Folkers, Greg (NIH/NIAID) [E] [b6]
Sent: Tuesday, June 29, 2021 3:58 PM
Subject: Wash Examiner: Trump COVID testing czar testifies coronavirus most likely originated in Wuhan lab

Trump COVID testing czar testifies coronavirus most likely originated in Wuhan lab

by Jerry Dunleavy, Justice Department Reporter |
| June 29, 2021 02:37 PM

The COVID-19 testing czar for former President Donald Trump says the "most likely" origin for the pandemic was an accidental escape from a Wuhan lab, testifying Tuesday as one of four expert witnesses during a House Republican effort to get to the bottom of how the coronavirus emerged.

Brett Giroir, an assistant secretary of health and a member of Trump's White House Coronavirus Task Force, said: "I assess that the most likely origin was an accidental infection of laboratory personnel from the Wuhan Institute of Virology, with secondary transmission to the local population and subsequent spread to hundreds of millions of people around the world."

Giroir, a former four-star admiral in the U.S. Public Health Service Commissioned Corps, spoke Tuesday as part of a panel organized by House Republicans on the Select Subcommittee on the Coronavirus Crisis.

"There is now an increasing body of circumstantial evidence pointing to a lab leak origin of the virus," Giroir said. "The bottom line is: I believe it's just too much of a coincidence that a worldwide pandemic caused by a novel bat coronavirus that cannot be found in nature started just a few miles away from a secretive laboratory doing potentially dangerous research on bat coronaviruses. Sometimes, the most obvious explanation is indeed the correct one."

A State Department fact sheet released in January contended Wuhan lab researchers "conducted experiments involving the bat coronavirus identified by Wuhan virologists in January 2020 as its closest sample to COVID-19" and that the lab "has a published record of conducting 'gain-of-function' research to engineer chimeric viruses." The fact sheet also asserted the lab "engaged in classified research, including laboratory animal experiments, on behalf of the Chinese military" and that lab workers became sick with coronavirus-like symptoms in autumn 2019.

The National Institutes of Health's RePORTER website said the agency provided $15.2 million to Peter Daszak's New York-based EcoHealth Alliance over the years, with $3.74 million toward understanding bat coronavirus emergence. Daszak, a key member of the World Health Organization-China joint study team earlier this year, maintained a working relationship with Wuhan lab "bat lady" Shi Zhengli, sending at least $600,000 in NIH funding for bat coronavirus research.

Giroir said: "It is essential that Congress provides leadership for a comprehensive, transparent, and unbiased investigation to determine the most likely origin of the virus, whether the NIH funded, directly or indirectly, or approved of, explicitly or tacitly, potentially dangerous research within the Wuhan lab, and what the U.S. can do to minimize the possibility of future pandemics and enable rapid global containment of any suspicious infectious outbreak."

He added that the WHO couldn't be relied upon for an investigation because it has no authority to do anything in China without direct approval from the Communist Party.

NIH DEFENDS DELETING GENETIC SEQUENCES OF COVID-19

The Biden administration and the United States's allies are largely pinning hopes for a second COVID-19 origins investigation in China on the WHO, despite the WHO-China joint study team's visit to Wuhan earlier this year that essentially dismissed the lab leak hypothesis.

David Asher, who led the Trump State Department's Bureau of Arms Control, Verification, and Compliance investigation into COVID-19's origins, said China should be punished for its role in the pandemic.

"We should stop funding the Chinese Communist research into biology. This dangerous gain-of-function collaboration with China has to end ... We've gotta enforce our treaty compliance, that should be a focus across the board," Asher said, adding, "Sanctions — China needs to be coerced. They need to feel the pain."

Asher added: "Whether the Chinese did this deliberately or not in terms of creating this pathogen — I think the chances are they were working on it and it was funded by the military, I'm very confident of that — but whether they released it or not deliberately or just had an accident, I think the answer is they probably had an accident, but that doesn't matter, because they allowed it to be weaponized in the wake of its release."

The State Department concluded in April that China has "engaged in activities with dual-use applications, which raise concerns regarding its compliance with Article I of the Biological Weapons Convention" and that "the United States does not have sufficient information to determine whether China eliminated its assessed historical biological warfare program, as required under Article II of the Convention."

Asher said: "What we found truly disturbed us: that the Chinese were working on a military-supported program, which they did not declare under the Biological Weapons Convention — so they lied. It involved coronaviruses, which they said they weren't working on at the Wuhan institute."

The former State Department official called for a 9/11-like commission to investigate COVID-19's origins.

Dr. Steven Quay and Richard Muller, scientists who earlier this month wrote a piece for the *Wall Street Journal* which contended that "the most compelling reason to favor the lab leak hypothesis is firmly based in science," also testified on Tuesday.

Quay, the founder of Atossa Therapeutics, said Tuesday: "I believe the evidence conclusively establishes that the COVID pandemic was not a natural process but instead came from a laboratory in Wuhan, China, and that it has the fingerprints of genetic manipulation through a process called 'gain-of-function' research."

Muller, an emeritus professor of physics at the University of California, Berkeley, said: "Some people say we will never know, not until China confesses or unless there is a whistleblower."

"Well, we have a whistleblower. It was the virus itself. it came here, it came out of China, it came to us, and it carried with it genetic information."

From: Morens, David (NIH/NIAID) [E] [b6 b6]
Sent: 10/21/2021 2:17:02 PM
To: Peter Daszak ([b6]) [b6]; Keusch, Jerry ([b6]) [b6]; Kessler, Robert ([b6]) [[b6]]
Subject: FW: SARS-CoV-2 and NIAID-supported Bat Coronavirus Research https://bit.ly/3n6kojC

Fom NIH website

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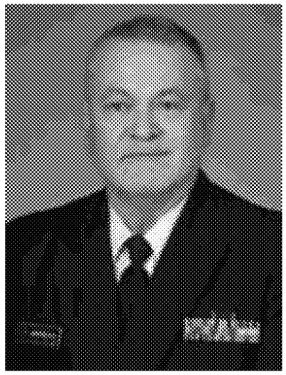


From: Folkers, Greg (NIH/NIAID) [E] b6
Sent: Wednesday, October 20, 2021 5:16 PM
Subject: SARS-CoV-2 and NIAID-supported Bat Coronavirus Research https://bit.ly/3n6kojC

SARS-CoV-2 and NIAID-supported Bat Coronavirus Research

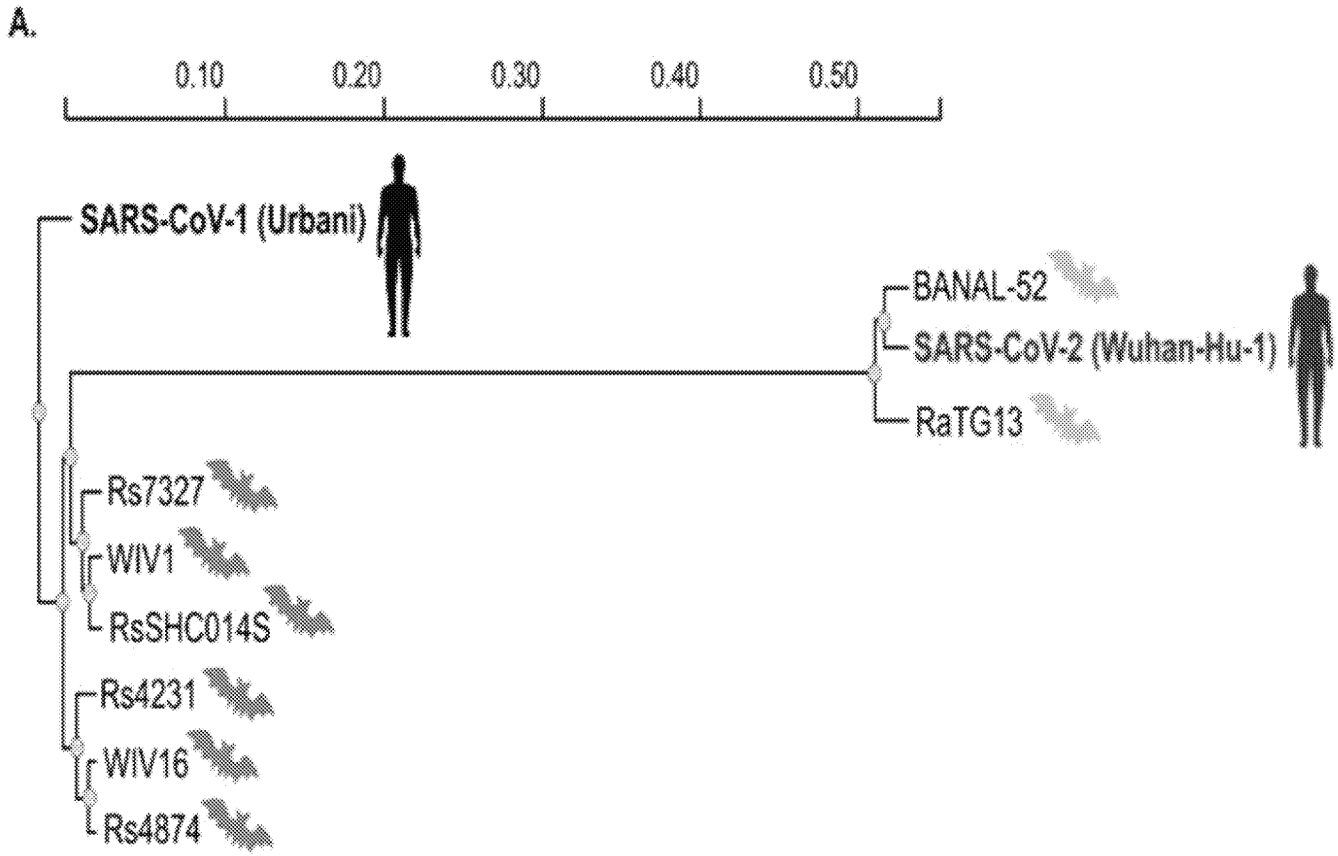
An Analysis: Evolutionary Distance of SARS-CoV-2 and Bat Coronaviruses Studied Under the NIH-supported Research Grant to EcoHealth Alliance

The research that NIH approved under the grant to EcoHealth Alliance with a subaward to the Wuhan Institute of Virology in Wuhan, China sought to understand how animal coronaviruses, especially bat coronaviruses, evolve naturally in the environment and have the potential to become transmissible to the human population. This research included studying viral diversity in bat reservoirs, surveying people who work in live animal markets or other occupations with high exposure to wildlife for evidence of bat coronavirus infection and analyzing data to predict which newly discovered viruses pose the greatest threat to human health.

Coronaviruses use a protein called spike to bind to a protein on the surface of a host cell to facilitate infection. Some coronaviruses, including SARS-CoV-1 (the cause of the SARS outbreak in 2003) and SARS-CoV-2 (the cause of the COVID-19 pandemic), use the angiotensin converting enzyme-2 (ACE2) protein to help enter and infect host cells. In order to study animal coronaviruses circulating in nature, the investigators replaced the spike protein from a well-characterized bat coronavirus, WIV1-CoV, with the spike protein of animal coronaviruses recently discovered in bats in China. Using techniques common in virology, experiments involved a single round of infection in several cell lines, and in some cases, in mice that were genetically modified to express the human version of ACE2. All other aspects of the mice, including the immune system, remained unchanged. The ACE2 transgenic mice were used to determine if spike proteins from bat coronaviruses discovered in China were capable of binding human ACE2, and therefore, whether the bat coronaviruses themselves, which were already present in the environment, could potentially infect humans and cause disease. WIV1-CoV is not known to cause infection in humans but has been shown in the laboratory to infect both human cells and ACE2 transgenic mice (ref), making it an ideal tool to use for these studies. Several of the bat coronaviruses used in these experiments were also found to be capable of replicating in ACE2 transgenic mice, indicating that the spike protein from the naturally occurring bat coronaviruses from which they were made could bind ACE2 in vivo.

Questions have been raised about whether this NIH-funded research had a role in the emergence of SARS-CoV-2. In this regard, the chimeric viruses that were studied (i.e., the WIV-1 virus with the various spike proteins obtained from bat viruses found in nature) were so far distant from an evolutionary standpoint from SARS-CoV-2 (Figure 1) that they could not have possibly been the source of SARS-CoV-2 or the COVID-19 pandemic. The body of the scientific data from this award including the bat coronavirus sequences published in the scientific literature and public databases makes this conclusion readily apparent to anyone with experience in and knowledge of virus phylogeny and evolutionary biology.

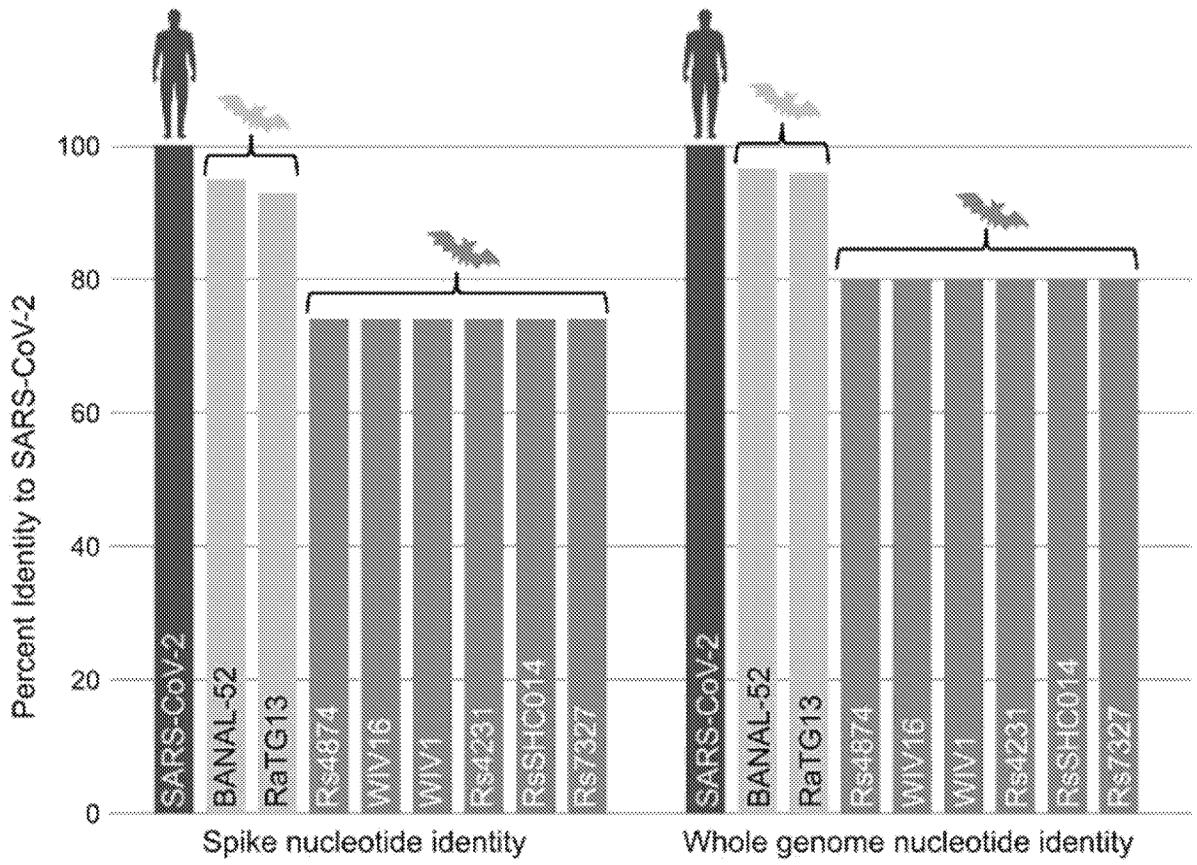
Figure 1. Relationship of bat coronaviruses to SARS-CoV-1 and SARS-CoV-2.



A) A phylogenetic tree based on nucleotide sequences of indicated coronavirus spike proteins demonstrating the evolutionary distance of SARS-CoV-2 with the bat coronaviruses experimentally studied under the NIH grant to EcoHealth Alliance (blue bat icons). Bat coronaviruses most closely related to SARS-CoV-2, none of which were studied in the EcoHealth grant, are denoted with orange bat icons. The scale bar represents the number of nucleotide substitutions per site.

Credit
NIAID

B.



B) Comparison of the nucleotide sequence identity of indicated coronaviruses to SARS-CoV-2. The left panel shows the percent identity of indicated coronavirus spike nucleotide sequences to SARS-CoV-2. The right panel shows the percent nucleotide identity of the indicated full coronavirus genomes to SARS-CoV-2.
Despite the similarity of RaTG13 and BANAL-52 bat coronaviruses (orange bars) to SARS-CoV-2 (red bars), experts agree that even these viruses are far too divergent to have been the progenitor of SARS-CoV-2, further highlighting that the bat coronaviruses studied under the EcoHealth Alliance grant (blue bars) could not have been the source of SARS-CoV-2 and the COVID-19 pandemic. Several other similarly divergent viruses that failed to replicate in cells are not shown (ref).

Credit
NIAID

The above figure shows the sequence relationships between SARS-CoV-1, SARS-CoV-2 and the naturally occurring bat coronaviruses used in experiments under the NIH grant to EcoHealth Alliance and reported in the scientific literature (ref) or annual progress reports. From this analysis, it is evident that the viruses studied under the EcoHealth Alliance grant are very far distant from SARS-CoV-2. Included for comparison is RaTG13, one of the closest bat coronavirus relatives to SARS-CoV-2 collected by the Wuhan Institute of Virology (ref) and BANAL-52, one of several bat coronaviruses recently identified from bats living in caves in Laos (ref). Although RaTG13 and BANAL-52 are 96-97% identical to SARS-CoV-2 at the nucleotide level (>900 nucleotide differences across the entire genome), the difference actually represents decades of evolutionary divergence from SARS-CoV-2. Experts in evolutionary biology and virology have made it clear that even the closest known relatives of SARS-CoV-2, which were not studied under the EcoHealth Alliance grant, are evolutionarily too distant from SARS-CoV-2 to have been the progenitor of the COVID-19 pandemic (ref, ref). Field studies continue the search for more proximate progenitors.

Content last reviewed on October 20, 2021

From: Morens, David (NIH/NIAID) [E] [b6] ([b6])
Sent: 6/29/2021 8:46:55 PM
To: Peter Daszak ([b6]) [[b6]]; Keusch, Jerry ([b6]) [[b6]]; Rich Roberts ([b6]) [[b6]]
Subject: FW: Webcast -- GOP Oversight committee hearing 6/29/2021: Led By Science: The COVID-19 Origin Story https://bit.ly/3jns1lz

Giroir testifying before the Republicans today, this may be where he said that covid was man made.

David

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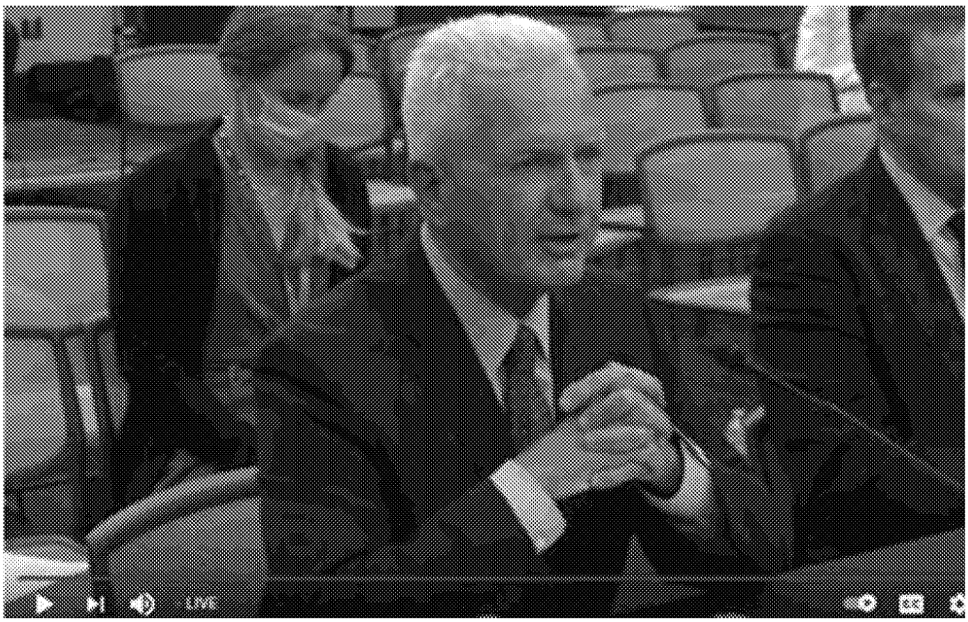
b6

From: Folkers, Greg (NIH/NIAID) [E] b6
Sent: Tuesday, June 29, 2021 2:19 PM

Subject: Webcast -- GOP Oversight committee hearing 6/29/2021: Led By Science: The COVID-19 Origin Story https://bit.ly/3jns1lz



From: Morens, David (NIH/NIAID) [E] [b6] ([b6])
Sent: 10/5/2021 11:34:58 AM
To: Taubenberger, Jeffery (NIH/NIAID) [E] ([b6]); Peter Daszak ([b6]) [b6]; Keusch, Jerry ([b6]) [b6]
Subject: FW: Wpost: NIH Director Francis S. Collins will step down by year's end

David

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301 496 4409
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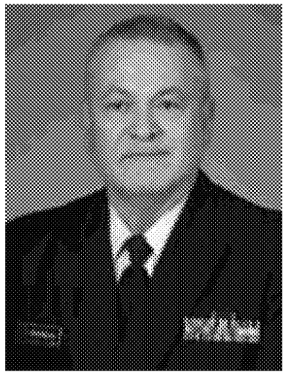

From: Folkers, Greg (NIH/NIAID) [E] b6
Sent: Monday, October 4, 2021 11:00 PM
Subject: Wpost: NIH Director Francis S. Collins will step down by year's end

NIH Director Francis S. Collins will step down by year's end

By
Lenny Bernstein
and
Carolyn Y. Johnson

Today at 10:21 p.m. EDT

National Institutes of Health Director Francis S. Collins, who headed the government's effort to map the entire human genetic code and two decades later became one of the most recognizable leaders in the battle against the coronavirus pandemic, will leave his post by the end of this year, NIH will announce Tuesday.

After more than 12 years directing the nation's premier biomedical research center, Collins, a 71-year-old physician-geneticist, will return to his lab at the National Human Genome Research Institute, part of NIH. He is the longest-tenured director of the Bethesda, Md.,-based NIH, which he ran through the Obama and Trump administrations and into the first year of the Biden presidency.

No decision has been made on an interim director, an NIH official said. In the midst of the pandemic, Biden will nominate a new director who must be confirmed by the evenly divided Senate.

In an interview, Collins said he went on a retreat by himself in May to assess the pros and cons of stepping down and eventually concluded that this was the year to do it. He said he did not want to get too far into the Biden administration before making the move and was confident NIH's role in developing therapeutics, tests and vaccines for the coronavirus had reached "a pretty stable place." The NIH partnered with Moderna to produce a highly effective coronavirus vaccine with stunning speed.

"There comes a time where an institution like NIH really benefits from new vision, new leadership," he said. "This was the right timing."

A born-again Christian who wrote a book about reconciling science and religion, Collins came into his job in 2009 facing many questions — and some sharp criticism — about whether a man of faith should lead a data-driven research institution that includes world-renowned scientists among its 18,000 employees.

How NIH chief Francis Collins is trying to get people of faith to wake up to coronavirus realities

He will step down at a time when such questions have given way to the politicization of science and sometimes violent disagreement about even well-proved medical facts.

"Every issue, the polarization gets deeper and deeper, the tribes have formed their views and it's very hard to see how we step back from that," he said.

Over the 12 years of Collins's tenure, NIH budget has risen from $30 billion to $41.3 billion and support from Congress has mostly remained steady. He has appointed most of the current heads of NIH's 27 institutes and centers.

Along the way, Collins, who still sometimes rides a Harley-Davidson motorcycle and breaks into song for occasions large and small, became one of the more public faces of science in the United States, especially as the pandemic continued. Collins plays an acoustic guitar decorated with a double-helix and sang the national anthem at Nationals Park in 2016.

"Francis Collins is a brilliant scientist and an amazing administrator, and a real humanist and a pretty good guitar player and singer too," said Eric Lander, who worked with Collins on the Human Genome Project, which finished identifying and mapping all 20,000 human genes in 2000.

"Time after time, Francis was able to bring a vision to his institute at NIH, and then the whole NIH, to see what the next challenges would be that the scientific community could rally around. It was a huge thing," Lander said.

But early in Collins's tenure a deadly infection killed six people at NIH Clinical Center, the hospital where patients come for cutting edge treatments as part of clinical trials. In 2016, Collins was forced to replace the leadership of the Clinical Center after an independent review determined that patient safety had become "subservient to research demands." And NIH has struggled to substantially add more people of color among the scientists who receive its grants.

The NIH passes out about 80 percent of its money to researchers at academic institutions around the U.S. and internationally, spending about 20 percent for the work conducted in its own labs.

"We have increased modestly the number of NIH grantees who are people of color, but it's still well below" their proportion in the general population, Collins said. NIH has done a better job of bringing women into leadership positions, he said. In 2019, Collins said he would no longer appear on all-male panels at scientific meetings.

Born in Staunton, Va., and home-schooled through the sixth grade, Collins became one of the world's top genetic researchers, helping to discover the genes responsible for cystic fibrosis and neurofibromatosis, a condition that causes tumors to form in the spine and brain.

Under Collins, NIH launched ambitious projects that took advantage of the scientific expertise he was able to tap, his experience leading the genome project — which involved scientists in six nations — and the money at his command.

They include the Cancer Moonshot championed by then vice president Biden in 2016; a large initiative to study the human brain; the All of Us Research Program that is enrolling 1 million Americans in a gigantic database to help examine a wide range of factors that affect health; a precision medicine project that would use the information from those research studies to better treat cancer and other diseases by targeting patients' individual characteristics; a project to strengthen genomic research in Africa; and most recently an effort to understand long-haul covid-19 symptoms that plague 10 percent to 30 percent of people who develop the infection.

"As NIH director, you get to help coordinate that kind of high risk, as well as high reward, program," Collins said.

Then came the pandemic, which would thrust Collins into his most public role as a communicator, force him to accelerate scientific research with sometimes breathtaking results and deliver a few of the lowest moments of his career.

"He has a knack for taking very complex topics and breaking them down in a way that people can understand," said Jeff Zients, the White House Coronavirus Response Coordinator. "I think that's very underappreciated in public health.

"I do think he is a force for good. And that he always leads with the data and the science and the facts and brings tremendous credibility to the public health arena."

NIH's best-known triumph of the pandemic is its work with the company Moderna to develop one of the three coronavirus vaccines in less than a year. The timeline and effectiveness of the vaccine were beyond what most thought possible when the effort began.

NIH also has worked with drug companies to develop therapeutics and at-home testing after the Centers for Disease Control and Prevention initially botched the rollout of the U.S. coronavirus testing program.

Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases, who has known Collins for decades, now interacts with him every day as part of the pandemic response.

He said one of the most important contributions Collins has made during the pandemic was his presence on Saturday morning calls with pharmaceutical companies, in an effort to persuade them to recruit Black and Hispanic people into vaccine trials.

"That is extremely noteworthy — that the director of NIH would join me and my programmatic colleagues on the nuts and bolts of what you need to do to get more African Americans and Hispanics involved in the clinical trials. He didn't have to do that."

But as President Trump veered from scientific fact in 2020, Collins considered stepping down. Collins came to Fauci's office after hours on a winter evening to tell his friend that he was thinking of moving on.

"I said, 'Please don't do this,'" Fauci recalled in a conversation that Collins acknowledged in the interview. "I was pleading with him. For the good of NIH, he stayed on."

Nor did Collins envision the culture war over vaccines and mask-wearing that has plagued the U.S. coronavirus response, a situation he called a "major heartbreak.

"I did not dream that we would end up with fantastic, historic [vaccine test] results and here we are in October 2021 with 70 million" people unvaccinated and hundreds of thousands dead "as a result of a culture war," Collins said.

"I did not imagine that possible in the United States of America."

From: Morens, David (NIH/NIAID) [E] [b6 (b6)]
Sent: 7/16/2021 10:10:06 PM
To: Peter Daszak [b6]; Gerald Keusch [b6]
BCC: Morens, David (NIH/NIAID) [E] [b6 (b6)]
Subject: just reported

Senior Biden officials including Jake Sullivan have just reported to the media that they have concluded the "lab leak" theory is highly credible and must be pursued. d

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

From: Morens, David (NIH/NIAID) [E] [b6] ([b6])
Sent: 8/13/2021 3:22:48 PM
To: Peter Daszak ([b6]) [[b6]]; Kessler, Robert ([b6]) [[b6]]; Keusch, Jerry ([b6]) [[b6]]
Subject: FW: WaPo: In new documentary, WHO scientist says Chinese officials pressured investigation to drop lab-leak hypothesis

In the paper this am

David

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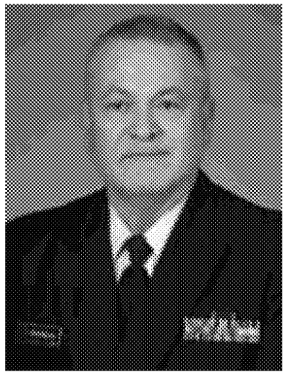
301 496 4409
[b6]



From: Embry, Alan (NIH/NIAID) [E] [b6]
Sent: Thursday, August 12, 2021 10:43 PM

To: NIAID OD AM <NIAIDODAM@niaid.nih.gov>
Subject: WaPo: In new documentary, WHO scientist says Chinese officials pressured investigation to drop lab-leak hypothesis

In new documentary, WHO scientist says Chinese officials pressured investigation to drop lab-leak hypothesis

https://www.washingtonpost.com/world/2021/08/12/who-origins-embarek/

The World Health Organization expert who led a controversial joint probe into the origins of the coronavirus pandemic says in a documentary airing Thursday night on Danish television that Chinese colleagues influenced the presentation of their findings.

Speaking to Danish documentarians, Peter Ben Embarek said Chinese researchers on the team had pushed back against linking the origins of the pandemic to a research laboratory in Wuhan in a report about the investigation. "In the beginning, they didn't want anything about the lab [in the report], because it was impossible, so there was no need to waste time on that," Ben Embarek said during the interview. "We insisted on including it, because it was part of the whole issue about where the virus originated."

In its report released earlier this year, the WHO-China team said it was "very unlikely" that the virus, officially named SARS-CoV-2, could have accidentally leaked from the Wuhan Institute of Virology or another facility in the Chinese city where infections were first found. The joint team of researchers said it would not recommend further investigation into the issue.

A discussion of whether to include the lab-leak theory at all lasted until 48 hours before the conclusion of the mission, Ben Embarek told the Danish reporters. In the end, Ben Embarek's Chinese counterpart eventually agreed to discuss the lab-leak theory in the report "on the condition we didn't recommend any specific studies to further that hypothesis." Asked in the documentary whether the report's "extremely unlikely" wording about the lab-leak theory was a Chinese requirement, Ben Embarek said "it was the category we chose to put it in at the end, yes." But he added that this meant it was not impossible, just not likely.

Ben Embarek said one similar scenario, in which a lab employee inadvertently could have brought the virus to Wuhan after collecting samples in the field, could be considered both a lab-leak theory and a hypothesis of direct infection from a bat, which was described as "likely" in the report.

"A lab employee infected in the field while collecting samples in a bat cave — such a scenario belongs both as a lab-leak hypothesis and as our first hypothesis of direct infection from bat to human. We've seen that hypothesis as a likely hypothesis," Ben Embarek said.

In further comments during the interview that were not included in the documentary but were incorporated in an account by the Danish channel TV2 on its website, Ben Embarek suggested that there could have been "human error" but that the Chinese political system does not allow authorities to acknowledge that.

"It probably means there's a human error behind such an event, and they're not very happy to admit that," Ben Embarek was quoted as saying. "The whole system focuses a lot on being infallible, and everything must be perfect," he added. "Somebody could also wish to hide something. Who knows?"

Asked for comment, Ben Embarek initially said the interview had been mistranslated in English-language media coverage. "It is a wrong translation from a Danish article," he wrote, declining to comment further and referring The Washington Post to the WHO. He did not immediately respond to follow-up questions.

WHO spokesman Tarik Jasarevic also said that the comment was mistranslated and that the interview took place "months ago."

"There are no new elements nor [a] change of the position [that] all hypothesis are on the table and WHO works with member states on the next step," Jasarevic said, referring to comments by senior officials with the global health organization about the probe.

The documentary, titled "The Virus Mystery," is scheduled to air on TV2 on Thursday evening. Ben Embarek had cooperated with the documentary filmmakers, even going so far as to film his trip to China for them on his phone to provide an inside look at a closed-off trip.

Ben Embarek led a team of international scientists on a mission to China in January to work with local officials to investigate the origins of a pandemic that has so far led to more than 200 million confirmed cases and at least 4.3 million deaths worldwide.
From the start, the trip was mired in controversy. Beijing delayed approval for the WHO trip, pushing back the researchers' arrival, while some of the international experts on the team were criticized for prior links to Chinese research.

Even once it arrived, the WHO team, subject to strict quarantine procedures, had only two weeks in the field to conduct research.
After the team's report was released in late March, it grew only more disputed. The team looked at four different scenarios for how the virus first spread to humans, labeling the idea of zoonotic spread from animals to humans as "most likely."

Other, less likely scenarios included that the virus could have been imported to China on frozen food — a theory pushed repeatedly by Chinese officials but seen as unlikely by many international experts. The "lab-leak" theory, the subject of intense speculation in the United States, was dubbed the least likely scenario, and the WHO team said it should no longer be investigated. Even skeptics of the theory found the dismissal a surprise.

At a news conference marking the release of the report, WHO Director General Tedros Adhanom Ghebreyesus said the scenario still needed closer study. "Although the team has concluded that a laboratory leak is the least likely hypothesis, this requires further investigation,

potentially with additional missions involving specialist experts, which I am ready to deploy," Tedros said.
Ben Embarek and other researchers on the team have hinted at immense pressure during the trip from all sides, with as many as 60 Chinese colleagues working with not only scientists but also public health figures.

"The politics was always in the room with us on the other side of the table," he told Science Magazine during an interview published in February. In a statement released on Thursday, the WHO spoke of the need for "next steps" in the investigation into the coronavirus's origins.

It also said that China and other, unnamed U.N. member states had written to the organization to question the basis for further study into theories of origin linked to the labs in Wuhan, with these critics suggesting that "the origins study has been politicized, or that WHO has acted due to political pressure."

"In order to address the 'lab hypothesis,' it is important to have access to all data and consider scientific best practice and look at the mechanisms WHO already has in place. WHO is only focused on science, providing solutions and building solidarity," the statement read.

The WHO-led study is only one point of ongoing investigation. Later this month, the U.S. intelligence community is expected to complete a 90-day review of the evidence about the origins of the coronavirus.

From: Morens, David (NIH/NIAID) [E] [b6 ([b6])]
Sent: 10/21/2021 1:26:42 PM
To: Peter Daszak ([b6]) [[b6]]; Kessler, Robert ([b6]) [[b6]]; Keusch, Jerry ([b6]) [b6]
Subject: FW: House Energy & Commerce GOP Leaders Statement on Documents Released by the NIH

David

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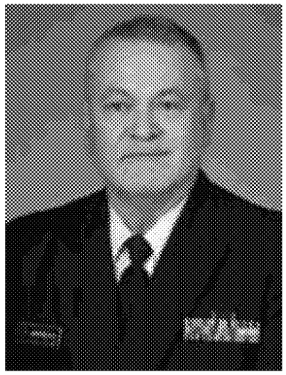

From: Folkers, Greg (NIH/NIAID) [E] b6
Sent: Thursday, October 21, 2021 9:24 AM
Subject: House Energy & Commerce GOP Leaders Statement on Documents Released by the NIH

Energy & Commerce GOP Leaders Statement on Documents Released by the NIH

10.20.21

Washington, D.C. — House Energy and Commerce Committee Republican Leader Cathy McMorris Rodgers (R-WA), Subcommittee on Health Republican Leader Brett Guthrie (R-KY), and Subcommittee on Oversight and Investigations Republican Leader Morgan Griffith (R-VA), released a statement in response to the National Institutes of Health (NIH) turning over a limited number of previously requested documents related to the origins of the COVID-19 pandemic.

As leaders of the House committee with jurisdiction over public health, the leaders have sent four letters to the NIH since March 18, 2021, asking the NIH to help inform a complete, scientific investigation into the COVID-19 pandemic.

Their statement:

"We are reviewing these documents sent to us by the NIH, including EcoHealth Alliance's Year Five progress report, which should have been submitted to the NIH two years earlier. We now know for certain that EcoHealth Alliance violated the terms of one of their grants that funded research in China.

"We are glad that the NIH is finally pursuing unpublished data from EcoHealth Alliance as we have urged for months, and as we pressed the NIH to do in June. However, it's unacceptable that the NIH delayed asking EcoHealth Alliance to submit unpublished data about risky research that they were required to do under the terms of their grant.

"The NIH has acknowledged that EcoHealth violated the terms of its grant and has been non-compliant. Yet, at the same time, NIH takes the word of this grant policy violator that EcoHealth is fully accounting for its research and that none of it had anything to do with the pandemic.

"We need full compliance with Congressional oversight. These documents are only the first step from the NIH in rebuilding public trust. They must be fully transparent about any research they have funded in China and how they will ensure proper oversight of risky research in the future. They owe it to the American people to be a better partner in revealing how this pandemic started. Every day that goes by, it will be harder to get answers to best prepare us in preventing future pandemics."

CLICK HERE to read the NIH's letter to the Energy and Commerce Committee Republican leaders.

CLICK HERE to read the EcoHealth Alliance Year Five progress report.

CLICK HERE to read the NIH genetic analysis document.

From: Morens, David (NIH/NIAID) [E] [b6] ([b6])
Sent: 8/15/2021 7:32:05 PM
To: Peter Daszak ([b6]) [[b6]]; Kessler, Robert ([b6]) [[b6]]; Keusch, Jerry ([b6]) [[b6]]
Subject: FW: WaPo: In new documentary, WHO scientist says Chinese officials pressured investigation to drop lab-leak hypothesis

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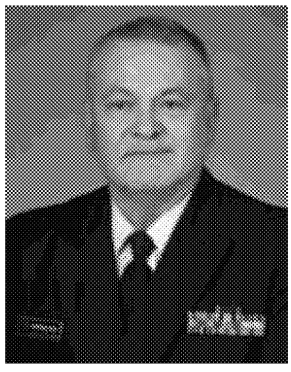

From: Folkers, Greg (NIH/NIAID) [E] [b6]
Sent: Sunday, August 15, 2021 9:07 AM

Subject: WaPo: In new documentary, WHO scientist says Chinese officials pressured investigation to drop lab-leak hypothesis

In new documentary, WHO scientist says Chinese officials pressured investigation to drop lab-leak hypothesis

https://www.washingtonpost.com/world/2021/08/12/who-origins-embarek/

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The WHO-led study is only one point of ongoing investigation. Later this month, the U.S. intelligence community is expected to complete a 90-day review of the evidence about the origins of the coronavirus.

From: Morens, David (NIH/NIAID) [E] [b6] ([b6])
Sent: 7/28/2021 1:51:52 PM
To: Peter Daszak ([b6]) [[b6]]; Keusch, Jerry [b6]) [[b6]]
Subject: FW: Senate Committee on Foreign Relations: Risch, Menendez, Rubio, Warner Stress Importance of Pursuing COVID Origins

David

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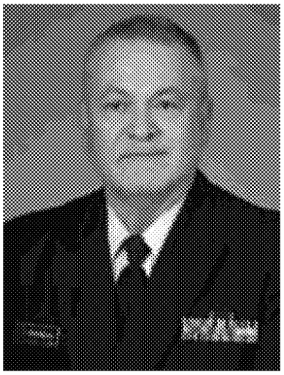

From: Folkers, Greg (NIH/NIAID) [E] [b6]
Sent: Wednesday, July 28, 2021 8:15 AM

Subject: Senate Committee on Foreign Relations: Risch, Menendez, Rubio, Warner Stress Importance of Pursuing COVID Origins

July 27, 2021

Risch, Menendez, Rubio, Warner Stress Importance of Pursuing COVID Origins

WASHINGTON – U.S. Senators Jim Risch (R-Idaho) and Bob Menendez (D-N.J.), ranking member and chairman of the Senate Foreign Relations Committee, along with U.S. Senators Marco Rubio (R-Fla.) and Mark Warner (D-Va.), vice chairman and chairman of the Senate Select Committee on Intelligence, today sent a letter to President Biden asking the administration to take three crucial steps to get to the bottom of the origins of the COVID-19 pandemic in order to prevent a similar calamity in the future.

"The PRC's refusal to cooperate with the World Health Organization (WHO) investigation into COVID-19 origins, the gag order it imposed on Chinese scientists and medical personnel, and its ongoing obfuscation and disinformation campaign regarding the pandemic have caused severe hardship worldwide," **wrote the senators**. "As the United States emerges from the pandemic, we believe that, in addition to addressing gaps in international pandemic prevention, preparedness, and response, including within our own government, three crucial steps are necessary to prevent a similar calamity in the future."

These steps include:

- Directing the intelligence community to continue prioritizing a thorough investigation into the origins of COVID-19 until there is a conclusion in which the United States has a high degree of confidence;
- Working with allies and partners to use all available resources and tools to pressure Beijing into permitting a transparent forensic investigation in the People's Republic of China; and
- Completing a thorough review of existing and prior U.S. government support or funding for research collaboration with the PRC related to gain-of-function, synthetic biology, biotechnology, or other research areas that pose dual-use concerns.

"We expect that Congress will remain fully informed of and consulted on your efforts to reach definitive conclusions regarding the origins of this pandemic, as well as any concrete policy recommendations," **concluded the senators**. "We stand ready to work with your administration in a bipartisan manner to seek answers to these important questions."

Full text of the letter can be found here and below:

Dear Mr. President:

The threat to international health and security posed by the Chinese Communist Party's (CCP) repressive and opaque governance of the People's Republic of China (PRC) has become glaringly apparent over the past eighteen months, particularly given the PRC's efforts to conceal the severity and scope of the outbreak of the SARS-CoV-2 virus that caused the COVID-19 pandemic. The PRC's refusal to cooperate with the World Health Organization (WHO) investigation into COVID-19 origins, the gag order it imposed on Chinese scientists and medical personnel, and its ongoing obfuscation and disinformation campaign regarding the pandemic have caused severe hardship worldwide.

We were therefore glad to see your May 26, 2021, statement directing the intelligence community to "redouble their efforts to collect and analyze information that could bring us closer to a definitive conclusion" with regard to the pandemic's origin. As the United States emerges from the pandemic, we believe that, in addition to addressing gaps in

international pandemic prevention, preparedness, and response, including within our own government, three crucial steps are necessary to prevent a similar calamity in the future.

First, we agree that the intelligence community must lead a thorough investigation into the origins of COVID-19. Identifying where the virus originated and how it first spread will be critical to preventing future pandemics. If the 90-day effort you have announced does not yield conclusions in which the United States has a high degree of confidence, we urge you to direct the intelligence community to continue prioritizing this inquiry until such conclusions are possible.

A full and impartial investigation that carefully considers all credible theories, backed by all available evidence, is critical. This includes theories suggested in an open letter by 18 distinguished experts to *Science Magazine* on May 14, 2021, which argued that "theories of accidental release from a lab and zoonotic spillover both remain viable."

We believe the intelligence community should examine relevant research at the Wuhan Institute of Virology (WIV) and associated facilities, such as the Wuhan Center for Disease Prevention and Control and the Wuhan Institute of Biological Products. This investigation must evaluate evidence regarding WIV researchers who fell ill in the fall of 2019. It should identify other details of any researchers at the WIV who were working on coronavirus projects, and attempts by the PRC government to silence or disappear them; details of any WIV gain-of-function research specific to coronaviruses or other potential human pathogens; laboratory safety standards and practices for such research; and details of any research in synthetic biology and biotechnology connected to the Military-Civil Fusion strategy, and other military work or funding at the WIV.

Additionally, this investigation must examine any evidence pointing to the possible transmission of SARS-CoV-2 from animals to humans, including specific zoonotic transmission chains, and the most probable timing, location, and contributing factors of any zoonotic spillover events.

We also believe that the investigation should address PRC efforts to prevent international inquiries into the origins of SARS-CoV-2, and other actions PRC authorities have taken to obscure the nature of the virus and its transmission. The U.S. government should examine the international agreements to which the PRC is a party that require disclosure and cooperation in the event of a viral outbreak like SARS-CoV-2, assess whether the PRC violated any of these agreements, and analyze its motivations for doing so.

The investigation should also include details on the collection and analytic guidance the Intelligence Community used from the start of the SARS-CoV-2 pandemic to the present to support policy and programmatic requirements.

Second, the U.S. government should lead efforts by the international community and the WHO to seek a transparent forensic investigation in the PRC. The PRC has an obligation to the international community to allow a full, unfettered, impartial, and scientific investigation into COVID-19 origins. In light of the PRC's continued stonewalling of WHO efforts, the U.S. government should work with our allies and partners to use all available resources and tools to pressure Beijing to permit a serious investigation.

Third, the United States must complete a thorough review of existing and prior U.S. government support or funding for research collaboration with the PRC related to gain-of-function, synthetic biology, biotechnology, or other research areas that pose dual-use concerns. U.S. taxpayer funding should not support any collaboration with PRC entities that pose health, economic or security risks for the United States. The PRC has demonstrated lax biosecurity standards, violated the International Health Regulations (2005), attempted to steal intellectual property related to COVID-19 vaccines, and may be in violation of the Biological Weapons Convention. The United States should not be partnering with or funding any country that exhibits these risk factors.

As part of a formal review, we therefore urge you to analyze the following: any direct or indirect U.S. taxpayer funding or engagement with entities in China, including the WIV, regarding gain-of-function research or other forms of research related to viruses, pathogens, and toxins; whether any such research for civilian purposes was diverted for military research; any U.S. taxpayer funding that was used to support gain-of-function research in China during the U.S. moratorium on such research from 2014-2017; and steps taken, if any, to apply additional scrutiny to direct or indirect

U.S. government funding, including sub-grants, to support gain-of-function studies in China, including at WIV, after the U.S. government lifted the moratorium on gain-of-function research in 2017.

We expect that Congress will remain fully informed of and consulted on your efforts to reach definitive conclusions regarding the origins of this pandemic, as well as any concrete policy recommendations. *The U.S. Innovation and Competition Act* (S. 1260), which recently passed the U.S. Senate, requires a report to Congress on many of the matters described in this letter. We stand ready to work with your administration in a bipartisan manner to seek answers to these important questions.

Thank you for your attention to and cooperation on these important issues.

Sincerely,

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From: Morens, David (NIH/NIAID) [E] [b6] ([b6])
Sent: 8/18/2021 3:31:51 PM
To: Peter Daszak ([b6]) [b6]; Kessler, Robert ([b6]) [b6]; Keusch, Jerry ([b6]) [b6]
Subject: FW: NYT: 'In the Same Breath' Review: Wuhan 2019, or When Normalcy Ended

David

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301 496 4409
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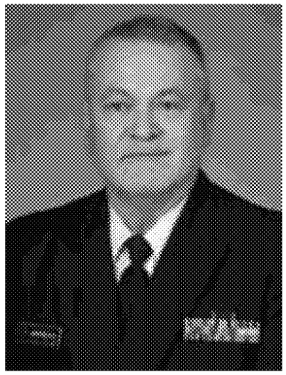

From: Folkers, Greg (NIH/NIAID) [E] b6
Sent: Tuesday, August 17, 2021 5:42 PM
Subject: NYT: 'In the Same Breath' Review: Wuhan 2019, or When Normalcy Ended

Critic's Pick

'In the Same Breath' Review: Wuhan 2019, or When Normalcy Ended

In her latest documentary, the director of "One Child Nation" revisits the pandemic as it unfolded in China as well as in the United States.

A scene from the documentary "In the Same Breath."Credit...HBO Documentary Films

By Manohla Dargis

Aug. 17, 2021, 4:35 p.m. ET

When you hear about filmmakers in conflict zones, you may flash on countries like Syria or Afghanistan. The movies produced in theaters of war often follow a similar arc: The documentarian parachutes in to take stock of a catastrophe. The focus tends to be on rubble, blood and suffering — the spectacle. In her short, stellar career, the Chinese filmmaker Nanfu Wang has repeatedly returned to a less obvious conflict zone in which the war for proverbial hearts and minds mostly takes place through state propaganda.

Her latest, "In the Same Breath," is a clear, razor-sharp look at the pandemic. And, as she did with her documentary "One Child Nation" (made with Jialing Zhang), Wang vividly fuses the political with the personal. In mid-January 2020, she flew to China with her toddler to visit her family for the New Year, a trip the two had made before. (Born in China, Wang has lived in the United States for years.) Over images of fireworks exploding in the night sky, she ruefully says that "this was the last moment I can remember when life still felt normal." And then she fills the screen with a rush of images: a blur of hospitals, X-rays, news reports and other visions from our Covid-19 world.

Back then, few — and certainly not Wang — knew that all normalcy was quickly disappearing when she briefly left her son with her mother, flying back to the States. The same day she flew out, China began shutting down Wuhan, the center of the outbreak. By isolating the city, China was trying to contain the virus and the pneumonialike respiratory disease it caused. At the same time, people elsewhere were traveling for the Lunar New Year's celebration (*chunyun*), which is thought to be the biggest mass migration in the world, involving billions of trips. You know the rest of this story, or may think you do: There was no stopping the virus, though, as Wang suggests, it surely could have been attenuated.

Agilely marshaling a wealth of found and original material — as well as 10 camera people across China, some of whom remain anonymous — Wang brings you back to the first stages of the pandemic, before the Wuhan shutdown, before the virus had been officially named. She pulls out cellphone videos, collects news reports and finds some extremely eerie surveillance footage from inside a clinic in Wuhan. It's unsettling, at times haunting, to watch people just going about their business, sometimes jammed together in celebration or just living their everyday, poignantly normal life, while others cough, stagger into emergency rooms and, in some distressing images, lie helpless in the streets.

Some of this will be familiar given the enormity of the disaster and its coverage. And there are moments here that recall the recent documentary "76 Days," an immersive account of the Wuhan shutdown from inside the city. Yet Wang brings new insights to the crisis, and she manages to both surprise and alarm you. She also quickens your pulse, and not just through the brisk editing, notably during the short period when she's separated from her child. But even after her husband safely brings their son home, a sense of profound urgency — and mystery — suffuses the movie as she toggles between the past and near-present, and revisits what was known and what was hidden.

To that end, as she has in her earlier work, Wang shrewdly and methodically homes in on China's propaganda machine, showing how misinformation shapes ordinary life, how it defines a people's consciousness of themselves and of the country. She is unrelentingly hard on its leadership. Nothing if not a crack dialectician, she repeatedly underscores the disconnect between what was happening on the ground in China, in hospitals and elsewhere, and how the government reacted to a situation that was spiraling out of its control. In speeches, conferences and smiling news reports, officials and their mouthpieces insisted that everything was fine. It was a message that, as Wang reminds you with crushing lucidity, American officials were sending to their people, too.

One of the attractions of Wang's work is how she inserts herself into her movies in a way that never slides into solipsistic narcissism. Rather, she uses her own history and identity — as a daughter and as a mother, as a Chinese national and as an American transplant — to open up other histories and identities, telling stories that are invariably greater than any one person.

If "In the Same Breath" — the title becomes more resonant with each new scene and shock — were simply about China and its handling (mishandling) of the pandemic, it would be exemplary. But the story that she tells is larger and deeper than any one country because this is a story that envelops all of us, and it is devastating.

In the Same Breath
Not rated. Running time: 1 hour 35 minutes. Watch on HBO platforms.

From: Morens, David (NIH/NIAID) [E] [b6 b6]
Sent: 10/14/2021 8:52:22 PM
To: Keusch, Gerald T [b6]; Peter Daszak [b6] [b6]; Kessler, Robert [b6] [b6]; Peter Hotez [b6] [b6]; Gale, Jason [j.gale@bloomberg.net]
Subject: RE: Nature: 'I hope you die': how the COVID pandemic unleashed attacks on scientists/Dozens of researchers tell Nature they have received death threats, or threats of physical or sexual violence.

I called b6 and told him I would speak to him either off the record or on.

He immediately called our NIH folks and asked to speak to me on the record, but so far HHS hasn't cleared it.

I am going to check again today. I am still on leave with b6 and not checking things closely.

David

David M. Morens, M.D.
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Senior Advisor to the Director
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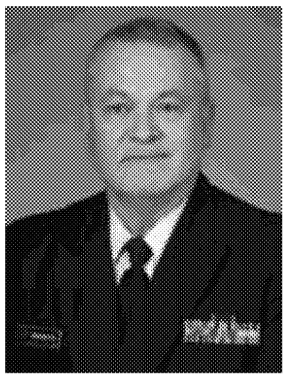
☎ b6 (assistant: Whitney Robinson)
301 496 4409
b6



From: Keusch, Gerald T [b6]
Sent: Thursday, October 14, 2021 4:47 PM
To: Morens, David (NIH/NIAID) [E] [b6]; Peter Daszak ([b6]) [b6]; Kessler, Robert ([b6]) [b6]; Peter Hotez ([b6]) [b6]; Gale, Jason <j.gale@bloomberg.net>
Subject: RE: Nature: 'I hope you die': how the COVID pandemic unleashed attacks on scientists/Dozens of researchers tell Nature they have received death threats, or threats of physical or sexual violence.

Shameful. I saw Peter Hotez sitting there in the photo, and I know about his experiences too antedating CoV-2 because he is a proponent of vaccines and immunization programs.

We need more and more pushback. I know that [b6] is planning to write about the disbanding of our Lancet Task Force, having spoken to him at length, and while I have no idea how he will put it together I am pretty sure he will include comments from me that push back on Sachs "holier than thou" stance, as I provided information on all the other non-negotiable demands he made that seriously infringed on the integrity of the Task Force's work and the necessary fire wall that must be in place between an expert evaluation panel and the sponsor of the panel to maximize objective assessment.

Jerry

From: Morens, David (NIH/NIAID) [E] [b6]
Sent: Thursday, October 14, 2021 3:17 PM
To: Peter Daszak ([b6]) [b6]; Keusch, Gerald T [b6]; Kessler, Robert ([b6]) [b6]; Peter Hotez ([b6]) [b6]; Gale, Jason <j.gale@bloomberg.net>
Subject: FW: Nature: 'I hope you die': how the COVID pandemic unleashed attacks on scientists/Dozens of researchers tell Nature they have received death threats, or threats of physical or sexual violence.

Does this ring any bells?

David

David M. Morens, M.D.
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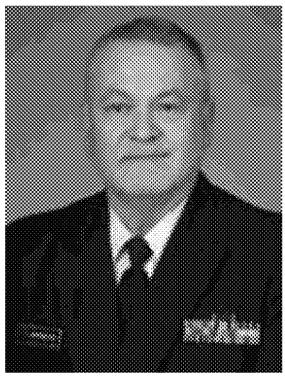
301 496 4409
b6



From: Folkers, Greg (NIH/NIAID) [E] b6
Sent: Thursday, October 14, 2021 3:08 PM
Subject: Nature: 'I hope you die': how the COVID pandemic unleashed attacks on scientists/Dozens of researchers tell Nature they have received death threats, or threats of physical or sexual violence.

- NEWS FEATURE
- 13 October 2021

'I hope you die': how the COVID pandemic unleashed attacks on scientists

Dozens of researchers tell *Nature* they have received death threats, or threats of physical or sexual violence.

- Bianca Nogrady

Public-health researcher Tara Kirk Sell (centre) experienced online and e-mail attacks after talking about COVID-19 in the media.Credit: US House of Representatives' Committee on Science, Space, and Technology

Infectious-diseases physician Krutika Kuppalli had been in her new job for barely a week in September 2020, when someone phoned her at home and threatened to kill her.

Kuppalli, who had just moved from California to the Medical University of South Carolina in Charleston, had been dealing with online abuse for months after she'd given high-profile media interviews on COVID-19, and had recently testified to a US congressional committee on how to hold safe elections during the pandemic. But the phone call was a scary escalation. "It made me very anxious, nervous and upset," says Kuppalli, who now works at the World Health Organization (WHO) in Geneva, Switzerland.

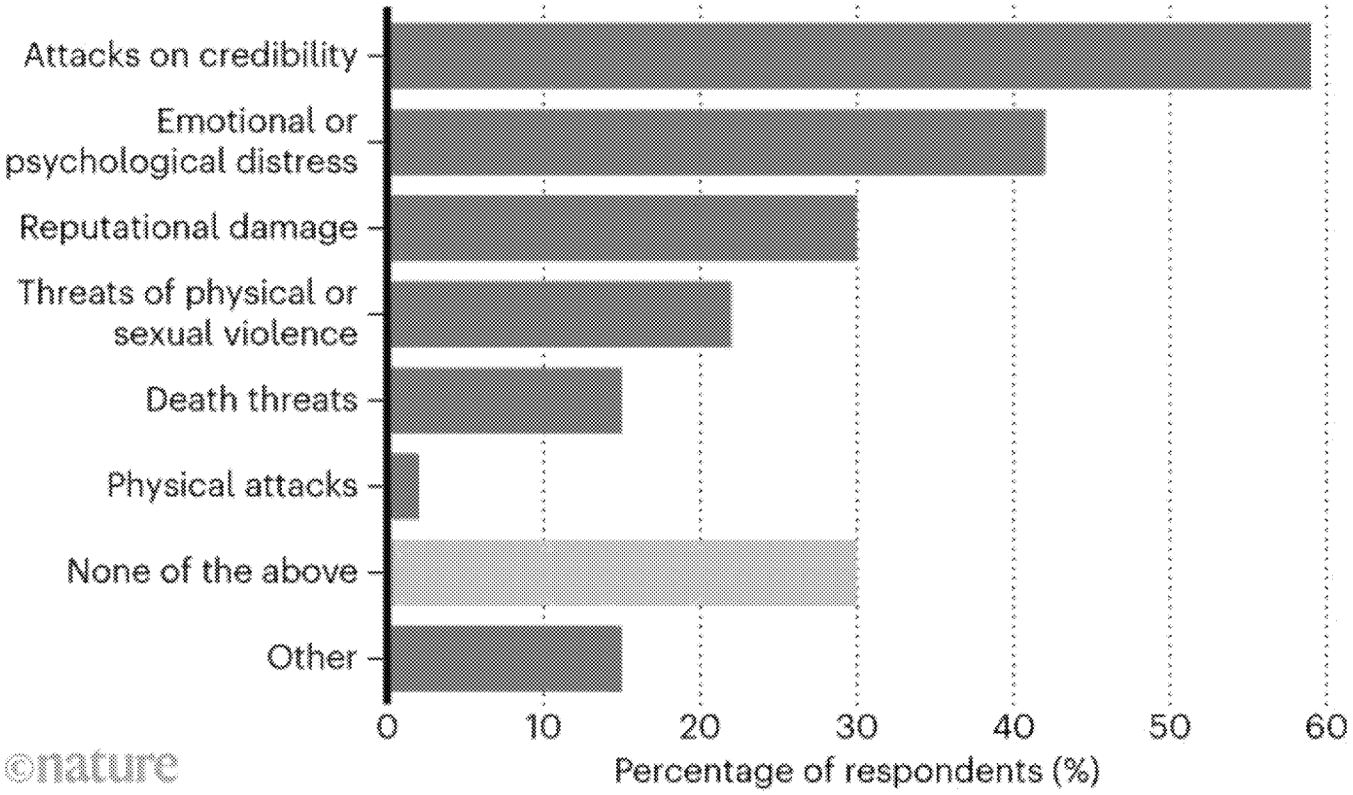
She called the police, but didn't hear that they took any action. The threatening e-mails, calls and online comments continued. The police officer who visited Kuppalli after a second death-threat call suggested she should get herself a gun.

Kuppalli's experience during the pandemic is not uncommon. A survey by *Nature* of more than 300 scientists who have given media interviews about COVID-19 — many of whom had also commented about the pandemic on social media — has found wide experience of harassment or abuse; 15% said they had received death threats (see 'Negative impacts').

NEGATIVE IMPACTS

In a *Nature* survey of scientists who have commented about COVID-19, 15% of 321 respondents said they had received death threats.

Question: Have you experienced any of the following negative impacts after speaking about COVID-19 to the media, or posting on social media? (You may select multiple options.)



Source: *Nature* analysis

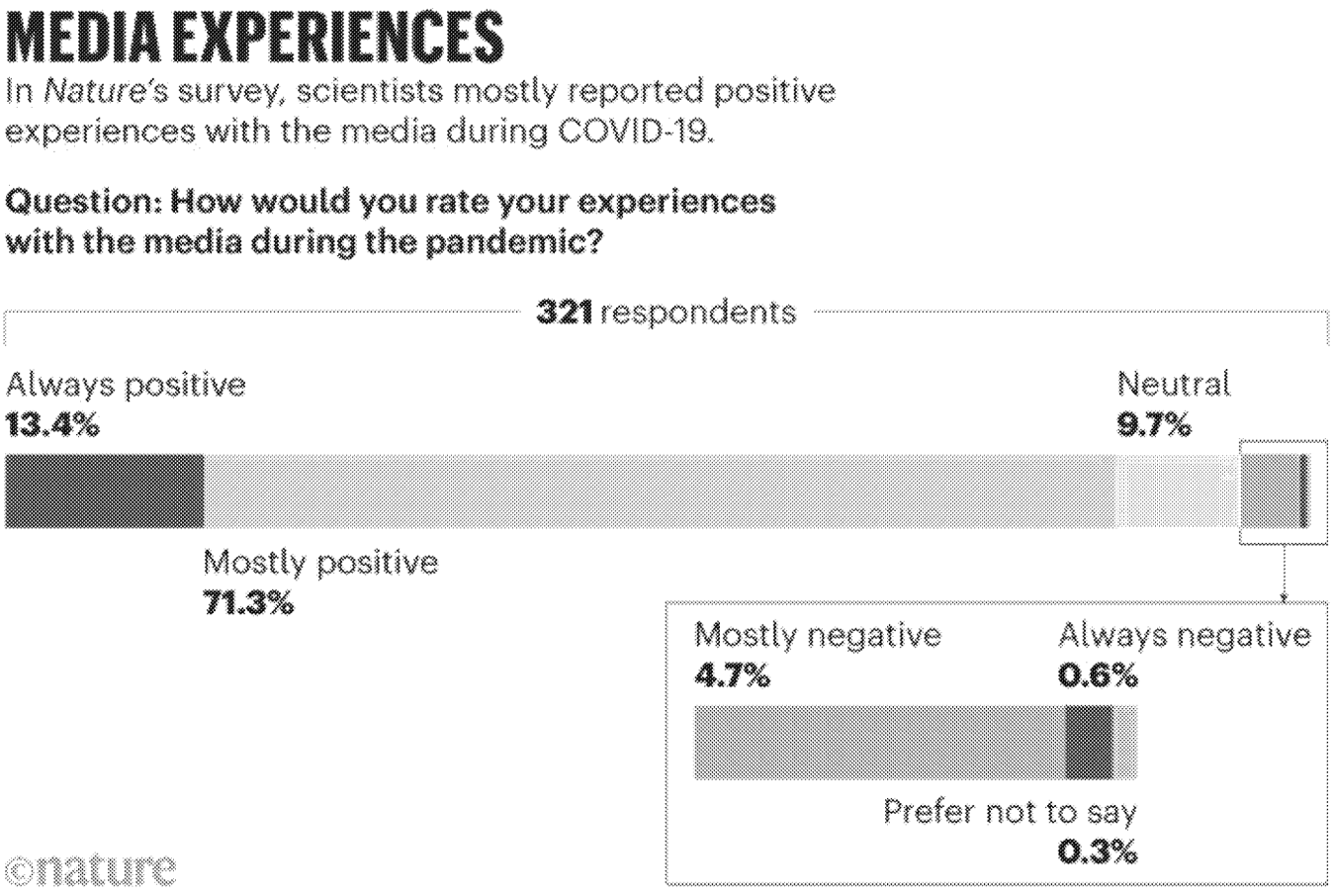
Some high-profile examples of harassment have been well documented. Anthony Fauci, head of the US National Institute of Allergy and Infectious Diseases, was assigned personal security guards after he and his family received death threats; UK chief medical adviser Chris Whitty was grabbed and shoved in the street; and German virologist Christian Drosten received a parcel with a vial of liquid labelled 'positive' and a note telling him to drink it. In one extraordinary case, Belgian virologist Marc Van Ranst and his family were placed in a safe house when a military sniper went on the run after leaving a note outlining his intentions to target virologists.

These examples are extreme. But in *Nature*'s survey, more than two-thirds of researchers reported negative experiences as a result of their media appearances or their social media comments, and 22% had received threats of physical or sexual violence. Some scientists said that their employer had received complaints about them, or that their home address had been revealed online. Six scientists said they were physically attacked (see Supplementary information for survey data tables).

Coordinated social-media campaigns and threatening e-mails or phone calls to scientists are not new: topics such as climate change, vaccination and the effects of gun violence have drawn similar attacks in the past. But even scientists who had a high profile before COVID-19 told *Nature* that the abuse was a new and unwelcome phenomenon tied to the

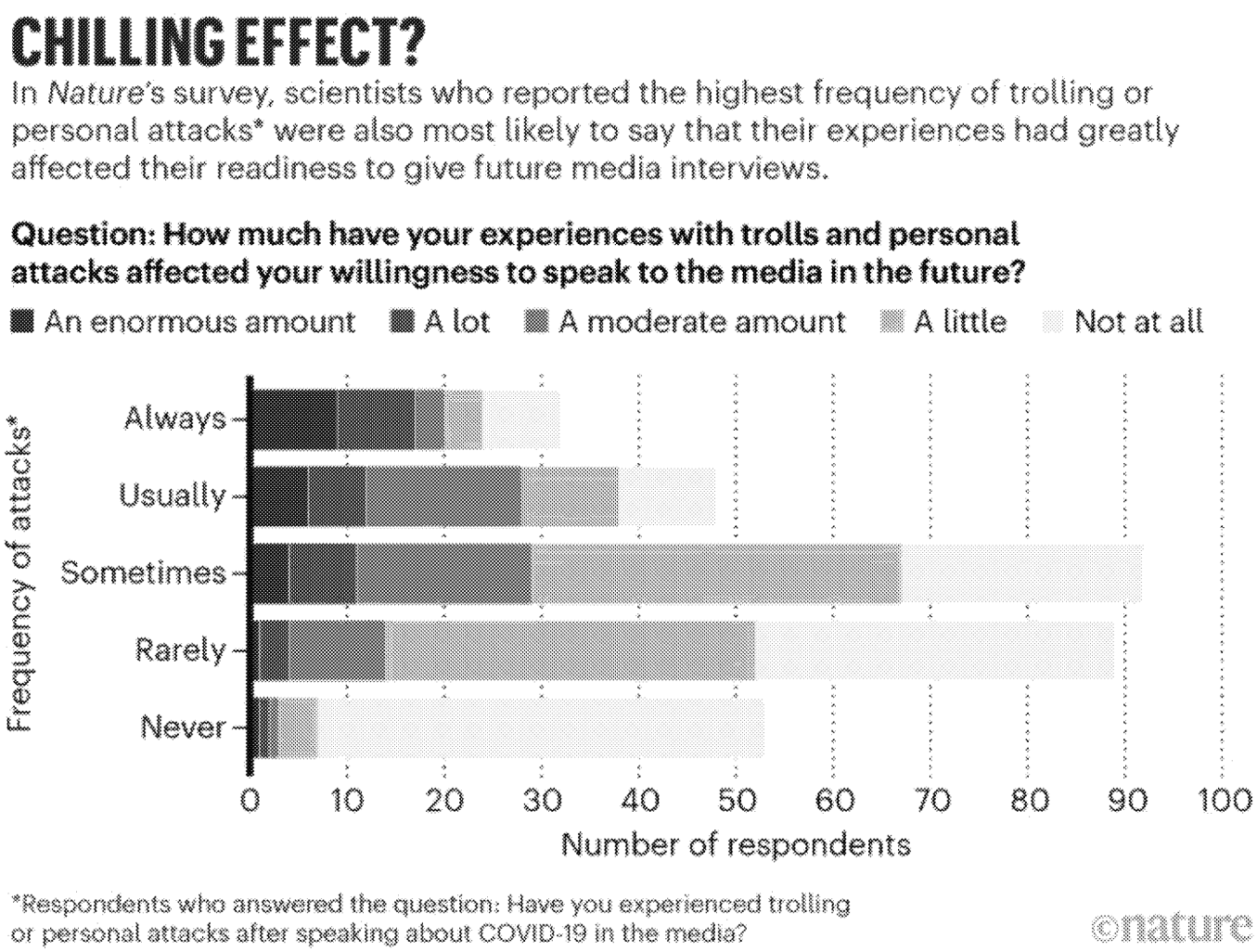
pandemic. Many wanted the extent of the problem discussed more openly. “I believe national governments, funding agencies and scientific societies have not done enough to publicly defend scientists,” one researcher wrote in their survey response.

Some researchers say that they have learnt to cope with the harassment, accepting it as an unpleasant but expected side effect of getting information to the public. And 85% of survey respondents said that their experiences of engaging with the media were always or mostly positive, even if they were harassed afterwards (see ‘Media experiences’). “I think scientists need training for how to engage with the media and also about what to expect from trolls — it’s just a part of digital communication,” one wrote.



Source: *Nature* analysis

But *Nature*’s survey suggests that even though researchers try to shrug off abuse, it might already have had a chilling effect on scientific communication. Those scientists who reported higher frequencies of trolling or personal attacks were also most likely to say that their experiences had greatly affected their willingness to speak to the media in the future (see ‘Chilling effect?’).



Source: *Nature* analysis

That is concerning during a global pandemic which has been accompanied by a battery of disinformation and misinformation, says Fiona Fox, chief executive of the UK Science Media Centre (SMC) in London — an organization that collates scientific comment and organizes press briefings for journalists. "It's a great loss if a scientist who was engaging with the media, sharing their expertise, is taken out of a public debate at a time when we've never needed them so badly," she says.

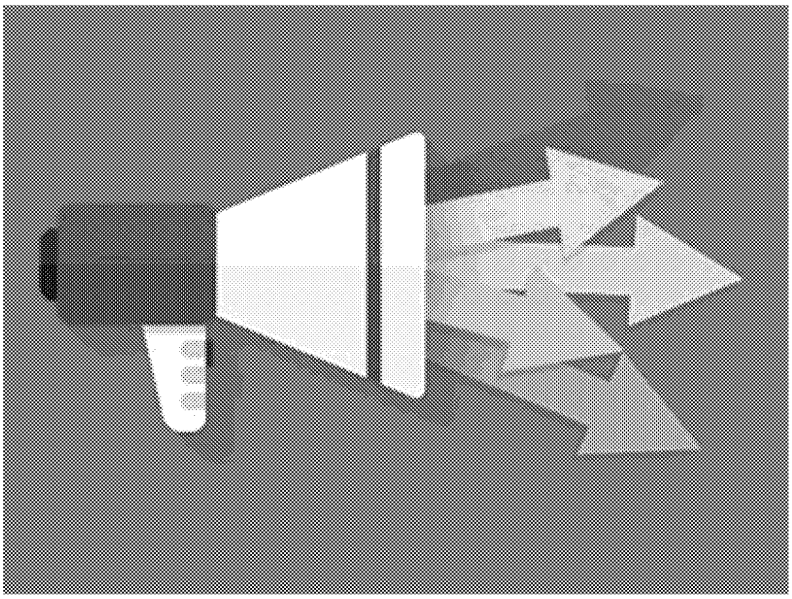
Tracking harassment

In June, the Australian SMC in Adelaide asked researchers on its COVID-19 media lists about their experiences. The centre had been alerted to online bullying and hate campaigns directed at scientists, and wanted to know whether it was a broader problem, says Lyndal Byford, the centre's director of news and partnerships.

Byford shared the results with *Nature*. Fifty researchers answered the SMC's informal survey. Nearly one-third reported experiencing emotional or psychological distress after talking about COVID-19; 6 people (12%) reported receiving death threats, and 6 said they had received threats of physical or sexual violence. "I think any organization involved in helping scientists communicate would find that quite disturbing," Byford says.

To get a broader sense of the scale of harassment, *Nature* adapted the Australian SMC's survey, and asked science media centres in the United Kingdom, Canada, Taiwan, New Zealand and Germany to send it to scientists on their

COVID-19 media lists. *Nature* also e-mailed researchers in the United States and Brazil who had been prominently quoted in the media.



"I had to be with bodyguards with guns" — attacks on scientists during the pandemic

The results are not a random sample of researchers who have given media interviews on COVID-19, because they represent only the experiences of the 321 scientists who chose to respond (predominantly in the United Kingdom, Germany and the United States). But the numbers reveal that researchers in many countries are facing abuse related to the pandemic, and the proportions reported were higher than in the Australian survey. More than one-quarter of respondents to the *Nature* survey said they always or usually received comments from trolls or were personally attacked after speaking in the media about COVID-19. And more than 40% reported experiencing emotional or psychological distress after making media or social media comments.

Politicized science

To some extent, this harassment of scientists reflects their rising status as public figures. "The more prominent you are, the more abuse you're going to get," says historian Heidi Tworek at the University of British Columbia in Vancouver, Canada, who is studying online abuse of health communicators in the pandemic. Most US public-health departments have also received harassment directed at staff and officials, adds Beth Resnick, a public-health researcher at Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, who has surveyed 580 departments in a study that is not yet published.

And such attacks might have little to do with the science itself and more to do with who's talking. "If you're a woman, or a person of colour from a marginalized group, that abuse will probably include abuse of your personal characteristics," says Tworek. For instance, Canada's chief public-health officer Theresa Tam is Asian Canadian, and abuse levelled against her included a layer of racism, Tworek says. Kuppalli, a female scientist of colour, says she also experienced this. Abusers told her she "needs to go back where she came from".

Krutika Kuppalli.Credit: Kathryn Van Aernum

Both the Australian SMC and *Nature*'s survey, however, found no clear difference between the proportions of violent threats received by men and women. "We were surprised," Byford says. "We really felt women would be bearing more of a brunt in terms of the abuse that they got."

Some aspects of COVID-19 science have become so politicized that it is hard to mention them without attracting a storm of abuse. Epidemiologist Gideon Meyerowitz-Katz at the University of Wollongong in Australia, who has gained a following on Twitter for his detailed dissection of research papers, says that two major triggers are vaccines and the anti-parasite drug ivermectin — controversially promoted as a potential COVID-19 treatment without evidence it was effective. "Any time you write about vaccines — anyone in the vaccine world can tell you the same story — you get vague death threats, or even sometimes more specific death threats and endless hatred," he says. But he's found the passionate defence of ivermectin surprising. "I think I've received more death threats due to ivermectin, in fact, than anything I've done before," he says. "It's anonymous people e-mailing me from weird accounts saying 'I hope you die' or 'if you were near me I would shoot you'."

Gideon Meyerowitz-Katz.Credit: Daniel Naidel

Andrew Hill, a pharmacologist at the University of Liverpool's Institute of Translational Medicine, received vitriolic abuse after he and his colleagues published a meta-analysis in July. It suggested ivermectin showed a benefit, but Hill and his co-authors then decided to retract and revise the analysis when one of the largest studies they included was withdrawn because of ethical concerns about its data (A. Hill *et al. Open Forum Inf. Dis.* **8**, ofab394; 2021). After that, Hill was besieged with images of hanged people and coffins, with attackers saying he would be subject to 'Nuremberg trials', and that he and his children would 'burn in hell'. He has since closed his Twitter account.

In Brazil, microbiologist-turned-science-communicator Natalia Pasternak also noticed online attacks against her increasing when she spoke about the unproven COVID-19 treatments being promoted by the Brazilian government, which include ivermectin, the antimalarial drug hydroxychloroquine and the antibiotic azithromycin. In 2018, Pasternak founded the *Instituto Questão de Ciência* — the Question of Science Institute — with the aim of promoting the use of scientific evidence in policymaking and discourse. When COVID-19 happened, Brazil "became the first country in the world to actually promote pseudoscience as a public policy, because we promote the use of unproven medications for COVID-19", Pasternak says.

She appeared on major television stations and produced her own YouTube show, called the Plague Diary. Commenters criticized her voice and appearance, or argued that she wasn't a real scientist. But, Pasternak says, the attacks rarely challenged what she was saying.

Some attackers have also tried to use the law to silence their targets. A group of supporters of Brazilian president Jair Bolsonaro tried to sue Pasternak for defaming him when she likened Bolsonaro to a plague on her YouTube show; the

lawsuit was dismissed. And Van Ranst has been sued for defamation by a Dutch protester who opposes vaccination and public-health measures such as lockdowns in Belgium and the Netherlands.

Another topic that attracts high volumes of abuse is the question of SARS-CoV-2's origins. Both the Australian and UK SMCs say they have struggled to find scientists who are willing to comment publicly on the issue for fear of getting attacked. Fox says the UK SMC has approached more than 20 scientists to participate in a briefing on this question, but all declined.

Virologist Danielle Anderson, now at the Peter Doherty Institute for Infection and Immunity at the University of Melbourne in Australia, received intense, coordinated online and e-mail abuse after writing a fact-checking critique in early 2020 of an article suggesting that SARS-CoV-2 might have leaked from China's Wuhan Institute of Virology (WIV). At the time, she was based at the Duke–National University of Singapore Medical School in Singapore, but had collaborated with the WIV since the epidemic of severe acute respiratory syndrome (SARS) in 2002–04. "Eat a bat and die, bitch," one e-mail read.

Virologist Danielle Anderson received abuse after critiquing an article on SARS-CoV-2's origins.Credit: James Bugg

Another researcher with a long-standing WIV collaboration, Peter Daszak, president of EcoHealth Alliance in New York City, has also received abuse. Daszak, who travelled to Wuhan in January as part of a WHO-coordinated inquiry into the origins of SARS-CoV-2, says he's had a letter containing white powder sent to his home, had his address posted online and regularly receives death threats.

Harassment has cut both ways when it comes to SARS-CoV-2's origins. Alina Chan, a postdoctoral researcher at the Broad Institute of MIT and Harvard in Cambridge, Massachusetts, has received abuse for her work on the idea that the pandemic might have resulted from exposure to a virus at a laboratory or research site (sometimes also called the 'lab leak' hypothesis). Ultimately, she says, abusive attacks are counterproductive to the people making them. "They make the people on their own side appear unreasonable and dangerous," she says. "Second, they make it difficult to hold people accountable because now everyone is distracted by having to address the excessively abusive attacks."

Coping strategies

For researchers who receive online abuse, individual coping strategies include trying to ignore it; filtering and blocking e-mails and social-media trolls; or, for abuse on specific social-media platforms, deleting their accounts. But it's not easy.

"It is very harrowing if every day, you open up your e-mails, your Twitter, you get the death threats, you get abuse every single day, undermining your work," says Hill. It also takes time to go through messages and filter out abusers, he says. That led to his decision to delete his Twitter account.

Kuppalli has kept her social-media presence, but is more careful about how she uses it. Her rule is now not to respond to comments or posts when she is upset or angry or, in some cases, not to reply at all. "I just don't read the comments and I don't engage."

Trish Greenhalgh, a health researcher and doctor at the University of Oxford, UK, said on Twitter in March that she had received "malicious abuse" from another academic and was blocking her abuser's followers to make it harder for them to target her. She had previously tweeted that if anyone abused her PhD students, she would try to identify the abuser and report them to their employer.

From: Morens, David (NIH/NIAID) [E] [b6] ([b6])
Sent: 6/24/2021 4:45:56 PM
To: Peter Daszak ([b6]) [[b6]]; Rich Roberts ([b6]) [[b6]]; Keusch, Jerry ([b6]) [[b6]]; Taubenberger, Jeffery (NIH/NIAID) [E] ([b6]) [[b6]]; Breman, Joel (NIH/FIC) [V] ([b6]) [[b6] ([b6])]
Subject: FW: Nautilus: When a Good Scientist Is the Wrong Source/How a bad "fact" helped the lab-leak hypothesis go viral.

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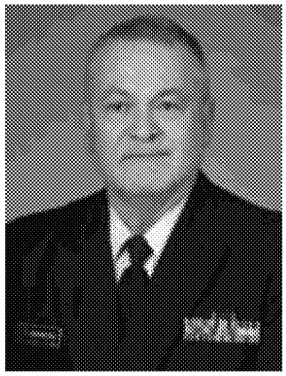

From: Folkers, Greg (NIH/NIAID) [E] b6
Sent: Thursday, June 24, 2021 12:18 PM
Subject: Nautilus: When a Good Scientist Is the Wrong Source/How a bad "fact" helped the lab-leak hypothesis go viral.

When a Good Scientist Is the Wrong Source

How a bad "fact" helped the lab-leak hypothesis go viral.

By Thomas Levenson June 23, 2021

Six weeks ago, a reporter, Nicholas Wade, published what seemed to be a blockbuster story, one that, if true, would expose the greatest scandal in recent history. SARS-CoV-2, he wrote, or SARS2 for short, the virus that has driven the global COVID-19 pandemic, had likely been modified in a lab at the Wuhan Institute of Virology, from which it then escaped into the wild. "Neither the natural emergence nor the lab escape hypothesis can yet be ruled out," Wade wrote. "But it seems to me that proponents of lab escape can explain all the available facts about SARS2 considerably more easily than can those who favor natural emergence."

Wade, a former *New York Times* science reporter, best known for promoting a genetic basis to racial hierarchies, first placed his piece at the self-publishing site Medium on May 2. The story really took wing when it was reposted three days later at the *Bulletin of the Atomic Scientists*. It was an extraordinary assertion, and as the saying goes, such claims need extraordinary proof.

Validation came from one of the most prominent biologists of the last half century.

That validation came, it seemed, from one of the most prominent biologists of the last half century, the Nobel laureate David Baltimore, who confirmed one of the key pillars of the argument. Some features in a brief genetic sequence in the virus seemed to suggest that a human, in a lab experiment, had put it there. When he first saw the sequence, Baltimore is quoted as saying, "I said to my wife it was the smoking gun for the origin of the virus."

With that a bad "fact" was born: a seemingly simple statement about reality that turns out to be not so simple—and deeply misleading. The Baltimore quote sealed the deal, not just because of what was said, but who was saying it.

It's standard practice in science journalism to seek confirmation of key facts from experts who are not directly involved in the research that lies at the center of any given story, the reporter's equivalent of peer review. That's what Wade needed, a source that could transform his long chain of inference, his series of ifs and assertions about what evolution can and cannot do, into a statement that (to use Isaac Newton's phrase) "cannot fail but to be true."

That's what Baltimore provided. "Smoking gun" is the critical phrase; it leaves no room for doubt. It confirmed, or seemed to, that the 4 million and counting who have died of COVID were victims of human choices and mistakes.

Baltimore's picture could appear in the dictionary next to "authority." He won his Nobel Prize for work on the molecular genetics of tumor viruses. He has run a trio of the world's most important research institutions, as director of the Whitehead Institute at MIT, then as president first at Rockefeller University, and then at Caltech. After stepping down, he continued to run an active lab, investigating basic questions about gene regulation and expression. If there were anyone whose word one could accept on a question of who did what to a virus it would seem to be Baltimore.

And yet Baltimore got this one wrong—and has retreated from his earlier emphatic support for Wade's claims. But like most retractions in media stories, Baltimore's admission has made little impact, and the originally reported "fact" has continued to feed the ongoing promotion of the lab-escape hypothesis.

Wade asserted that a particular arrangement of a specific sequence in the viral genome, called a codon, was unlikely to have gotten there naturally. There are actually six different codons for arginine, and the one found in a particular region of the SARS-CoV-2 genome called the furin cleavage site does occur less frequently in viruses than it does in the human genome. An even more telling detail to Wade is that this uncommon arginine codon shows up twice in that small segment of the virus's genome. For that to occur naturally, Wade wrote, "a chain of events has to happen, each of which is quite unlikely."

That's what Baltimore assented to. But scientists say Wade misdescribed critical links in his chain. Scripps Research virologist Kristian Andersen led an early inquiry into the possible role of a lab escape in the origin of the virus, which concluded that it "is not a laboratory construct," a finding that Wade termed "poor science" in his article. After Baltimore's quote became public, Andersen re-entered the argument, and became one of a number of researchers to challenge many of the details Wade relied on. Andersen told *Nature* that Wade's claim that steps in the emergence of the virus were too improbable to have occurred is not true. Rather, the pandemic virus uses that codon about 3 percent of the time that its genome calls for arginine—not common, but not impossibly scarce either—and, importantly, that other coronaviruses make use of it too, at similar or greater frequency.

This is a phenomenon that few outside science and journalism fully grasp.

Columbia University virologist Vincent Racaniello says the unusual pairing of a particular codon that Wade saw as decisive actually points *away* from laboratory manipulation. "We have some idea why this codon is rare in RNA viruses," Racaniello says. Selection pressures have been identified that would discourage its use in viral genomes. But, he says, "We don't know why it's not zero. The fact that it is conserved in many viruses means that it's beneficial in some way we don't understand." This is the kind of mystery that evolution throws at researchers all the time. Racaniello adds that if a lab researcher was trying to modify a virus to measure its effect, the researcher wouldn't use the codon pairing identified by Wade because its effect would be too unpredictable.

As Wade's claims attracted more media interest, seemingly validated by Baltimore's seal of approval, similar critiques began to appear, pointing out how Wade shaded his interpretation of the details toward one conclusion—lab escape—and away from a natural origin. In a *New York Times* interview, Andersen said while both lab and natural scenarios are possible, "they are not equally likely—precedence, data and other evidence strongly favor natural emergence as a highly likely scientific theory for the emergence of SARS-CoV-2, while the lab leak remains a speculative hypothesis based on conjecture."

It may seem surprising that Andersen, a well-regarded biologist, could correct Baltimore, a legend. It's not. This is an example of a phenomenon that few outside science, and especially journalists inexperienced in covering cutting-edge research, fully grasp. Biology is a discipline in which the details make all the difference; there are more of them than seems possible; and if a given expert is not expert in the right domain, their answers are not that useful. Baltimore certainly is *an* authority, but his jurisdiction does not extend to all the complexity that nature displays.

Baltimore has mostly accepted such corrections. In an email to *Nature*, he said that Andersen could be correct that evolution produced SARS-CoV-2, but adds that "there are other possibilities and they need careful consideration, which is all I meant to be saying." He walked his quote further back in an interview with *Los Angeles Times* columnist Michael Hiltzik, saying that he "should have softened the phrase 'smoking gun' because I don't believe that it proves the origin of the furin cleavage site but it does sound that way."

And yet the "fact" of a smoking gun lives on. Donald G. McNeil Jr., a former colleague of Wade's who covered the pandemic at *The New York Times* until he recently resigned, posted a long essay on Medium endorsing Wade's conclusions, a piece that was cited by David Leonhardt in a *Times* "explainer" on the state of the debate. Leonhardt concluded that dismissing the lab escape possibility "appears to be a classic example of groupthink, exacerbated by partisan polarization." The issue, as Leonhardt saw it, turns on America's political conflicts, and not the strength or weakness of the specific scientific evidence available. A reporter whose career has centered on Washington and

economic coverage would find this plausible; it is not, however, a judgment based on the expertise needed to assess competing scientific arguments.

Wade has not backed off his claim that the pandemic was probably caused by a lab-engineered virus that escaped. Baltimore's recant hasn't changed a thing, Wade argues, writing to the *Los Angeles Times*' Hiltzik that he believes "the totality of the quote" still supports his case.

Bad "facts" have played an indispensable role in advancing the lab-escape allegation to its current prominence. In the past week, lab-escape speculation with little or no critical scrutiny reached into entertainment media. NPR's *Fresh Air* aired an episode featuring a reporter, not a scientist, advancing the lab allegation, with no expert on zoonosis in sight, while Jon Stewart retailed Wuhan lab conspiracy theories on *The Late Show with Stephen Colbert*, riffing, "I think we owe a great debt of gratitude to science. Science has, in many ways, helped ease the suffering of this pandemic," pausing for a beat, and then going for the rimshot: "which was more than likely caused by science."

Meanwhile, the research seeking to trace the origins of SARS-CoV-2 continues. Identifying the specific animal origins for human diseases is difficult at the best of time—it took well over a decade to track down the source for the first SARS epidemic, and the complete sequence of transmission behind the Ebola outbreaks is still being pursued. Even so, evidence is trickling in, like a recent survey of bat populations in Southeast Asia turned up a number of newly identified viruses related to the one causing the human pandemic.[1] That study is itself no smoking gun, but it is a reminder: the investigation into the most likely origin of the SARS-CoV-2 is ongoing, and may take a very long time, given the space and near-infinite variety of the natural world that must be explored.

In the meantime, the true scandal of the COVID years continues to unfold. It's not breathless speculation on the origins of the virus, but rather that the United States and many other nations failed to prepare for the pandemic. Everywhere but China had months to anticipate its arrival, come up with strategies to limit transmission, and to ready their public health and medical systems to take care of those who did get sick. Six hundred thousand dead in the US and nearly 4 million worldwide are the brutal measure of that failure—and a reminder. It was human errors and choices that enabled a virus of still-uncertain origin to spark a global disaster.

Thomas Levenson is Professor of Science Writing at the Massachusetts Institute of Technology. He is the author, most recently, of Money for Nothing: The Scientists, Fraudsters and Corrupt Politicians Who Reinvented Money, Panicked a Nation, and Made the World Rich. *Follow him on Twitter @TomLevenson.*

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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 25 Aug 2016 18:45:00 +0000
To: Baric, Ralph; Dreier, Thomas (OS/ASPR/BARDA); Erlandson, Karl (OS/ASPR); Hensley, Lisa (NIH/NIAID) [E]; Munster, Vincent (NIH/NIAID) [E]; Subbarao, Kanta (NIH/NIAID) [E]
Cc: Spiro, David (NIH/NIAID) [E]
Subject: MERS Model Workshop Draft Manuscript
Attachments: MERS Workshop Manuscript 8-25-2016.docx, Excler MERS KSA WG EID 2016.pdf, Development of MCMs to MERS-CoV EID 2016.pdf

Hi Everyone,
I know it's been a while since the MERS Model workshop, but David and I have put together a draft manuscript that we would like to submit to EID for publication. We've put this together based on the detailed summary provided by the science writer. Since you all were part of the organizing committee for the workshop, we thought it would be good to have you as co-authors writing on behalf of the entire group. We're asking for your comments and feedback first, and then we will circulate an updated draft to the larger presenter/panelist group. If possible, we would appreciate it if you could please send any comments back to us by September 12th. Please also let me know if you'd prefer not to be listed as an author, or are otherwise unable to participate in preparing the paper.

In addition to the draft, I've also attached two recent, related, EID papers. Our thought is that this paper would be a follow on to these two. Please let me know if you have any questions.

Thanks!
Erik

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MERS-CoV Animal Models: Current Status and the Path to Clinical Trials

Erik J. Stemmy Ph.D.[1], Ralph Baric[2], Tom Dreier[3], Karl Erlandson[3], Lisa Hensley[4], Vincent J Munster[5], Kanta Subbarao[6], and David J. Spiro Ph.D.[1], on behalf of the Workshop Speakers and Panelists.

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Running Title: MERS-CoV Animal Model Workshop Summary

Keywords: MERS-CoV, animal models, medical countermeasures,

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Abstract (Word Count: 101)

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) continues to be a public health threat. A major focus of recent research has been the development of suitable animal models to advance understanding of MERS CoV pathogenesis and to establish a platform in which potential medical countermeasures can be evaluated. The National Institute of Allergy and Infectious Diseases (NIAID) convened a workshop on February 29th and March 1st, 2016 to review the current status of MERS-CoV animal models and to consider the path forward to support clinical trials of promising vaccines and therapeutics. This report will summarize both the workshop and expert panel recommendations.

Word Count: 2,144

Introduction

Since its emergence in 2012 the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) has been reported in 27 countries ranging from the Middle East and North Africa to Asia and North America. As of August 2016 1,791 cases have been reported to the WHO, including 633 deaths (WHO 2016). The high case fatality rate coupled with the lack of approved medical countermeasures (MCMs) and an incomplete understanding of transmission dynamics highlight the potential pandemic risk. A major emphasis of research has been the development suitable animal models in which to test novel vaccines and therapeutics against MERS-CoV. A number of recent advances have been reported in mice (Cockrell, Peck et al. 2014, Zhao, Li et al. 2014, van Doremalen and Munster 2015, Baseler, de Wit et al. 2016, Tao, Garron et al. 2016), New Zealand white rabbits (Haagmans, van den Brand et al. 2015, Houser, Gretebeck et al. 2016), non-human primates (Falzarano, de Wit et al. 2014, Johnson, Via et al. 2015), and camelids (Adney, van Doremalen et al. 2014, Adney, Bielefeldt-Ohmann et al. 2016). As a means to advance MERS-CoV model development, the National Institute of Allergy and Infectious Diseases (NIAID) convened a workshop to bring together stakeholders to: 1) discuss current knowledge about MERS-CoV pathogenesis in humans as it relates to development of animal models; 2) consider the current status of MERS-CoV animal model development; 3) evaluate the potential for standardization of experimental conditions (e.g. variables such as viral challenge strain, route of inoculation, dose, etc); 3) identify existing gaps and/or hurdles hindering animal model development; and 4) consider potential regulatory pathways for promising MCMs. This report will provide a summary of both the workshop and expert panel recommendations.

Clinical Experience with MERS-CoV

The lack of published clinical reports of MERS-CoV cases has made it difficult to assess the suitability of the MERS-CoV animal models under development in terms of clinical relevance to disease. One goal of the workshop was to facilitate discussion between clinicians with experience treating MERS-CoV cases and researchers developing animal models.

MERS-CoV in the Kingdom of Saudi Arabia, *Dr Hail Mater Alabdely, KSA Ministry of Health*.

The majority (1,436) of cases of MERS-CoV have occurred in the Kingdom of Saudi Arabia (KSA), particularly in the region around Riyadh. In response to the MERS-CoV epidemic the KSA Ministry of Health has deployed a computerized preparedness, surveillance, and response system on a national and local level, the main focus of which is rapid identification of MERS-CoV cases and improved infection control practices. Implementation of this system has allowed health authorities to more quickly identify an index case of MERS-CoV in the healthcare setting, resulting in fewer hospital outbreaks, and smaller hospital-associated clusters of cases (Alabdely, Workshop Presentation).

In KSA the case fatality rate since the virus emerged in 2012 has ranged from 41-60%, with a rate closer to 40% in recent outbreaks (Alabdely, Workshop Presentation). There are also likely to be a large number of mild or asymptomatic cases that are not easily recognized. A serosurvey of 10,000 individuals performed in KSA in 2012-2013 looked at the prevalence of MERS-CoV antibodies in the general population, as well as camel shepherds and slaughterhouse workers. The latter two groups had seroprevalence rates of 2.3% and 3.6% compared to 0.2% in the general population; using these data to extrapolate to the general population, almost 45,000 individuals may be seropositive for MERS-CoV in KSA (Muller, Meyer et al. 2015).

Of confirmed MERS-CoV cases in KSA, 38% are primary cases; 12% are in healthcare workers, 13% are household and 33% are hospitalized patients. Studies of case-mortality by age, suggest that mortality rises with patient age, especially for those over 51 years of age. Case mortality is higher for primary cases than for secondary cases, particularly for cases in hospitalized patients. Case fatality is higher for those with underlying medical conditions, particularly for individuals with diabetes, than for those persons who do not have such conditions. MERS-CoV case fatality is also much lower among healthcare workers and household contacts (Alabdely, Workshop Presentation).

MERS-CoV in the Republic of Korea, Dr Sang-Wan Park, Seoul National University College of Medicine. An outbreak of MERS-CoV occurred in the Republic of Korea (RoK) in 2015, starting from 1 imported case and resulting in a total of 186 cases, 36 of which were fatal (WHO 2016). In general, the clinical presentation of MERS-CoV cases in RoK was similar to those reported from KSA. In contrast to the cases in KSA, where the most prevalent comorbidity was diabetes, in RoK the major underlying disease was hypertension (Choi, Kang et al. 2016). Interestingly, the case fatality rate reported for the RoK outbreak was 20.4%, whereas other outbreaks report case fatality rates ranging from 36.5-65% (Choi, Kang et al. 2016).

MERS-CoV Animal Model Development

A number of animal models of MERS-CoV are being developed, and detailed reviews of small and large animal MERS-CoV have been published elsewhere (van Doremalen and Munster 2015, Baseler, de Wit et al. 2016, Shehata, Gomaa et al. 2016). With respect to mouse models, different molecular strategies have been pursued to incorporate human DPP4 (hDPP4) receptors: hDPP4 transduction (Zhao, Li et al. 2014), transgenic (Li, Wohlford-Lenane et al. 2016, Tao,

Garron et al. 2016) and humanized (Cockrell, Peck et al. 2014, Pascal, Coleman et al. 2015). Each of the models has advantages and disadvantages, though having a variety of models may be useful to address different research questions. For example, models expressing a humanized DPP4 receptor might be more physiologically relevant to human disease due to the fact that receptor expression is governed by native promoters, and could provide insight into viral pathogenesis. Because transient expression models can be rapidly deployed, they could be useful in addressing questions in special populations such as the elderly or for particular comorbidities (e.g. diabetes, hypertension) in mouse models previously developed for those conditions.

Given the variety of mouse models being developed it is important to understand the molecular and biological mechanisms that underlie the resulting phenotypes of each model. It is also important to understand other factors that affect the models, such as the strain and source of the animal and of the viral isolate. Currently, the models are still in their developmental stages and thus, it is premature to try to standardize mouse models at this time.

When infected with MERS-CoV New Zealand white rabbits develop mild disease phenotypes, which may be similar to cases of mild or asymptomatic disease in humans (Haagmans, van den Brand et al. 2015, Houser, Gretebeck et al. 2016). Recent work suggests that while rabbits may be of limited use in understanding MERS-CoV disease progression, they may be useful in examining transmission since virus is shed from their upper respiratory tract (Houser, Gretebeck et al. 2016).

NHP models of MERS-CoV exhibit mild to moderate disease, with some differences between the Rhesus Macaque and Common Marmoset models (Baseler, de Wit et al. 2016). These animals are important given that they have a natural receptor for MERS-CoV, however there can

be issues related to availability of animals and reagents. Additionally, advanced medical imaging systems may be useful in NHP studies of MCMs because they allow non-invasive measurements of the virus infection process. Differences in outcomes have also been noted between groups working on common marmosets (Baseler, de Wit et al. 2016). These differences could impact the downstream evaluation of MCMs, so to most effectively use these important models it is critical that this issue be resolved through collaborative work and exchange of reagents.

Recent work has also highlighted the use of dromedary camels and alpacas as models for MERS-CoV infection. Infected animals developed mild upper respiratory symptoms, and efficient transmission was observed between animals co-housed in barns (Adney, van Doremalen et al. 2014, Adney, Bielefeldt-Ohmann et al. 2016). Although camels are natural hosts for MERS-CoV their large size, long gestational period, and difficult temperament may limit their utility as models of MERS-CoV. Alpacas may be more useful in studies since they are smaller new-world camelids which also develop mild respiratory infections from MERS-CoV.

Panel Discussion

The workshop attendees and expert panelists engaged in a robust discussion of MERS-CoV animal models. The panel noted that impressive progress has been made, evidenced by the variety of animal models exhibiting a range of features, including novel mouse models that have unique and/or unexpected phenotypes. These models have great utility and allow for the study of the virus-host interactions, including immune interaction networks that can be associated with disease severity and protective immunity. Since individual models may only be able to reproduce

certain aspects of disease or disease severity, the panel noted that the use of multiple models may be necessary, particularly as work advances in special populations and comorbidities.

A key problem in the development of animal models is a lack of knowledge of disease pathogenesis in humans, as well as a lack of human clinical samples and viral isolates. The disease course and the associated pathology and immunology of MERS-CoV are not well defined, including: the role of innate immunity in pathogenic or protective outcomes; the nature of cellular immune responses; the immune responses associated with protective immunity; the susceptibility of various populations of immune cells to the virus; and the nature of cytokine responses and of inflammatory cell infiltrates. There is also an urgent need for more natural history data to better understand transmission between humans, between camels, and between humans and camels. Epidemiologic and virologic investigations should be done concomitantly with transmission studies in order to assess changes in the virus genome and viral evolution in the wild. Such information is needed for the development of preventatives and therapeutics.

MERS-CoV Medical Countermeasure Considerations

Although no approved MCMs exist for MERS-CoV, substantial basic discovery and preclinical work has been ongoing and was the subject of a recent review (Uyeki, Erlandson et al. 2016). With regard to the contribution of animal model development to MERS-CoV MCMs caution should still be used in interpreting data from studies in animal models. Since models are still being refined it is likely premature to discontinue vaccine/therapeutic leads based solely on data from animal models. For example, DPP4 has a critical role in immune homeostasis and groups have used various techniques to humanize or replace mouse DPP4 to make mice permissive to MERS-CoV infection. Until the models have been fully characterized it is possible that such

DPP4 alterations may have unintended consequences affecting immune regulation which could lead to misinterpretation of data from experiments evaluating the efficacy of MCMs.

For more advanced development of countermeasures, it will be important to make assessments (e.g. efficacy or PK/PD) in models at doses that are relevant for clinical usage. As more candidate vaccines and therapeutics advance to clinical trials, the panel noted the importance of having a clinical trial structure in place in areas with the potential for outbreaks. In addition to allowing access to patient populations, having common clinical trial protocols with appropriate controls will ensure data from multiple trials can be interpreted.

Conclusions and Expert Panel Recommendations

Given the appearance of SARS-CoV and MERS-CoV and the spread of their associated diseases through global travel, it is likely that other coronavirus health threats in humans and animals will arise in the future. Thus, this is a critical time for coronavirus research as threats from these viruses are expected to continue. The MERS-CoV outbreaks present an opportunity for collaborative interactive work among members the scientific community to address fundamental questions in virology, immunology, pathology, and to develop MCMs, that can be implemented as public health strategies.

Recommendations from the MERS-CoV Workshop

- **Further research into the biology of MERS-CoV animal models is necessary before models can be standardized.** Suggestions for the path forward included:
  - Exchanging viruses and testing them in multiple models to compare and understand each system.
  - Collaborative work to compare transgenic mouse models to further understand the molecular mechanisms that regulate immune-mediated disease severity and affect therapeutic responses.
  - Collaborative work between the groups developing NHP models to address significant discrepancies in results.

- **Studies of MERS-CoV pathogenesis in humans are urgently needed to inform the further development of animal models. Studies of human survivors would allow the development of reference reagents and provide a better understanding of the natural response to infection.** Suggestions for future work included:
  - Increased availability of autopsy results, clinical specimens, and virus isolates.
  - Further research into the disease course and associated pathology/immunology of human infection, including: including the role of innate immunity in pathogenic or protective outcomes, the nature of cellular immune responses, immune responses associated with protective immunity, the susceptibility of various populations of immune cells to the virus, and the nature of cytokine responses and of inflammatory cell infiltrates.
- **Further research into MERS-CoV natural history data to better understand transmission dynamics between humans, and between humans and camels.**

Acknowledgements

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MERS-CoV Animal Model Workshop Speakers and Panelists: Danielle Adney, Hail Mater Alabdely, Kimberly Armstrong, Ralph Baric, Luis Enjuanes, Karl Erlandson, Robert Fisher, Matthew Frieman, Susan Gerber, Frederick Hayden, Lisa Hensley, Katherine Houser, Reed Johnson, Vasee Moorthy, Vincent Munster, Sang Won Park, Stanley Perlman, Chien-Te Kent Tseng, Kanta Subbarao

Commented [SE([2]: Please add/edit acknowledgements as necessary.

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Toward Developing a Preventive MERS-CoV Vaccine—Report from a Workshop Organized by the Saudi Arabia Ministry of Health and the International Vaccine Institute, Riyadh, Saudi Arabia, November 14–15, 2015

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Middle East respiratory syndrome (MERS) remains a serious international public health threat. With the goal of accelerating the development of countermeasures against MERS coronavirus (MERS-CoV), funding agencies, nongovernmental organizations, and researchers across the world assembled in Riyadh, Saudi Arabia, on November 14–15, 2015, to discuss vaccine development challenges. The meeting was spearheaded by the Saudi Ministry of Health and co-organized by the International Vaccine Institute, South Korea. Accelerating the development of a preventive vaccine requires a better understanding of MERS epidemiology, transmission, and pathogenesis in humans and animals. A combination of rodent and nonhuman primate models should be considered in evaluating and developing preventive and therapeutic vaccine candidates. Dromedary camels should be considered for the development of veterinary vaccines. Several vaccine technology platforms targeting the MERS-CoV spike protein were discussed. Mechanisms to maximize investment, provide robust data, and affect public health are urgently needed.

Middle East respiratory syndrome (MERS) remains a serious public health threat within Saudi Arabia and internationally, as recently illustrated by an outbreak in South Korea with potential pandemic risk (*1*–*7*). A vaccine (or vaccines) targeting the MERS coronavirus (MERS-CoV), which causes the disease, will be a critical component of future public health prevention measures (*8*–*10*). With the goal of accelerating the development of countermeasures against MERS-CoV, funding agencies, nongovernmental organizations, and researchers across the world assembled in Riyadh, Saudi Arabia, on November 14–15, 2015, to discuss current data and research progress to enhance understanding of disease progression from MERS-CoV infection, vaccine development, the challenges of developing treatment measures (e.g., unclear disease mechanisms and transmission patterns), preclinical development and animal models, the landscape of emerging technologies and scientific platforms, and considerations for clinical development. One primary objective of the meeting was to articulate a coordinated action plan that aligns efforts and resources. The meeting was spearheaded by the Ministry of Health (MOH) of Saudi Arabia and co-organized by the International Vaccine Institute, Seoul, South Korea.

Development of MERS-CoV Animal Models

When developing countermeasures against MERS-CoV infection, rodents and small animal models that mimic human disease hallmarks would be useful in initial screening studies before the measure is tested in larger animals (e.g., nonhuman primates and, potentially, camels). Although upper respiratory tract disease develops more severely in the latter (*11*), studying immune correlates of protection and vaccine efficacy in camels (the only natural host besides bats and humans identified thus far) may reveal vulnerabilities of MERS-CoV that may be exploited for human vaccine strategies.

The development of MERS vaccines faces several challenges. Existing small animal species do not naturally express the primary receptor that MERS-CoV uses to infect humans, the human dipeptidyl-peptidase 4 (hDPP4)

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receptor (*12–19*). This lack results in the animal's inability to sustain infection and for clinical illness to develop from MERS-CoV. Larger animal models, such as nonhuman primates, have not yet been optimized to consistently mimic the disease patterns observed in human infection (which is incompletely understood) and also have associated logistical challenges because that work must be completed in Biosafety Level 3 facilities.

Mouse DDP4 cannot support MERS-CoV infection (*16*). Although efforts have been made to adapt MERS-CoV itself to exhibit human disease phenotypes in rodents, greater success has been achieved through the development of specialized mouse models that express hDPP4 (*20–22*). Mouse strains that globally express hDPP4 are susceptible to infection by MERS-CoV, and the mice display lower respiratory tract infection, weight loss, and increased respiratory rate, but also encephalitis, which makes the strains highly lethal. Human DPP4 expression is, however, transient and limited to the lung after Ad5-hDPP4 transduction by intranasal inoculation (*21*). These infected transgenic mice exhibit transcriptional activation of genes encoding classic antiviral cytokines (interferon [IFN]-β, IFN-γ, and MX-1) and pro-inflammatory cytokines (interleukin [IL]-2, IL-6, IL-12, p40, IL-1-α, and tumor necrosis factor [TNF]-α), as well as chemokines (granulocyte-colony stimulating factor [G-CSF], monocyte chemoattractant protein-1 [MCP-1], interferon gamma-induced protein 10 [IP-10], CXC motif ligand 1 [CXCL-1], macrophage protein 1 [MIP-1], and chemokine (C-C motif) ligand 5 [CCL5 or RANTES]), in contrast with the negligible gene activation of infected nontransgenic mice. IL-1, IL-6, TNF-α, G-CSF, MCP-1, IP-10, CXCL-1, MIP-1, RANTES, and interferon-induced GTP-binding protein (MX-1) have been detected in the lungs and brains of infected transgenic mice (*20*).

However, formation of hybrid mouse–human DPP4 dimers in transgenic mice could affect immune regulation and lead to poorly understood outcomes that could confuse the interpretation of disease natural history and vaccine efficacy. Alternatively, a minimally modified version of mouse DPP4, by mutation of 2 amino acids, can support MERS-CoV infection. Mice with this mutation experience severe lower respiratory tract infection, although they do not exhibit brain infection (*16*). In addition, Pascal et al. have developed mice that express hDPP4, under the control of its endogenous promoter and the 3¢ untranslated region, and show lung-specific infection and inflammation (*22*). Further testing may prove that vaccine evaluation in these small animal models could lead to a better understanding of immunogenicity and efficacy of vaccine candidates and the therapeutic measures being considered for evaluation in larger animals and humans.

Among current nonhuman primate models, rhesus macaques display mild-to-moderate clinical signs on viral challenge (*23*), whereas the common marmoset is reported to exhibit more severe signs of infection (*24*,*25*) and could be a better model for the severe clinical syndrome observed in MERS-CoV–infected persons. However, not all research groups have been able to replicate severe disease outcomes in marmosets. Factors contributing to this could include variations in physical location, age, and origin of the marmosets; challenge virus strains and stocks; route and dose of inoculation; and in protocols. To be able to provide robust and reproducible outcomes, these nonhuman primate models need additional development, optimization, and standardization.

Camels are also being used to evaluate MERS-CoV infection, and findings from Adney et al. showed that these animals are unique in that they experience an upper respiratory tract infection. Although we do not know the efficiency of airborne versus droplet or another mode of transmission, viral shedding from the upper respiratory tract might explain the efficiency of camel–camel and camel–human transmission (*11*,*26*). Although camels do not display the severe disease symptoms observed in infected humans (*26*), a camel infection model remains useful for understanding the disease in camels and identifying potential immune correlates of protection induced by vaccination. Veterinary countermeasures could form part of a One Health strategy to forestall zoonotic transmission to humans (*1*). Hesitation to implement animal vaccination strategies in camels once a vaccine becomes available can be attributed to the absence of severe disease in camels (only upper respiratory tract infection with rhinitis) and to skepticism among key groups regarding zoonotic transmission of MERS-CoV to humans (e.g., camel breeders).

Although the animal models for evaluating MERS-CoV infection represent progress, they do not recapitulate the pathogenesis of severe human disease. A combination of both small and large animal models should be considered for evaluation of preventive and therapeutic candidates for MERS. Regardless of the chosen model, comparing and interpreting results effectively and reducing discrepancies among laboratories will be crucial for researchers to agree on a set of standards with respect to experimental design, including variables for age of animals, specimen handling, route of administration, type of virus challenge, inoculation schedule, sample collection, and disease scoring algorithms.

Pipeline of MERS-CoV Vaccine and Antibody Technologies

Building on the experience from the closely related severe acute respiratory syndrome coronavirus (SARS-CoV) (*27*), researchers have been actively working to understand MERS-CoV genetics to inform vaccine and therapeutic development efforts. They quickly demonstrated that the

spike (S) protein, a viral surface glycoprotein, was essential for recognition of hDPP4 and viral entry into cells and likely represented a prime target for immunogen design for the development of vaccines and monoclonal antibodies (*18*,*28*,*29*). At the workshop, we reviewed various approaches—all in preclinical development and all based on the S protein or one of its components, including nanoparticles, subunit proteins and peptides, DNA, various viral vectors, and live attenuated MERS-CoV.

Nanoparticles formed with MERS-CoV S protein, under development by Novavax (Gaithersburg, Maryland, USA), have been shown to induce virus neutralizing antibodies (NAbs) in mice after a single injection; proprietary adjuvants enhance this response (*30*). Vaccines using antigens expressed from the baculovirus platform developed by Novavax have been evaluated in human subjects in the context of phase I and phase II clinical studies for other infectious diseases without notable vaccine-related safety concerns (*31*–*33*).

Portions of the S protein, specifically the receptor-binding domain (*8*,*29*,*34*–*36*), are also being developed as subunit vaccines. As Jiang et al. demonstrated, these fragments map to a "critical neutralizing region" and induce strong immune responses and NAbs in mouse models (*37*,*38*). Moreover, the subunit vaccines have been shown to protect transgenic mice when challenged with MERS-CoV, indicating that vaccines focused on the receptor-binding domain may be sufficient for protective immunity to develop against the virus (*39*,*40*).

Several viral vectors, including adenovirus (*41*,*42*), modified vaccinia Ankara (MVA) (*43*,*44*), and measles virus (*45*), are also under development by different groups. Various lengths of S protein are being expressed on these platforms and are able to generate antibodies in animals that can neutralize MERS-CoV in vitro and, at least for some vector platforms, also generate cellular immune responses (*43*,*45*). For MVA- and measles virus–based vaccines, these responses confer protection in hDPP4-expressing mice (*43*,*45*). MVA constructs, which have established safety profiles in humans, have been tested in camels and can induce protective immunity, representing a potential veterinary technology (*46*). Moreover, on the basis of supportive data from animal studies, these MVA constructs will soon enter clinical trials. Vaccines based on live attenuated viruses historically have been shown to be highly efficacious; they are also safe and generally well tolerated. Enjuanes and others reported to the group the development of 2 engineered MERS-CoV vaccine candidates. One candidate was based on a propagation-defective MERS-CoV strain, and another was a live attenuated virus with 3 safety guards that used a MERS-CoV infectious cDNA clone (*47*). An inactivated SARS-CoV vaccine was shown to be safe and able to induce NAbs in a phase I trial (*48*).

DNA vaccines are generally perceived as a safe, stable platform for in vivo antigen expression. A SARS-CoV DNA vaccine, which expresses the SARS-CoV S protein, has been shown to induce NAbs and functional T-cell responses in humans (*49*). GeneOne (Blue Bell, Pennsylvania, USA) is developing a proprietary, full-length S protein DNA vaccine candidate that has been shown to induce NAbs and highly functional T cells in various animal models and protect rhesus macaques from infection after MERS-CoV challenge when the vaccine is administered with electroporation to enhance uptake of the plasmid DNA (*50*). Concerns remain regarding the immunogenicity of DNA vaccines in humans, although the effects of using therapeutic vaccination strategies for other diseases raise the potential for DNA-only approaches (*51*). In addition, using a prime-boost format, Modjarrad et al. showed that a full-length S protein DNA vaccine, followed by an S-protein boost, can increase NAb titers, reduce the clinical severity of MERS, and increase the durability of protection in macaques (*52*).

To complement active immunization approaches, researchers are also advancing several prophylactic or therapeutic approaches against MERS-CoV using NAb technologies through preclinical development. Because these NAbs target epitopes of the S protein (or specifically the receptor-binding domain), they can cause precise and potent inhibitory effects on viral entry in small and large animal models (*53*). The mechanisms of neutralization have been uncovered and are typically mediated by blocking MERS-CoV binding to hDPP4 (*22*,*52*,*54*–*56*). As the supplementary agents of antibodies, the peptidic MERS-CoV fusion inhibitors targeting the conserved region in the S protein HR1 domain region are highly potent in inhibiting infection of MERS-CoV strains, including those resistant to NAbs. Intranasal administration of the peptides protected hDPP4-transgenic mice from MERS-CoV challenge, suggesting that, alone or in combination with NAbs, these peptides could be used to prevent and treat MERS-CoV infection (*37*,*39*,*57*).

Further characterization of these technologies and the potential for combination approaches are ongoing as investigators tackle questions related to viral escape (*58*,*59*). Preliminary results indicate that viruses that evade antibody neutralization have reduced viral fitness, demonstrating that escape can occur but comes at a cost to fitness. Nevertheless, continued investigation and surveillance are warranted. Marasco et al. noted that sequencing of circulating strains will be critical to monitor viral evolution (*60*), which will only be possible with increased sample- and data-sharing. Ongoing studies related to cross-reactivity with human tissue and the effects of polyclonal and non-neutralizing antibodies are also underway as passive immunotherapy becomes more accepted to prevent and treat MERS-CoV infection.

Overall, selecting specific technologies and approaches that warrant further development is difficult, given the diversity of models and readouts and the concomitant need for greater standardization in the field. Although each technology presents unique advantages and deficiencies related to desired immunogenicity, safety, durability of protection, need for adjuvant, and manufacturing considerations, some technologies have a long track record in the clinic, which would potentially simplify their development and regulatory pathway. Given the public health urgency, these platforms (or combinations thereof) should be made a priority.

The experience with SARS-CoV offers a sobering lesson: countermeasures that advance on the basis of promising preclinical data may ultimately exacerbate disease in humans. Antibody-dependent enhancement of infectivity has been observed in cell culture in which a human promonocyte cell line is used (*61*–*63*). In mice and hamsters vaccinated with a recombinant native full-length SARS-CoV S protein trimer, serum IgG developed that blocked binding of the S protein to the ACE2 receptor and neutralized SARS-CoV infection in vitro. SARS-CoV entered human B-cell lines in an FcγRII-dependent and ACE2-independent fashion, indicating that antibody-dependent enhancement of virus entry is a novel cell entry mechanism of SARS-CoV. Vaccinated animals showed no signs of enhanced lung pathology or hepatitis, and viral load was undetectable or greatly reduced in lungs after challenge with SARS-CoV (*64*). However, in the presence or absence of adjuvant, vaccination of mice with viruslike particles or inactivated virus induced eosinophilic immunopathologic changes in young and aged mice (*65*–*67*). The pulmonary immunopathologic features, on challenge with SARS-CoV, were associated with Th2-type immunopathology with prominent eosinophil infiltration. Although no enhancement of immunopathologic features has been observed in MERS-CoV–vaccinated and –challenged animals, future studies of MERS-CoV vaccines in animals and humans should consider that possibility.

Vaccine Development Considerations for MERS-CoV

To date, commitment to open communication regarding MERS-CoV vaccine development has been haphazard, and leaders in the field are calling for a new approach that integrates resources to accelerate science and enhance biosecurity. New norms and standards are under development by the World Health Organization (WHO) to streamline sample collection (type, storage and availability, quality control); and information dissemination and publication. Combining resources available in Saudi Arabia, South Korea, the United States, Europe, and beyond to develop countermeasures for MERS-CoV, an "open innovation" paradigm shift can maximize public sector investment, provide robust information for a systems-level approach, and deliver the necessary public health effect that is urgently needed.

The Saudi Arabia MOH, working with Saudi academic institutions, WHO, and other stakeholders, recognizes the crucial role it has to play in defining the public health goals that will guide vaccine development efforts for MERS-CoV (*68*,*69*). Researchers, vaccine developers and health authorities must understand how a vaccine is expected to fit into the larger public health strategy to combat MERS (e.g., target populations and vaccination strategies, level of efficacy, safety profile for a vaccine), as well as the pathway to future vaccine testing (e.g., design of efficacy trial), licensure and access. Few vaccine developers in the MERS arena have experience conducting preclinical and clinical research in the Middle East, and the Saudi MOH and Saudi Food and Drug Authority have a valuable role to play in defining the expectations for future clinical studies and in educating developers on the associated regulatory pathway.

Summary

The potential threat posed by MERS-CoV necessitates a multipronged approach to the development of effective countermeasures. Salient public health messages from the workshop included the following points:

1. Accelerating the development of a vaccine requires a better understanding of MERS-CoV epidemiology, transmission, and pathogenesis in humans and animals. This information will help develop target product profiles for human and veterinary vaccines, which in turn will facilitate planning for efficacy trials and inform development strategies.
2. Because current animal models do not fully reflect hallmarks of severe human disease, a combination of both rodents and nonhuman primate models should be considered in evaluating and developing preventive and therapeutic candidates under standardized conditions.
3. Current vaccine development strategies involve a variety of technology platforms, primarily targeting the MERS-CoV S protein. Given the public health urgency, platforms (or combinations thereof) with an established safety track record in humans should be given priority. Other target species such as dromedary camels should also be considered for the development of veterinary vaccines as a One Health approach.
4. Attention should be paid to lessons learned from SARS-CoV vaccine development efforts, particularly to signs of potential disease enhancement in various animal models.

5. Therapeutic antibodies are recognized as potentially useful tools in MERS prevention and treatment, but the concern around escape mutants with increased fitness, although concern is not limited to this technology type, warrants continued investigation and surveillance. Such an approach could be considered alone or in combination with vaccine approaches. As supplementary agents, the peptidic fusion inhibitors may be developed as MERS prophylactics and therapeutics.
6. An opportunity exists for greater coordination around specific technology platforms and to ensure that appropriate incentives are considered to stimulate research and development collaboration from academia, industry, nongovernmental organizations, and governments.
7. The Saudi Arabia MOH, working with WHO and other stakeholders, has a crucial role to play in defining the public health goals that will guide vaccine development efforts.

Next Steps: Establishing a New Paradigm for Collaboration

Funding agencies, nongovernmental organizations, and companies recognize the need for cooperation and have resolved to formalize a collaborative model. The field recognizes the opportunity to set a precedent for how it collaborates as a global community in the context of an emerging disease, building on lessons learned from the recent international response to the Ebola epidemic. Although still subject to consultation, key components of a partnership(s) were identified, including coordinating funding, sharing samples/data, advancing preclinical models, beginning clinical trials in regions having outbreaks, and standardizing assays and reagents for testing.

Exact partnership structures remain to be determined but should at the very least allow for coordination of activities through frequent, transparent, and open discussions among funding agencies and stakeholders. Future models, including a formalized consortium of players who would make a long-term commitment to advance selected products through development phases, can be contemplated once technologies are evaluated more rigorously. Regardless of the final partnership structure(s), the core of any collaborative strategy should include sharing of data and samples and standardizing laboratory assays to ensure that everyone learns from each other, are able to compare technologies, and ultimately accelerate the development of new solutions.

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Development of Medical Countermeasures to Middle East Respiratory Syndrome Coronavirus

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Preclinical development of and research on potential Middle East respiratory syndrome coronavirus (MERS-CoV) medical countermeasures remain preliminary; advancements are needed before most countermeasures are ready to be tested in human clinical trials. Research priorities include standardization of animal models and virus stocks for studying disease pathogenesis and efficacy of medical countermeasures; development of MERS-CoV diagnostics; improved access to nonhuman primates to support preclinical research; studies to better understand and control MERS-CoV disease, including vaccination studies in camels; and development of a standardized clinical trial protocol. Partnering with clinical trial networks in affected countries to evaluate safety and efficacy of investigational therapeutics will strengthen efforts to identify successful medical countermeasures.

From September 2012 through April 27, 2016, a total of 1,728 laboratory-confirmed Middle East respiratory syndrome coronavirus (MERS-CoV) infections, leading to 624 deaths (36% case-fatality proportion), had been reported to the World Health Organization (WHO) (*1*). Most infections (75%) have been identified in Saudi Arabia (*2*). Zoonotic transmission from exposure to MERS-CoV–infected Arabian camels, known as dromedaries, or their raw milk and limited, nonsustained human-to-human transmission have been reported, including large outbreaks in healthcare facilities (*3*–*5*). The recovery of infectious MERS-CoV in virus cultures of specimens from bed sheets, bedrails, intravenous fluid hangers, and radiograph equipment indicates the potential for fomite transmission of the virus in hospitals providing care for MERS-CoV patients (*6*). However, sustained human-to-human transmission has not been documented, and some case-patients have no identified source of exposure to MERS-CoV. As of April 2016, a total of 26 countries had reported locally acquired or exported cases from the Arabian Peninsula, including 2 cases in the United States identified during May 2014 in healthcare personnel who became ill after working in Saudi Arabia (*7*,*8*). A traveler who visited Saudi Arabia, Qatar, the United Arab Emirates, and Bahrain and then returned to South Korea infected with MERS-CoV in mid-2015 triggered 184 MERS-CoV cases, resulting in 38 deaths in multiple health facilities and 1 additional case in a person who traveled to China (*9*,*10*).

Human infections with MERS-CoV are expected to continue to occur on the Arabian Peninsula because of the prevalence of MERS-CoV in dromedaries and the cultural importance of these camels (i.e., for food, milk, and racing purposes) in the region. During the 2003 outbreak of severe acute respiratory syndrome (SARS) in China, civet cats, the suspected reservoir of SARS coronavirus (SARS-CoV), were culled aggressively; no outbreaks were identified after 2004. In contrast, culling of camels is culturally impractical in the Middle East, and MERS-CoV zoonotic infections of humans have continued since 2012.

The potential for emergence of MERS-CoV mutations that could facilitate sustained community transmission and global dissemination cannot be predicted. No vaccines against or specific treatments for human infection with SARS-CoV, MERS-CoV, or other coronaviruses have been approved. Since 2013, efforts have focused on furthering development of animal models, vaccines, and therapies against MERS-CoV (*11*,*12*). In this report, we update the current state of development for MERS-CoV medical countermeasures, including regulatory challenges in the United States, and draw attention to areas in immediate need of increased infrastructure support for development of these countermeasures.

Strategies for Potential Use of MERS-CoV Medical Countermeasures

MERS-CoV infection could theoretically be prevented by vaccination, pre- or postexposure antiviral chemoprophylaxis, or passive immunoprophylaxis of persons in affected countries at increased risk for MERS-CoV exposure (e.g., healthcare personnel, persons who work with camels) or

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persons at higher risk for more severe disease, including persons >65 years of age and those with chronic medical conditions. Therapeutic drugs with specific activity against MERS-CoV (e.g., antiviral drugs, immunotherapeutic treatments) or that target the host immune response could be used for treatment of human illness caused by MERS-CoV infection or for pre- or postexposure prophylaxis. Before human clinical trials of potential MERS-CoV medical countermeasures are started, proof-of-concept data must be obtained from in vivo studies of experimentally infected animals. Such data may indicate a product's potential efficacy and provide a mechanism for selection of available medical countermeasure candidates. In addition, MERS-CoV vaccines could be developed for animals and used for vaccination of dromedaries on the Arabian Peninsula and in source countries for camel imports to the Horn of Africa to reduce MERS-CoV transmission among camels and possibly from camels to humans.

Animal Models and Virus Strains

Preclinical development of MERS-CoV medical countermeasures has been hindered by several factors, including limited data on the natural history of MERS-CoV infection in humans; the lack of a small animal model that is naturally susceptible to MERS-CoV; and the inability to consistently replicate severe human disease in MERS-CoV–infected nonhuman primates (NHPs). Another factor is limited access to clinical samples and recent virus isolates; for example, a MERS-CoV strain isolated from a patient in 2012, rather than a more recently isolated strain, is currently used by most investigators worldwide.

Small animal and NHP models are useful for testing potential medical countermeasures for efficacy (Table 1). Studies in mice, both dipeptidyl peptidase-4 (DPP4 or cluster differentiation 26) transduced and transgenic, and in rabbits, hamsters, and ferrets have been reviewed elsewhere (*16*,*20*,*21*). These small animal models have been used for screening potential MERS-CoV medical countermeasures (*13*,*14*,*22*).

The major NHP models under development include rhesus macaques and common marmosets (*17*,*18*,*23*). Overall, common marmosets appear to be better suited than rhesus macaques for therapeutic studies designed to target severe disease because marmosets show slightly slower onset of illness and longer duration and severity of disease and their small size requires lower doses of therapeutic drugs. However, the marmoset model has not been standardized and is not consistent between laboratories (*18*,*24*,*25*). Furthermore, the size of marmosets substantially limits sequential blood sampling for virologic or pharmacokinetic testing. Challenges to the development of NHP models include determination and standardization of the optimal MERS-CoV challenge dose and of the volume and route of exposure, as well as the limited availability of NHPs, especially marmosets.

Large animal models in development include camels and camelids such as alpacas (*19*,*26*,*27*). These models may be vital in understanding the virology and immunology

Table 1. Animal models under development for MERS-CoV, United States*

Source	Species	Genetic modification	Pathology
Perlman Laboratory, University of Iowa, Iowa City, IA	Mouse	Expressing human DPP4 from adenovirus 5 vector	Transient and localized expression of human DPP4, mild infection (*13*)
University of Texas Medical Branch, Galveston, TX	Mouse	Knock-in of human DPP4, constitutive promoter	Expression of human DPP4 throughout the animal, including brain, resulting in relentless weight loss and death within days postinfection (*14*)
Regeneron Pharmaceuticals, Inc., Tarrytown, NY	Mouse	Knock-in of human DPP4, natural promoter	Stable expression of human DPP4 under a natural promotor (e.g., limited to the lung, absent in the brain), with viral replication and lung pathology (*15*)
NIAID Rocky Mountain Laboratories, Hamilton, MT USA; NIH/NIAID/Laboratory of Infectious Diseases, Bethesda, MD, USA	New Zealand white rabbit	Wild-type	MERS-CoV spike protein binds wild-type rabbit DPP4 molecule that allows for attachment and infection by MERS-CoV; intranasal infection leads to mild pulmonary disease and increased viral titers (*16*)
NIAID Rocky Mountain Laboratories	Rhesus macaque	Wild-type	Acute localized to widespread pneumonia with transient clinical disease, similar to mild/moderate human MERS-CoV cases; multifocal, mild to marked interstitial pneumonia, with virus replication occurring mainly in alveolar pneumocytes was observed without evidence of systemic infection (*17*)
NIAID Rocky Mountain Laboratories	Marmoset	Wild-type	MERS-CoV spike protein binds wild-type marmoset DPP4. Multiple routes of infection used; similar to more severe human MERS-CoV cases; lethality observed (*18*)
NIAID Rocky Mountain Laboratories	Dromedaries	Wild-type	Infection studies in a small number of dromedaries underway in a large animal BSL-3 facility in the United States (*19*)

*MERS-CoV, Middle East respiratory syndrome coronavirus; DPP4, dipeptidyl peptidase-4; NIAID, National Institute of Allergy and Infectious Diseases, National Institutes of Health; BSL-3, Biosafety level 3.

of MERS-CoV infection in dromedaries, a natural host. In addition, serologic evidence of MERS-CoV infection in alpacas has been reported in Qatar (*28*). Major gaps for all animal models include a lack of consensus and availability of the optimal animal model to replicate severe human illness from MERS-CoV infection; limited availability of currently or recently circulating MERS-CoV strains; the lack of understanding of clinically relevant symptoms that can be incorporated into clinical scores or used as a signal to begin treatment in animal models; and competition for funding, laboratory space, availability of animals, and expertise with other emerging or reemerging infectious diseases, such as Ebola virus disease and Zika virus disease.

Diagnostic Devices

Critical issues for facilitating appropriate clinical management of MERS-CoV cases and for implementing infection prevention and control measures in healthcare facilities is the prompt diagnosis of MERS-CoV infection and the monitoring of prolonged viral shedding in severely ill patients and their healthcare and family contacts. Outside of the United States, several commercial and in-house academic laboratory reverse transcription PCR (RT-PCR) molecular assays are available for research, diagnostic, and viral load monitoring purposes. These assays can measure MERS-CoV RNA in samples from symptomatic patients and their asymptomatic contacts. Contributing factors to recent large clusters of MERS-CoV infection in hospitals in Saudi Arabia and South Korea may be linked to inadequate infection-control procedures and prolonged shedding of MERS-CoV. MERS-CoV RNA has been detected for 24–31 days after onset of fever in hospitalized patients (*29*,*30*).

The Secretary of the US Department of Health and Human Services declared a potential public health emergency on May 29, 2013, regarding MERS-CoV infection that could have a high potential to affect national security or the health and security of US citizens living abroad. The US Food and Drug Administration (FDA) subsequently issued an emergency use authorization to the Centers for Diseases Control and Prevention (CDC) for an in vitro molecular diagnostic test to diagnose MERS-CoV infection in multiple types of clinical specimens from symptomatic patients. The use of this test was later expanded to include the ability to test asymptomatic contacts of a person infected with MERS-CoV who traveled from Saudi Arabia to the United States. The CDC made this test available to multiple US public health laboratories, the US Department of Defense, and WHO laboratories worldwide. Although the test has been distributed extensively, it is limited in terms of the CDC's ability to scale up the supply of reagents to support a surge in MERS-CoV cases in the United States and in other countries where the test has been made available. Therefore, an emergency use authorization was issued on July 17, 2015, for the commercially developed RealStar MERS-CoV RT-PCR Kit U.S. (Altona Diagnostics GmbH, Hamburg, Germany) for use in the in vitro qualitative detection of MERS-CoV RNA in tracheal aspirate or tracheal secretion samples (*31*). Although this commercial assay is a first step in bridging the diagnostic test availability gap in case of a surge scenario, the current coverage, at least in the United States, is insufficient until alternative, FDA-cleared commercial tests are available (Table 2).

A worldwide gap exists in the lack of readily available, simple, rapid, and accurate diagnostic tests for use in outpatient and inpatient clinical settings where the ability of the facility to use currently available, higher complexity molecular tests is limited. The lack of commercial development of MERS-CoV assays may be partially related to the limited availability of clinical specimens and MERS-CoV isolates from infected patients. Availability of serum specimens from RT-PCR–confirmed MERS-CoV patients who survived can help facilitate development of serologic tests. If paired acute and convalescent serum samples are available, serologic tests can be used to confirm MERS-CoV infection when viral shedding is not detectable, and for surveillance purposes such as measuring population exposures and immunity to MERS-CoV infection.

Table 2. Diagnostics candidates for MERS-CoV*

Source	Method	Status
TIB MolBiol, Berlin, Germany	upE and ORF1a RT-PCR assays	Research use only, not for in vitro diagnostic use; company intent to pursue in vitro diagnostic use unknown (*32*)
Fast-track Diagnostics, Sliema, Malta	hCoV-EMc	In vitro diagnostic for use in the European Community (*33*)
Altona Diagnostics, Hamburg, Germany	RT-PCR Kit	In vitro diagnostic for use in the European Community, FDA EUA (*31*,*33*)
Primerdesign, Chandler's Ford, UK	Novel Coronavirus hCoV-MERS RT-PCR Kit	Research use only, not for in vitro diagnostic use; company intent to pursue in vitro diagnostic use unknown (*33*)
US Centers for Disease Control and Prevention, Atlanta, GA, USA	Real-time RT-PCR assay	Available in all US PHL/LRN laboratories and many international governmental laboratories, FDA EUA (*31*)

*MERS, Middle East respiratory syndrome; CoV, coronavirus; upE, upstream of E gene; ORF1a, open reading frame 1a polyprotein; RT-PCR, reverse transcription PCR; hCoV-EMc, Human Coronavirus–Erasmus Medical Center/2012; FDA, US Food and Drug Administration; EUA, emergency use authorization; CDC, US Centers for Disease Control and Prevention; PHL/LRN, Public Health Laboratory/Laboratory Response Network.

Therapeutic Drugs

No investigational therapeutic drugs have been evaluated for treatment of MERS-CoV patients in prospective randomized controlled clinical trials. Potential therapeutic drugs for MERS-CoV patients include available approved drugs with nonspecific properties, such as immunomodulators, small-molecule drugs with broad antiviral activity, repurposed FDA-approved small-molecule drugs that show activity against MERS-CoV in vitro (Table 3) (*34*,*35*), and newly developed monoclonal or polyclonal antibody therapies with specific activity against MERS-CoV (Table 4) (*54*).

One promising approach has been to investigate libraries of drugs approved by the FDA and the European Medicines Agency. Considering development times and manufacturing requirements for new products, repurposing of existing drugs might potentially facilitate a rapid response to outbreaks of emerging viruses (see Regulatory section for a discussion on repurposing). Other early-stage work on MERS-CoV therapeutics includes studies focusing on the essential viral replication steps of fusion, proteolysis, and RNA polymerization (Table 3) (*54*).

Immunotherapeutics under evaluation consist of convalescent plasma and monoclonal and polyclonal antibodies. Most of the monoclonal antibodies in development have specific neutralizing activity against the MERS-CoV spike protein (*55*,*56*). Platforms are being developed to rapidly discover monoclonal antibodies, either from fully human convalescent blood or from transgenic animals, which can be manufactured on a large scale and are likely to have a good safety profile. The most advanced immunotherapeutic for MERS-CoV uses a transchromosomal bovine production system to produce fully human polyclonal MERS-CoV antibodies; a phase I study of this product was recently implemented (*57*; https://clinicaltrials.gov/ct2/show/NCT02788188). Preliminary results from immunoprophylaxis or treatment studies have shown efficacy of fully human monoclonal or polyclonal antibodies in MERS-CoV-infected mice and NHPs (Table 4). Although fully human monoclonal antibodies typically have a good safety

Table 3. MERS-CoV small molecule and biologics treatment candidates*

Source	Drug	Target	Anti–MERS-CoV activity	Status
NIAID Rocky Mountain Laboratories, Hamilton, MT, USA	Ribavirin + IFN	Polymerase + Immunomodulator	Active in cell culture and NHP	Approved for hepatitis C virus, compassionate use for MERS-CoV (*36*–*38*)
University of Hong Kong, Hong Kong	Interferon B1b	Immunomodulator	Active in cell culture	Preclinical development (*24*)
Hemispherix Biopharma, Philadelphia, PA, USA	Alferon N	Immunomodulator	Active in cell culture	Approved for human papillomavirus, orphan drug designation granted by the European Medicines Agency (*39*)
Romark Laboratories, Tampa, FL, USA	Nitazoxanide	Host functions, glycosylation	Active in cell culture	Approved for cryptosporidia and giardia, in clinical trials for influenza virus (*40*)
AbbVie, North Chicago, IL, USA	Lopinavir	Protease	Active in cell culture, NHP models	Approved for HIV (*24*)
BioCryst Pharmaceuticals, Durham, NC, USA	BCX4430	Polymerase	Active in cell culture and (Ad5)-DPP4 mouse	Clinical trial for Ebola virus (*41*)
Sarafianos Laboratory, Columbia, MO, USA†	SSYA10–001	Helicase	Active in cell culture	Broadly active against coronaviruses (*42*)
Planet Biotechnology, Hayward, CA, USA	Immunoadhesin (DPP4-Fc)	Spike/binding	Active in cell culture	Preclinical development (*43*)
New York Blood Center, New York, NY, USA	HR2P-M2	Spike/fusion	Active in mouse models	Preclinical development (*44*)
Loyola University, Chicago, Stritch School of Medicine, Maywood, IL, USA	Protease inhibitors	MERS-CoV PLpro, MERS-CoV 3CLpro5	Active in cell culture	Preclinical development (*45*)
University of Maryland, College Park, MD. USA; Rega Institute, Katholieke Universiteit Leuven, Leiden, Belgium; NCATS; NIAID; University of Leiden, South Holland, the Netherlands	FDA-approved drug screens	Multiple host targets	Active in cell culture; chloroquine and chlorpromazine are promising	Multiple screening efforts (*34*,*35*)

*MERS-CoV, Middle East respiratory syndrome coronavirus; NIAID, National Institute of Allergy and Infectious Diseases, National Institutes of Health; IFN, interferon; NHP, nonhuman primate; DPP4, dipeptidyl peptidase-4; spike, MERS-CoV spike protein; PLpro, papain-like protease; 3CLpro, 3C-like protease; NCATS, National Center for Advancing Translational Sciences, NIAID; FDA, US Food and Drug Administration.
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Table 4. MERS-CoV immunotherapeutic treatment candidates*

Source	Drug	Target	Anti–MERS-CoV activity	Status
Multiple	IVIG	Spike, immune system	Unknown	Intravenous (VIG is available and has been used for the treatment of ≥1 MERS-CoV patients with unknown clinical benefit (*40*).
King Abdullah International Medical Research Center, Riyadh, Saudi Arabia	Convalescent serum	Spike, immune system	Ad5-DPP4 mouse efficacy	A pilot clinical trial of convalescent plasma treatment of MERS-CoV patients is ongoing but not recruiting in Saudi Arabia (*46*)
Sanford Applied Biosciences, Sioux Falls, SD, USA	Transgenic bovine polyclonal	Spike	Ad5-DPP4 mouse and NHP studies	Preclinical development (*47*)
National Cancer Institute, NIH, Bethesda, MD, USA	M336, M337, M338	Spike	MERS-CoV neutralization	Preclinical development (*48*)
Tsinghua University, Beijing, China	MERS-4, MERS-27	Spike	MERS-CoV neutralization	Preclinical development (*49*)
Dana Farber Institute, Boston, MA, USA	3B11, 1F8, 3A1, 80R	Spike	MERS-CoV neutralization	Preclinical development (*50*)
New York Blood Center, New York, NY, USA	Mersmab1	Spike	MERS-CoV neutralization	Preclinical development (*51*)
Regeneron Pharmaceuticals, Tarrytown, NY, USA	REGN3051, REGN3048	Spike	MERS-CoV neutralization and humanized DPP4 mouse studies	Preclinical development (*22*)
Juntendo University, Tokyo, Japan	2F9 and YS110	CD26	VLP neutralization	Preclinical development (*52*)
Humabs Biomed SA, Bellinzona, Switzerland	LCA60	Spike	Ad5-DPP4 mouse	Preclinical development (*53*)

*MERS-CoV, Middle East respiratory syndrome coronavirus; spike, MERS-CoV spike protein; MG, immunoglobulin; Ad5-DPP4, adenovirus 4 virus expressed dipeptidyl peptidase-4; NHP, nonhuman primate; DPP4, dipeptidyl peptidase-4; CD26, dipeptidyl peptidase-4; VLP, virus-like particle.

profile and a defined set of preclinical toxicology studies, challenges to development of immunotherapeutics include ensuring the absence of antibody-dependent enhancement of disease and reducing the risk for generation of escape mutant viruses that would be resistant to treatment.

Vaccines

Human Vaccination

Development of MERS-CoV candidate vaccines was initiated by the National Institute for Allergy and Infectious Diseases at the National Institutes of Health, academic investigators, and several companies (Table 5). Most candidate vaccines are still being evaluated in animal models. They have generally targeted the spike protein of MERS-CoV and are recombinant virus, subunit, DNA, or virus-like vector vaccines (*60*,*63*–*67*). One live-attenuated MERS-CoV candidate vaccine is in early development (*66*). Preliminary studies for several other MERS-CoV vaccine candidates have been initiated, and early results demonstrate immunogenicity; 2 have progressed to NHP challenge, and a phase 1 clinical study in adults of 3 different doses of a DNA plasmid vaccine that expresses the MERS-CoV spike protein was started in January 2016 (*61*). Ongoing assessment of antigenic evolution of circulating MERS-CoV strains is essential for informing vaccine development (*68*).

A concern that must be addressed in the development of MERS-CoV vaccines is the potential for causing antibody-dependent enhancement of disease upon virus challenge, such as what was observed with a SARS-CoV candidate vaccine upon SARS-CoV challenge (*69*). The lack of a precedent of coronavirus vaccines for humans poses another challenge for the evaluation of MERS-CoV vaccines for humans, although vaccines against other animal coronaviruses are safe and in use in animals.

Camel Vaccination

Considering the cultural importance of dromedaries on the Arabian Peninsula for meat, milk, and racing, prevention of camel-to-camel MERS-CoV transmission and reduction of spread from dromedaries to humans by camel vaccination is being investigated by government, academic, and commercial investigators (Table 6). Young camels appear to be at high risk for MERS-CoV infection and could be a priority group for vaccination (*73*,*74*); the loss of maternal MERS-CoV antibodies ≈5–6 months after birth suggests a short time window for vaccination (*75*). A major challenge to this approach is that dromedaries can be reinfected with MERS-CoV; a study by Farag et al. found no correlation between MERS-CoV RNA levels and neutralizing antibodies in camels (*76*), suggesting that antibodies may not be protective against infection. Because older camels can be reinfected, a camel vaccination strategy may require multiple dosing and booster vaccination to increase effectiveness over time. Experimental MERS-CoV infection studies and vaccine studies of a small number of dromedaries have been conducted in large animal Biosafety Level 3 facilities

Table 5. Human vaccine candidates for MERS-CoV targeting spike protein*

Source	Vaccine	Status
Novavax, Gaithersburg, MD, USA	Spike protein trimer in 40 nm particle; likely adjuvanted	Mouse immunogenicity shown (*58*)
NIAID/Vaccine Research Center, Bethesda, MD, USA	Two candidate vaccine approaches: DNA spike prime-S1 protein boost and S1 prime-S1 boost	Mouse and NHP immunogenicity shown; NHP[2] (macaque-radiological efficacy shown) (*59*)
GeneOne Life Science, Seoul, South Korea; Inovio Pharmaceuticals, Plymouth Meeting, PA, USA	DNA expressing spike; electroporation device	Mouse, NHP, and camel immunogenicity shown; NHP[2] (viremia, lung pathology) (*60*); Phase I study started (*61*)
Greffex, Aurora, CO, USA	Fully deleted adenovirus packaging vector	Mouse immunogenicity (*62*)
Erasmus University Rotterdam, Rotterdam, the Netherlands; University of Marburg, Marburg, Germany; Ludwig-Maximilians University, Munich, Germany	MVA vectored spike protein	Mouse immunogenicity and protection shown; clinical trials in planning stage (*63*,*64*)
New York Blood Center, New York, NY, USA; Shanghai Medical College, Shanghai, China	Spike receptor-binding domain subunit vaccine	Recombinant protein containing the 377–588-aa fragment of the S1 subunit (*65*)

*MERS-CoV, Middle East respiratory syndrome coronavirus; spike, MERS-CoV spike protein; NHP, non -human primate; MVA, modified vaccinia Ankara; S1, portion of spike protein with the receptor binding domain.

in the United States and overseas (*19*). In addition, 3 doses of a DNA vaccine containing the MERS-CoV spike protein induced humoral immunity in dromedaries (*60*). In a recent study, a modified vaccinia virus Ankara vaccine that expresses the MERS-CoV spike protein was administered intranasally and intramuscularly to dromedaries; when challenged intranasally with MERS-CoV, vaccinated dromedaries had fewer signs of respiratory infection and lower MERS-CoV titers in the upper respiratory tract compared with unvaccinated dromedaries (*77*). Alpacas (New World camelids) are being investigated as a suitable proxy for camels because of the lack of available dromedaries in the United States, the high cost of acquiring dromedaries, and the relatively smaller size of alpacas (*26*,*27*).

Regulatory Considerations for Medical Countermeasures in the United States

Regulatory considerations for MERS-CoV medical countermeasures in the United States are focused on a pathway to human clinical trials for drugs and vaccines through submission of investigational new drug applications. Investigational new drug submissions must adhere to requirements set forth in the Code of Federal Regulations, Title 21, Part 312 (21 CFR 312; http://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title21/21cfr312_main_02.tpl)._Several guidance documents exist on the FDA website related to virology, microbiology, pharmacology and toxicology, and clinical and medical considerations (*78*). The most appropriate approval pathway is likely to be product-specific and will require consideration of existing product data, proposed intended use and population for use, and validated endpoints for efficacy predictive of clinical benefit, if any. Likewise, data needed for consideration of an emergency use authorization, including dose finding and dose ranging, duration, and safety, can be obtained through sources such as investigational new drug clinical trials.

Repurposing of drugs approved by the FDA for other illnesses for a MERS-CoV indication can potentially be expedited or accelerated if 1) the mechanism of action for antiviral activity is defined, 2) there is no change to the approved final drug form and route of administration, 3) dosing does not exceed the currently approved dose and duration for the currently indicated population and adequate pharmacokinetics data support this dosing, and 4) the risk–benefit profile is acceptable for the intended population and indication. For example, the risk–benefit profile for an approved drug with an oncology indication may be unacceptable if the drug is repurposed for administration to a healthy population for MERS-CoV postexposure prophylaxis. However, data requirements to initiate human trials will depend on the characteristics of the drug product and its intended use against MERS-CoV. As such, sponsors should consider prioritizing drug development on the basis of the totality of scientific evidence and merit of the drug alone, not on whether the drug has been previously approved.

In the absence of a standardized and accepted animal model that simulates human disease from MERS-CoV infection, it is unclear how the FDA may be able to expedite licensure or approval when data are lacking. The best approach may be collection of preclinical safety data and implementation of adaptive human clinical trials. This approach was taken for medical countermeasures in response to the 2013–2016 Ebola virus disease outbreak.

For diagnostic devices, the current emergency use authorization pathway serves as a fast approach to make products available for emergency public health purposes. After an emergency has been terminated, Premarket Notifications for these products should be submitted to FDA for a more thorough evaluation as 510(k)s (http://www.fda.gov/

Table 6. Camel vaccine candidates for MERS-CoV targeting spike protein*

Source	Vaccine	Status
USG/Academic Institution Consortium	Recombinant and inactivated whole virus	Camel vaccination
NIAID Rocky Mountain Laboratories, Hamilton, MT, USA/Colorado State University, Fort Collins, CO, USA	Spike protein subunit vaccine/Advax adjuvant (baculovirus expressed)	Camel and alpaca vaccination studies (*70*,*71*)
Erasmus University Rotterdam, Rotterdam, the Netherlands; University of Marburg, Marburg, Germany; Ludwig-Maximilians University, Munich, Germany	MVA-vectored spike protein	Camel vaccination challenge studies (*71*,*72*)
Novavax AB, Uppsala, Sweden	Spike nanoparticles with adjuvant likely	In preclinical development
University of Pittsburgh, Pittsburgh, PA	Adenovirus vectored spike protein	In preclinical development (*72*)

*MERS-CoV, Middle East respiratory syndrome coronavirus; spike, MERS-CoV spike protein; USG, US government; NIAID, National Institute of Allergy and Infectious Diseases, National Institutes of Health; MVA, modified vaccinia Ankara.

MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/default.htm).

Clinical Experience and Medical Countermeasure Trials

The overarching goal for clinical research of MERS-CoV patients is to optimize clinical management and to identify effective therapies to improve survival. Although clinical data on some MERS-CoV patients have been published in case series (*58*,*79*,*80*), there is a need for much more epidemiologic, clinical, virologic, and immunologic data to improve the limited understanding of the pathogenesis of MERS-CoV infection in humans. Gaps include information on viral load and duration of viral shedding in blood, urine, respiratory, and other clinical specimens from infected persons; understanding of the innate and adaptive immune response to MERS-CoV infection; pathology data on the distribution of MERS-CoV in respiratory and extrapulmonary tissues in fatal cases; information from autopsies of persons who died of MERS-CoV; and an overall improved understanding of the pathogenesis of MERS-CoV in humans. Only 1 study has investigated MERS-CoV infection in autopsy tissues of a patient who died from the disease (*81*). Collaborations are especially needed to pool and systematically collect serial clinical specimens from MERS-CoV patients for virologic, immunologic, and biomarker analyses to correlate with clinical illness, and to conduct long-term follow-up of survivors of severe disease (*82*–*84*). Detailed understanding of host factors and cofactors associated with disease severity from asymptomatic infection to fatal illness is needed. Efforts to promote international sharing of clinical specimens and MERS-CoV isolates are needed to foster development of diagnostics, therapeutics, and vaccines.

Use of standardized clinical data collection instruments and common biologic sampling protocols for serial prospective data collection will facilitate data pooling from MERS-CoV cases and comparisons across clinical sites and countries. Global collaborations among clinical networks are also needed to implement clinical trials, preferably randomized controlled clinical trials, of MERS-CoV investigational therapeutics (*82*–*85*). Without an international agreement on protocols and systematic standardization of case reporting and data collection methods, haphazard or anecdotal reporting and analysis of disease course and outcome may continue. WHO and the International Severe Acute Respiratory and Emerging Infection Consortium are collaborating in adapting standardized protocols for controlled clinical trials for MERS-CoV (*83*).

Timelines for Clinical Trials of Medical Countermeasures

Prospective controlled clinical trials (ideally randomized clinical trials) of potential MERS-CoV therapies and vaccines in humans are needed urgently; however, there is uncertainty in estimating timelines for the development of potential MERS-CoV medical countermeasures because of the need to further characterize existing and new animal models, the unpredictability of demonstrating a favorable risk–benefit outcome during preclinical testing, and competition for resources with other emerging infectious diseases. In addition, the risk for antibody-dependent enhancement of disease may interrupt the timeline for conducting human clinical trials of MERS CoV vaccines and immunotherapeutics. Researchers of all potential MERS-CoV medical countermeasures should have preclinical toxicology data available before initiating human clinical trials. Although animal efficacy data are not technically required before implementing human clinical trials of potential countermeasures, such data are considered important for identifying the most promising medical countermeasure candidates, justifying risk in human volunteers, and informing the design of future clinical studies. Timeframes for the production of specimen panels and repositories to aid commercial diagnostic development are also contingent on obtaining adequate funding and clinical samples.

Conclusions

Although preclinical development and research on potential MERS-CoV medical countermeasures has achieved appreciable progress to date, such development is preliminary, and substantive challenges must be overcome before most potential countermeasures are ready for human

clinical trials. The only clinical trials of MERS-CoV medical countermeasures to date are phase I studies of 1 candidate vaccine and 1 immunotherapeutic that were both implemented in 2016 and are ongoing. Prioritization of animal models, standardization of representative virus strains, and establishment of clinical trial capabilities in areas where the virus is endemic among dromedaries are viewed as critical elements of effective MERS-CoV medical countermeasures development. Results of substantial progress in establishing the infrastructure and platforms for preclinical and advanced clinical development of countermeasures can serve as a model to enable more timely response to other emerging infectious diseases of global public health concern in the future.

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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 23 Sep 2016 18:50:53 +0000
To: Baric, Ralph; Erlandson, Karl (OS/ASPR); Hensley, Lisa (NIH/NIAID) [E]; Subbarao, Kanta (NIH/NIAID) [E]
Subject: RE: MERS Model Workshop Draft Manuscript
Attachments: MERS Workshop Manuscript 8-25-2016.docx, Excler MERS KSA WG EID 2016.pdf, Development of MCMs to MERS-CoV EID 2016.pdf

Hi Everyone,
Friendly reminder to please have a look at the attached draft manuscript from the MERS animal model workshop and to send me your comments.

Many thanks!
Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thursday, August 25, 2016 2:45 PM
To: Baric, Ralph (b)(6) Dreier, Thomas (OS/ASPR/BARDA) (b)(6) Erlandson, Karl (OS/ASPR) (b)(6) Hensley, Lisa (NIH/NIAID) [E] (b)(6) Munster, Vincent (NIH/NIAID) [E] (b)(6) Subbarao, Kanta (NIH/NIAID) [E] (b)(6)
Cc: Spiro, David (NIH/NIAID) [E] (b)(6)
Subject: MERS Model Workshop Draft Manuscript

Hi Everyone,
I know it's been a while since the MERS Model workshop, but David and I have put together a draft manuscript that we would like to submit to EID for publication. We've put this together based on the detailed summary provided by the science writer. Since you all were part of the organizing committee for the workshop, we thought it would be good to have you as co-authors writing on behalf of the entire group. We're asking for your comments and feedback first, and then we will circulate an updated draft to the larger presenter/panelist group. If possible, we would appreciate it if you could please send any comments back to us by September 12th. Please also let me know if you'd prefer not to be listed as an author, or are otherwise unable to participate in preparing the paper.

In addition to the draft, I've also attached two recent, related, EID papers. Our thought is that this paper would be a follow on to these two. Please let me know if you have any questions.

Thanks!
Erik

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MERS-CoV Animal Models: Current Status and the Path to Clinical Trials

Erik J. Stemmy Ph.D.[1], Ralph Baric[2], Tom Dreier[3], Karl Erlandson[3], Lisa Hensley[4], Vincent J Munster[5], Kanta Subbarao[6], and David J. Spiro Ph.D.[1], on behalf of the Workshop Speakers and Panelists.

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Running Title: MERS-CoV Animal Model Workshop Summary

Keywords: MERS-CoV, animal models, medical countermeasures,

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Abstract (Word Count: 101)

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) continues to be a public health threat. A major focus of recent research has been the development of suitable animal models to advance understanding of MERS CoV pathogenesis and to establish a platform in which potential medical countermeasures can be evaluated. The National Institute of Allergy and Infectious Diseases (NIAID) convened a workshop on February 29th and March 1st, 2016 to review the current status of MERS-CoV animal models and to consider the path forward to support clinical trials of promising vaccines and therapeutics. This report will summarize both the workshop and expert panel recommendations.

Word Count: 2,144

Introduction

Since its emergence in 2012 the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) has been reported in 27 countries ranging from the Middle East and North Africa to Asia and North America. As of August 2016 1,791 cases have been reported to the WHO, including 633 deaths (WHO 2016). The high case fatality rate coupled with the lack of approved medical countermeasures (MCMs) and an incomplete understanding of transmission dynamics highlight the potential pandemic risk. A major emphasis of research has been the development suitable animal models in which to test novel vaccines and therapeutics against MERS-CoV. A number of recent advances have been reported in mice (Cockrell, Peck et al. 2014, Zhao, Li et al. 2014, van Doremalen and Munster 2015, Baseler, de Wit et al. 2016, Tao, Garron et al. 2016), New Zealand white rabbits (Haagmans, van den Brand et al. 2015, Houser, Gretebeck et al. 2016), non-human primates (Falzarano, de Wit et al. 2014, Johnson, Via et al. 2015), and camelids (Adney, van Doremalen et al. 2014, Adney, Bielefeldt-Ohmann et al. 2016). As a means to advance MERS-CoV model development, the National Institute of Allergy and Infectious Diseases (NIAID) convened a workshop to bring together stakeholders to: 1) discuss current knowledge about MERS-CoV pathogenesis in humans as it relates to development of animal models; 2) consider the current status of MERS-CoV animal model development; 3) evaluate the potential for standardization of experimental conditions (e.g. variables such as viral challenge strain, route of inoculation, dose, etc); 3) identify existing gaps and/or hurdles hindering animal model development; and 4) consider potential regulatory pathways for promising MCMs. This report will provide a summary of both the workshop and expert panel recommendations.

Clinical Experience with MERS-CoV

The lack of published clinical reports of MERS-CoV cases has made it difficult to assess the suitability of the MERS-CoV animal models under development in terms of clinical relevance to disease. One goal of the workshop was to facilitate discussion between clinicians with experience treating MERS-CoV cases and researchers developing animal models.

MERS-CoV in the Kingdom of Saudi Arabia, *Dr Hail Mater Alabdely, KSA Ministry of Health*.

The majority (1,436) of cases of MERS-CoV have occurred in the Kingdom of Saudi Arabia (KSA), particularly in the region around Riyadh. In response to the MERS-CoV epidemic the KSA Ministry of Health has deployed a computerized preparedness, surveillance, and response system on a national and local level, the main focus of which is rapid identification of MERS-CoV cases and improved infection control practices. Implementation of this system has allowed health authorities to more quickly identify an index case of MERS-CoV in the healthcare setting, resulting in fewer hospital outbreaks, and smaller hospital-associated clusters of cases (Alabdely, Workshop Presentation).

In KSA the case fatality rate since the virus emerged in 2012 has ranged from 41-60%, with a rate closer to 40% in recent outbreaks (Alabdely, Workshop Presentation). There are also likely to be a large number of mild or asymptomatic cases that are not easily recognized. A serosurvey of 10,000 individuals performed in KSA in 2012-2013 looked at the prevalence of MERS-CoV antibodies in the general population, as well as camel shepherds and slaughterhouse workers. The latter two groups had seroprevalence rates of 2.3% and 3.6% compared to 0.2% in the general population; using these data to extrapolate to the general population, almost 45,000 individuals may be seropositive for MERS-CoV in KSA (Muller, Meyer et al. 2015).

Of confirmed MERS-CoV cases in KSA, 38% are primary cases; 12% are in healthcare workers, 13% are household and 33% are hospitalized patients. Studies of case-mortality by age, suggest that mortality rises with patient age, especially for those over 51 years of age. Case mortality is higher for primary cases than for secondary cases, particularly for cases in hospitalized patients. Case fatality is higher for those with underlying medical conditions, particularly for individuals with diabetes, than for those persons who do not have such conditions. MERS-CoV case fatality is also much lower among healthcare workers and household contacts (Alabdely, Workshop Presentation).

MERS-CoV in the Republic of Korea, Dr Sang-Wan Park, Seoul National University College of Medicine. An outbreak of MERS-CoV occurred in the Republic of Korea (RoK) in 2015, starting from 1 imported case and resulting in a total of 186 cases, 36 of which were fatal (WHO 2016). In general, the clinical presentation of MERS-CoV cases in RoK was similar to those reported from KSA. In contrast to the cases in KSA, where the most prevalent comorbidity was diabetes, in RoK the major underlying disease was hypertension (Choi, Kang et al. 2016). Interestingly, the case fatality rate reported for the RoK outbreak was 20.4%, whereas other outbreaks report case fatality rates ranging from 36.5-65% (Choi, Kang et al. 2016).

MERS-CoV Animal Model Development

A number of animal models of MERS-CoV are being developed, and detailed reviews of small and large animal MERS-CoV have been published elsewhere (van Doremalen and Munster 2015, Baseler, de Wit et al. 2016, Shehata, Gomaa et al. 2016). With respect to mouse models, different molecular strategies have been pursued to incorporate human DPP4 (hDPP4) receptors: hDPP4 transduction (Zhao, Li et al. 2014), transgenic (Li, Wohlford-Lenane et al. 2016, Tao,

Garron et al. 2016) and humanized (Cockrell, Peck et al. 2014, Pascal, Coleman et al. 2015). Each of the models has advantages and disadvantages, though having a variety of models may be useful to address different research questions. For example, models expressing a humanized DPP4 receptor might be more physiologically relevant to human disease due to the fact that receptor expression is governed by native promoters, and could provide insight into viral pathogenesis. Because transient expression models can be rapidly deployed, they could be useful in addressing questions in special populations such as the elderly or for particular comorbidities (e.g. diabetes, hypertension) in mouse models previously developed for those conditions.

Given the variety of mouse models being developed it is important to understand the molecular and biological mechanisms that underlie the resulting phenotypes of each model. It is also important to understand other factors that affect the models, such as the strain and source of the animal and of the viral isolate. Currently, the models are still in their developmental stages and thus, it is premature to try to standardize mouse models at this time.

When infected with MERS-CoV New Zealand white rabbits develop mild disease phenotypes, which may be similar to cases of mild or asymptomatic disease in humans (Haagmans, van den Brand et al. 2015, Houser, Gretebeck et al. 2016). Recent work suggests that while rabbits may be of limited use in understanding MERS-CoV disease progression, they may be useful in examining transmission since virus is shed from their upper respiratory tract (Houser, Gretebeck et al. 2016).

NHP models of MERS-CoV exhibit mild to moderate disease, with some differences between the Rhesus Macaque and Common Marmoset models (Baseler, de Wit et al. 2016). These animals are important given that they have a natural receptor for MERS-CoV, however there can

be issues related to availability of animals and reagents. Additionally, advanced medical imaging systems may be useful in NHP studies of MCMs because they allow non-invasive measurements of the virus infection process. Differences in outcomes have also been noted between groups working on common marmosets (Baseler, de Wit et al. 2016). These differences could impact the downstream evaluation of MCMs, so to most effectively use these important models it is critical that this issue be resolved through collaborative work and exchange of reagents.

Recent work has also highlighted the use of dromedary camels and alpacas as models for MERS-CoV infection. Infected animals developed mild upper respiratory symptoms, and efficient transmission was observed between animals co-housed in barns (Adney, van Doremalen et al. 2014, Adney, Bielefeldt-Ohmann et al. 2016). Although camels are natural hosts for MERS-CoV their large size, long gestational period, and difficult temperament may limit their utility as models of MERS-CoV. Alpacas may be more useful in studies since they are smaller new-world camelids which also develop mild respiratory infections from MERS-CoV.

Panel Discussion

The workshop attendees and expert panelists engaged in a robust discussion of MERS-CoV animal models. The panel noted that impressive progress has been made, evidenced by the variety of animal models exhibiting a range of features, including novel mouse models that have unique and/or unexpected phenotypes. These models have great utility and allow for the study of the virus-host interactions, including immune interaction networks that can be associated with disease severity and protective immunity. Since individual models may only be able to reproduce

certain aspects of disease or disease severity, the panel noted that the use of multiple models may be necessary, particularly as work advances in special populations and comorbidities.

A key problem in the development of animal models is a lack of knowledge of disease pathogenesis in humans, as well as a lack of human clinical samples and viral isolates. The disease course and the associated pathology and immunology of MERS-CoV are not well defined, including: the role of innate immunity in pathogenic or protective outcomes; the nature of cellular immune responses; the immune responses associated with protective immunity; the susceptibility of various populations of immune cells to the virus; and the nature of cytokine responses and of inflammatory cell infiltrates. There is also an urgent need for more natural history data to better understand transmission between humans, between camels, and between humans and camels. Epidemiologic and virologic investigations should be done concomitantly with transmission studies in order to assess changes in the virus genome and viral evolution in the wild. Such information is needed for the development of preventatives and therapeutics.

MERS-CoV Medical Countermeasure Considerations

Although no approved MCMs exist for MERS-CoV, substantial basic discovery and preclinical work has been ongoing and was the subject of a recent review (Uyeki, Erlandson et al. 2016). With regard to the contribution of animal model development to MERS-CoV MCMs caution should still be used in interpreting data from studies in animal models. Since models are still being refined it is likely premature to discontinue vaccine/therapeutic leads based solely on data from animal models. For example, DPP4 has a critical role in immune homeostasis and groups have used various techniques to humanize or replace mouse DPP4 to make mice permissive to MERS-CoV infection. Until the models have been fully characterized it is possible that such

DPP4 alterations may have unintended consequences affecting immune regulation which could lead to misinterpretation of data from experiments evaluating the efficacy of MCMs.

For more advanced development of countermeasures, it will be important to make assessments (e.g. efficacy or PK/PD) in models at doses that are relevant for clinical usage. As more candidate vaccines and therapeutics advance to clinical trials, the panel noted the importance of having a clinical trial structure in place in areas with the potential for outbreaks. In addition to allowing access to patient populations, having common clinical trial protocols with appropriate controls will ensure data from multiple trials can be interpreted.

Conclusions and Expert Panel Recommendations

Given the appearance of SARS-CoV and MERS-CoV and the spread of their associated diseases through global travel, it is likely that other coronavirus health threats in humans and animals will arise in the future. Thus, this is a critical time for coronavirus research as threats from these viruses are expected to continue. The MERS-CoV outbreaks present an opportunity for collaborative interactive work among members the scientific community to address fundamental questions in virology, immunology, pathology, and to develop MCMs, that can be implemented as public health strategies.

Recommendations from the MERS-CoV Workshop

- **Further research into the biology of MERS-CoV animal models is necessary before models can be standardized.** Suggestions for the path forward included:
  - Exchanging viruses and testing them in multiple models to compare and understand each system.
  - Collaborative work to compare transgenic mouse models to further understand the molecular mechanisms that regulate immune-mediated disease severity and affect therapeutic responses.
  - Collaborative work between the groups developing NHP models to address significant discrepancies in results.

- **Studies of MERS-CoV pathogenesis in humans are urgently needed to inform the further development of animal models. Studies of human survivors would allow the development of reference reagents and provide a better understanding of the natural response to infection.** Suggestions for future work included:
  - Increased availability of autopsy results, clinical specimens, and virus isolates.
  - Further research into the disease course and associated pathology/immunology of human infection, including: including the role of innate immunity in pathogenic or protective outcomes, the nature of cellular immune responses, immune responses associated with protective immunity, the susceptibility of various populations of immune cells to the virus, and the nature of cytokine responses and of inflammatory cell infiltrates.
- **Further research into MERS-CoV natural history data to better understand transmission dynamics between humans, and between humans and camels.**

Acknowledgements

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MERS-CoV Animal Model Workshop Speakers and Panelists: Danielle Adney, Hail Mater Alabdely, Kimberly Armstrong, Ralph Baric, Luis Enjuanes, Karl Erlandson, Robert Fisher, Matthew Frieman, Susan Gerber, Frederick Hayden, Lisa Hensley, Katherine Houser, Reed Johnson, Vasee Moorthy, Vincent Munster, Sang Won Park, Stanley Perlman, Chien-Te Kent Tseng, Kanta Subbarao

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Toward Developing a Preventive MERS-CoV Vaccine—Report from a Workshop Organized by the Saudi Arabia Ministry of Health and the International Vaccine Institute, Riyadh, Saudi Arabia, November 14–15, 2015

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Middle East respiratory syndrome (MERS) remains a serious international public health threat. With the goal of accelerating the development of countermeasures against MERS coronavirus (MERS-CoV), funding agencies, nongovernmental organizations, and researchers across the world assembled in Riyadh, Saudi Arabia, on November 14–15, 2015, to discuss vaccine development challenges. The meeting was spearheaded by the Saudi Ministry of Health and co-organized by the International Vaccine Institute, South Korea. Accelerating the development of a preventive vaccine requires a better understanding of MERS epidemiology, transmission, and pathogenesis in humans and animals. A combination of rodent and nonhuman primate models should be considered in evaluating and developing preventive and therapeutic vaccine candidates. Dromedary camels should be considered for the development of veterinary vaccines. Several vaccine technology platforms targeting the MERS-CoV spike protein were discussed. Mechanisms to maximize investment, provide robust data, and affect public health are urgently needed.

Middle East respiratory syndrome (MERS) remains a serious public health threat within Saudi Arabia and internationally, as recently illustrated by an outbreak in South Korea with potential pandemic risk (*1*–*7*). A vaccine (or vaccines) targeting the MERS coronavirus (MERS-CoV), which causes the disease, will be a critical component of future public health prevention measures (*8*–*10*). With the goal of accelerating the development of countermeasures against MERS-CoV, funding agencies, nongovernmental organizations, and researchers across the world assembled in Riyadh, Saudi Arabia, on November 14–15, 2015, to discuss current data and research progress to enhance understanding of disease progression from MERS-CoV infection, vaccine development, the challenges of developing treatment measures (e.g., unclear disease mechanisms and transmission patterns), preclinical development and animal models, the landscape of emerging technologies and scientific platforms, and considerations for clinical development. One primary objective of the meeting was to articulate a coordinated action plan that aligns efforts and resources. The meeting was spearheaded by the Ministry of Health (MOH) of Saudi Arabia and co-organized by the International Vaccine Institute, Seoul, South Korea.

Development of MERS-CoV Animal Models

When developing countermeasures against MERS-CoV infection, rodents and small animal models that mimic human disease hallmarks would be useful in initial screening studies before the measure is tested in larger animals (e.g., nonhuman primates and, potentially, camels). Although upper respiratory tract disease develops more severely in the latter (*11*), studying immune correlates of protection and vaccine efficacy in camels (the only natural host besides bats and humans identified thus far) may reveal vulnerabilities of MERS-CoV that may be exploited for human vaccine strategies.

The development of MERS vaccines faces several challenges. Existing small animal species do not naturally express the primary receptor that MERS-CoV uses to infect humans, the human dipeptidyl-peptidase 4 (hDPP4)

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receptor (*12–19*). This lack results in the animal's inability to sustain infection and for clinical illness to develop from MERS-CoV. Larger animal models, such as nonhuman primates, have not yet been optimized to consistently mimic the disease patterns observed in human infection (which is incompletely understood) and also have associated logistical challenges because that work must be completed in Biosafety Level 3 facilities.

Mouse DDP4 cannot support MERS-CoV infection (*16*). Although efforts have been made to adapt MERS-CoV itself to exhibit human disease phenotypes in rodents, greater success has been achieved through the development of specialized mouse models that express hDPP4 (*20–22*). Mouse strains that globally express hDPP4 are susceptible to infection by MERS-CoV, and the mice display lower respiratory tract infection, weight loss, and increased respiratory rate, but also encephalitis, which makes the strains highly lethal. Human DPP4 expression is, however, transient and limited to the lung after Ad5-hDPP4 transduction by intranasal inoculation (*21*). These infected transgenic mice exhibit transcriptional activation of genes encoding classic antiviral cytokines (interferon [IFN]-β, IFN-γ, and MX-1) and pro-inflammatory cytokines (interleukin [IL]-2, IL-6, IL-12, p40, IL-1-α, and tumor necrosis factor [TNF]-α), as well as chemokines (granulocyte-colony stimulating factor [G-CSF], monocyte chemoattractant protein-1 [MCP-1], interferon gamma-induced protein 10 [IP-10], CXC motif ligand 1 [CXCL-1], macrophage protein 1 [MIP-1], and chemokine (C-C motif) ligand 5 [CCL5 or RANTES]), in contrast with the negligible gene activation of infected nontransgenic mice. IL-1, IL-6, TNF-α, G-CSF, MCP-1, IP-10, CXCL-1, MIP-1, RANTES, and interferon-induced GTP-binding protein (MX-1) have been detected in the lungs and brains of infected transgenic mice (*20*).

However, formation of hybrid mouse–human DPP4 dimers in transgenic mice could affect immune regulation and lead to poorly understood outcomes that could confuse the interpretation of disease natural history and vaccine efficacy. Alternatively, a minimally modified version of mouse DPP4, by mutation of 2 amino acids, can support MERS-CoV infection. Mice with this mutation experience severe lower respiratory tract infection, although they do not exhibit brain infection (*16*). In addition, Pascal et al. have developed mice that express hDPP4, under the control of its endogenous promoter and the 3¢ untranslated region, and show lung-specific infection and inflammation (*22*). Further testing may prove that vaccine evaluation in these small animal models could lead to a better understanding of immunogenicity and efficacy of vaccine candidates and the therapeutic measures being considered for evaluation in larger animals and humans.

Among current nonhuman primate models, rhesus macaques display mild-to-moderate clinical signs on viral challenge (*23*), whereas the common marmoset is reported to exhibit more severe signs of infection (*24*,*25*) and could be a better model for the severe clinical syndrome observed in MERS-CoV–infected persons. However, not all research groups have been able to replicate severe disease outcomes in marmosets. Factors contributing to this could include variations in physical location, age, and origin of the marmosets; challenge virus strains and stocks; route and dose of inoculation; and in protocols. To be able to provide robust and reproducible outcomes, these nonhuman primate models need additional development, optimization, and standardization.

Camels are also being used to evaluate MERS-CoV infection, and findings from Adney et al. showed that these animals are unique in that they experience an upper respiratory tract infection. Although we do not know the efficiency of airborne versus droplet or another mode of transmission, viral shedding from the upper respiratory tract might explain the efficiency of camel–camel and camel–human transmission (*11*,*26*). Although camels do not display the severe disease symptoms observed in infected humans (*26*), a camel infection model remains useful for understanding the disease in camels and identifying potential immune correlates of protection induced by vaccination. Veterinary countermeasures could form part of a One Health strategy to forestall zoonotic transmission to humans (*1*). Hesitation to implement animal vaccination strategies in camels once a vaccine becomes available can be attributed to the absence of severe disease in camels (only upper respiratory tract infection with rhinitis) and to skepticism among key groups regarding zoonotic transmission of MERS-CoV to humans (e.g., camel breeders).

Although the animal models for evaluating MERS-CoV infection represent progress, they do not recapitulate the pathogenesis of severe human disease. A combination of both small and large animal models should be considered for evaluation of preventive and therapeutic candidates for MERS. Regardless of the chosen model, comparing and interpreting results effectively and reducing discrepancies among laboratories will be crucial for researchers to agree on a set of standards with respect to experimental design, including variables for age of animals, specimen handling, route of administration, type of virus challenge, inoculation schedule, sample collection, and disease scoring algorithms.

Pipeline of MERS-CoV Vaccine and Antibody Technologies

Building on the experience from the closely related severe acute respiratory syndrome coronavirus (SARS-CoV) (*27*), researchers have been actively working to understand MERS-CoV genetics to inform vaccine and therapeutic development efforts. They quickly demonstrated that the

spike (S) protein, a viral surface glycoprotein, was essential for recognition of hDPP4 and viral entry into cells and likely represented a prime target for immunogen design for the development of vaccines and monoclonal antibodies (*18*,*28*,*29*). At the workshop, we reviewed various approaches—all in preclinical development and all based on the S protein or one of its components, including nanoparticles, subunit proteins and peptides, DNA, various viral vectors, and live attenuated MERS-CoV.

Nanoparticles formed with MERS-CoV S protein, under development by Novavax (Gaithersburg, Maryland, USA), have been shown to induce virus neutralizing antibodies (NAbs) in mice after a single injection; proprietary adjuvants enhance this response (*30*). Vaccines using antigens expressed from the baculovirus platform developed by Novavax have been evaluated in human subjects in the context of phase I and phase II clinical studies for other infectious diseases without notable vaccine-related safety concerns (*31*–*33*).

Portions of the S protein, specifically the receptor-binding domain (*8*,*29*,*34*–*36*), are also being developed as subunit vaccines. As Jiang et al. demonstrated, these fragments map to a "critical neutralizing region" and induce strong immune responses and NAbs in mouse models (*37*,*38*). Moreover, the subunit vaccines have been shown to protect transgenic mice when challenged with MERS-CoV, indicating that vaccines focused on the receptor-binding domain may be sufficient for protective immunity to develop against the virus (*39*,*40*).

Several viral vectors, including adenovirus (*41*,*42*), modified vaccinia Ankara (MVA) (*43*,*44*), and measles virus (*45*), are also under development by different groups. Various lengths of S protein are being expressed on these platforms and are able to generate antibodies in animals that can neutralize MERS-CoV in vitro and, at least for some vector platforms, also generate cellular immune responses (*43*,*45*). For MVA- and measles virus–based vaccines, these responses confer protection in hDPP4-expressing mice (*43*,*45*). MVA constructs, which have established safety profiles in humans, have been tested in camels and can induce protective immunity, representing a potential veterinary technology (*46*). Moreover, on the basis of supportive data from animal studies, these MVA constructs will soon enter clinical trials. Vaccines based on live attenuated viruses historically have been shown to be highly efficacious; they are also safe and generally well tolerated. Enjuanes and others reported to the group the development of 2 engineered MERS-CoV vaccine candidates. One candidate was based on a propagation-defective MERS-CoV strain, and another was a live attenuated virus with 3 safety guards that used a MERS-CoV infectious cDNA clone (*47*). An inactivated SARS-CoV vaccine was shown to be safe and able to induce NAbs in a phase I trial (*48*).

DNA vaccines are generally perceived as a safe, stable platform for in vivo antigen expression. A SARS-CoV DNA vaccine, which expresses the SARS-CoV S protein, has been shown to induce NAbs and functional T-cell responses in humans (*49*). GeneOne (Blue Bell, Pennsylvania, USA) is developing a proprietary, full-length S protein DNA vaccine candidate that has been shown to induce NAbs and highly functional T cells in various animal models and protect rhesus macaques from infection after MERS-CoV challenge when the vaccine is administered with electroporation to enhance uptake of the plasmid DNA (*50*). Concerns remain regarding the immunogenicity of DNA vaccines in humans, although the effects of using therapeutic vaccination strategies for other diseases raise the potential for DNA-only approaches (*51*). In addition, using a prime-boost format, Modjarrad et al. showed that a full-length S protein DNA vaccine, followed by an S-protein boost, can increase NAb titers, reduce the clinical severity of MERS, and increase the durability of protection in macaques (*52*).

To complement active immunization approaches, researchers are also advancing several prophylactic or therapeutic approaches against MERS-CoV using NAb technologies through preclinical development. Because these NAbs target epitopes of the S protein (or specifically the receptor-binding domain), they can cause precise and potent inhibitory effects on viral entry in small and large animal models (*53*). The mechanisms of neutralization have been uncovered and are typically mediated by blocking MERS-CoV binding to hDPP4 (*22*,*52*,*54*–*56*). As the supplementary agents of antibodies, the peptidic MERS-CoV fusion inhibitors targeting the conserved region in the S protein HR1 domain region are highly potent in inhibiting infection of MERS-CoV strains, including those resistant to NAbs. Intranasal administration of the peptides protected hDPP4-transgenic mice from MERS-CoV challenge, suggesting that, alone or in combination with NAbs, these peptides could be used to prevent and treat MERS-CoV infection (*37*,*39*,*57*).

Further characterization of these technologies and the potential for combination approaches are ongoing as investigators tackle questions related to viral escape (*58*,*59*). Preliminary results indicate that viruses that evade antibody neutralization have reduced viral fitness, demonstrating that escape can occur but comes at a cost to fitness. Nevertheless, continued investigation and surveillance are warranted. Marasco et al. noted that sequencing of circulating strains will be critical to monitor viral evolution (*60*), which will only be possible with increased sample- and data-sharing. Ongoing studies related to cross-reactivity with human tissue and the effects of polyclonal and non-neutralizing antibodies are also underway as passive immunotherapy becomes more accepted to prevent and treat MERS-CoV infection.

Overall, selecting specific technologies and approaches that warrant further development is difficult, given the diversity of models and readouts and the concomitant need for greater standardization in the field. Although each technology presents unique advantages and deficiencies related to desired immunogenicity, safety, durability of protection, need for adjuvant, and manufacturing considerations, some technologies have a long track record in the clinic, which would potentially simplify their development and regulatory pathway. Given the public health urgency, these platforms (or combinations thereof) should be made a priority.

The experience with SARS-CoV offers a sobering lesson: countermeasures that advance on the basis of promising preclinical data may ultimately exacerbate disease in humans. Antibody-dependent enhancement of infectivity has been observed in cell culture in which a human promonocyte cell line is used (*61*–*63*). In mice and hamsters vaccinated with a recombinant native full-length SARS-CoV S protein trimer, serum IgG developed that blocked binding of the S protein to the ACE2 receptor and neutralized SARS-CoV infection in vitro. SARS-CoV entered human B-cell lines in an FcγRII-dependent and ACE2-independent fashion, indicating that antibody-dependent enhancement of virus entry is a novel cell entry mechanism of SARS-CoV. Vaccinated animals showed no signs of enhanced lung pathology or hepatitis, and viral load was undetectable or greatly reduced in lungs after challenge with SARS-CoV (*64*). However, in the presence or absence of adjuvant, vaccination of mice with viruslike particles or inactivated virus induced eosinophilic immunopathologic changes in young and aged mice (*65*–*67*). The pulmonary immunopathologic features, on challenge with SARS-CoV, were associated with Th2-type immunopathology with prominent eosinophil infiltration. Although no enhancement of immunopathologic features has been observed in MERS-CoV–vaccinated and –challenged animals, future studies of MERS-CoV vaccines in animals and humans should consider that possibility.

Vaccine Development Considerations for MERS-CoV

To date, commitment to open communication regarding MERS-CoV vaccine development has been haphazard, and leaders in the field are calling for a new approach that integrates resources to accelerate science and enhance biosecurity. New norms and standards are under development by the World Health Organization (WHO) to streamline sample collection (type, storage and availability, quality control); and information dissemination and publication. Combining resources available in Saudi Arabia, South Korea, the United States, Europe, and beyond to develop countermeasures for MERS-CoV, an "open innovation" paradigm shift can maximize public sector investment, provide robust information for a systems-level approach, and deliver the necessary public health effect that is urgently needed.

The Saudi Arabia MOH, working with Saudi academic institutions, WHO, and other stakeholders, recognizes the crucial role it has to play in defining the public health goals that will guide vaccine development efforts for MERS-CoV (*68*,*69*). Researchers, vaccine developers and health authorities must understand how a vaccine is expected to fit into the larger public health strategy to combat MERS (e.g., target populations and vaccination strategies, level of efficacy, safety profile for a vaccine), as well as the pathway to future vaccine testing (e.g., design of efficacy trial), licensure and access. Few vaccine developers in the MERS arena have experience conducting preclinical and clinical research in the Middle East, and the Saudi MOH and Saudi Food and Drug Authority have a valuable role to play in defining the expectations for future clinical studies and in educating developers on the associated regulatory pathway.

Summary

The potential threat posed by MERS-CoV necessitates a multipronged approach to the development of effective countermeasures. Salient public health messages from the workshop included the following points:

1. Accelerating the development of a vaccine requires a better understanding of MERS-CoV epidemiology, transmission, and pathogenesis in humans and animals. This information will help develop target product profiles for human and veterinary vaccines, which in turn will facilitate planning for efficacy trials and inform development strategies.
2. Because current animal models do not fully reflect hallmarks of severe human disease, a combination of both rodents and nonhuman primate models should be considered in evaluating and developing preventive and therapeutic candidates under standardized conditions.
3. Current vaccine development strategies involve a variety of technology platforms, primarily targeting the MERS-CoV S protein. Given the public health urgency, platforms (or combinations thereof) with an established safety track record in humans should be given priority. Other target species such as dromedary camels should also be considered for the development of veterinary vaccines as a One Health approach.
4. Attention should be paid to lessons learned from SARS-CoV vaccine development efforts, particularly to signs of potential disease enhancement in various animal models.

5. Therapeutic antibodies are recognized as potentially useful tools in MERS prevention and treatment, but the concern around escape mutants with increased fitness, although concern is not limited to this technology type, warrants continued investigation and surveillance. Such an approach could be considered alone or in combination with vaccine approaches. As supplementary agents, the peptidic fusion inhibitors may be developed as MERS prophylactics and therapeutics.
6. An opportunity exists for greater coordination around specific technology platforms and to ensure that appropriate incentives are considered to stimulate research and development collaboration from academia, industry, nongovernmental organizations, and governments.
7. The Saudi Arabia MOH, working with WHO and other stakeholders, has a crucial role to play in defining the public health goals that will guide vaccine development efforts.

Next Steps: Establishing a New Paradigm for Collaboration

Funding agencies, nongovernmental organizations, and companies recognize the need for cooperation and have resolved to formalize a collaborative model. The field recognizes the opportunity to set a precedent for how it collaborates as a global community in the context of an emerging disease, building on lessons learned from the recent international response to the Ebola epidemic. Although still subject to consultation, key components of a partnership(s) were identified, including coordinating funding, sharing samples/data, advancing preclinical models, beginning clinical trials in regions having outbreaks, and standardizing assays and reagents for testing.

Exact partnership structures remain to be determined but should at the very least allow for coordination of activities through frequent, transparent, and open discussions among funding agencies and stakeholders. Future models, including a formalized consortium of players who would make a long-term commitment to advance selected products through development phases, can be contemplated once technologies are evaluated more rigorously. Regardless of the final partnership structure(s), the core of any collaborative strategy should include sharing of data and samples and standardizing laboratory assays to ensure that everyone learns from each other, are able to compare technologies, and ultimately accelerate the development of new solutions.

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Development of Medical Countermeasures to Middle East Respiratory Syndrome Coronavirus

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Preclinical development of and research on potential Middle East respiratory syndrome coronavirus (MERS-CoV) medical countermeasures remain preliminary; advancements are needed before most countermeasures are ready to be tested in human clinical trials. Research priorities include standardization of animal models and virus stocks for studying disease pathogenesis and efficacy of medical countermeasures; development of MERS-CoV diagnostics; improved access to nonhuman primates to support preclinical research; studies to better understand and control MERS-CoV disease, including vaccination studies in camels; and development of a standardized clinical trial protocol. Partnering with clinical trial networks in affected countries to evaluate safety and efficacy of investigational therapeutics will strengthen efforts to identify successful medical countermeasures.

From September 2012 through April 27, 2016, a total of 1,728 laboratory-confirmed Middle East respiratory syndrome coronavirus (MERS-CoV) infections, leading to 624 deaths (36% case-fatality proportion), had been reported to the World Health Organization (WHO) (*1*). Most infections (75%) have been identified in Saudi Arabia (*2*). Zoonotic transmission from exposure to MERS-CoV–infected Arabian camels, known as dromedaries, or their raw milk and limited, nonsustained human-to-human transmission have been reported, including large outbreaks in healthcare facilities (*3*–*5*). The recovery of infectious MERS-CoV in virus cultures of specimens from bed sheets, bedrails, intravenous fluid hangers, and radiograph equipment indicates the potential for fomite transmission of the virus in hospitals providing care for MERS-CoV patients (*6*). However, sustained human-to-human transmission has not been documented, and some case-patients have no identified source of exposure to MERS-CoV. As of April 2016, a total of 26 countries had reported locally acquired or exported cases from the Arabian Peninsula, including 2 cases in the United States identified during May 2014 in healthcare personnel who became ill after working in Saudi Arabia (*7*,*8*). A traveler who visited Saudi Arabia, Qatar, the United Arab Emirates, and Bahrain and then returned to South Korea infected with MERS-CoV in mid-2015 triggered 184 MERS-CoV cases, resulting in 38 deaths in multiple health facilities and 1 additional case in a person who traveled to China (*9*,*10*).

Human infections with MERS-CoV are expected to continue to occur on the Arabian Peninsula because of the prevalence of MERS-CoV in dromedaries and the cultural importance of these camels (i.e., for food, milk, and racing purposes) in the region. During the 2003 outbreak of severe acute respiratory syndrome (SARS) in China, civet cats, the suspected reservoir of SARS coronavirus (SARS-CoV), were culled aggressively; no outbreaks were identified after 2004. In contrast, culling of camels is culturally impractical in the Middle East, and MERS-CoV zoonotic infections of humans have continued since 2012.

The potential for emergence of MERS-CoV mutations that could facilitate sustained community transmission and global dissemination cannot be predicted. No vaccines against or specific treatments for human infection with SARS-CoV, MERS-CoV, or other coronaviruses have been approved. Since 2013, efforts have focused on furthering development of animal models, vaccines, and therapies against MERS-CoV (*11*,*12*). In this report, we update the current state of development for MERS-CoV medical countermeasures, including regulatory challenges in the United States, and draw attention to areas in immediate need of increased infrastructure support for development of these countermeasures.

Strategies for Potential Use of MERS-CoV Medical Countermeasures

MERS-CoV infection could theoretically be prevented by vaccination, pre- or postexposure antiviral chemoprophylaxis, or passive immunoprophylaxis of persons in affected countries at increased risk for MERS-CoV exposure (e.g., healthcare personnel, persons who work with camels) or

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persons at higher risk for more severe disease, including persons >65 years of age and those with chronic medical conditions. Therapeutic drugs with specific activity against MERS-CoV (e.g., antiviral drugs, immunotherapeutic treatments) or that target the host immune response could be used for treatment of human illness caused by MERS-CoV infection or for pre- or postexposure prophylaxis. Before human clinical trials of potential MERS-CoV medical countermeasures are started, proof-of-concept data must be obtained from in vivo studies of experimentally infected animals. Such data may indicate a product's potential efficacy and provide a mechanism for selection of available medical countermeasure candidates. In addition, MERS-CoV vaccines could be developed for animals and used for vaccination of dromedaries on the Arabian Peninsula and in source countries for camel imports to the Horn of Africa to reduce MERS-CoV transmission among camels and possibly from camels to humans.

Animal Models and Virus Strains

Preclinical development of MERS-CoV medical countermeasures has been hindered by several factors, including limited data on the natural history of MERS-CoV infection in humans; the lack of a small animal model that is naturally susceptible to MERS-CoV; and the inability to consistently replicate severe human disease in MERS-CoV–infected nonhuman primates (NHPs). Another factor is limited access to clinical samples and recent virus isolates; for example, a MERS-CoV strain isolated from a patient in 2012, rather than a more recently isolated strain, is currently used by most investigators worldwide.

Small animal and NHP models are useful for testing potential medical countermeasures for efficacy (Table 1). Studies in mice, both dipeptidyl peptidase-4 (DPP4 or cluster differentiation 26) transduced and transgenic, and in rabbits, hamsters, and ferrets have been reviewed elsewhere (*16*,*20*,*21*). These small animal models have been used for screening potential MERS-CoV medical countermeasures (*13*,*14*,*22*).

The major NHP models under development include rhesus macaques and common marmosets (*17*,*18*,*23*). Overall, common marmosets appear to be better suited than rhesus macaques for therapeutic studies designed to target severe disease because marmosets show slightly slower onset of illness and longer duration and severity of disease and their small size requires lower doses of therapeutic drugs. However, the marmoset model has not been standardized and is not consistent between laboratories (*18*,*24*,*25*). Furthermore, the size of marmosets substantially limits sequential blood sampling for virologic or pharmacokinetic testing. Challenges to the development of NHP models include determination and standardization of the optimal MERS-CoV challenge dose and of the volume and route of exposure, as well as the limited availability of NHPs, especially marmosets.

Large animal models in development include camels and camelids such as alpacas (*19*,*26*,*27*). These models may be vital in understanding the virology and immunology

Table 1. Animal models under development for MERS-CoV, United States*

Source	Species	Genetic modification	Pathology
Perlman Laboratory, University of Iowa, Iowa City, IA	Mouse	Expressing human DPP4 from adenovirus 5 vector	Transient and localized expression of human DPP4, mild infection (*13*)
University of Texas Medical Branch, Galveston, TX	Mouse	Knock-in of human DPP4, constitutive promoter	Expression of human DPP4 throughout the animal, including brain, resulting in relentless weight loss and death within days postinfection (*14*)
Regeneron Pharmaceuticals, Inc., Tarrytown, NY	Mouse	Knock-in of human DPP4, natural promoter	Stable expression of human DPP4 under a natural promotor (e.g., limited to the lung, absent in the brain), with viral replication and lung pathology (*15*)
NIAID Rocky Mountain Laboratories, Hamilton, MT USA; NIH/NIAID/Laboratory of Infectious Diseases, Bethesda, MD, USA	New Zealand white rabbit	Wild-type	MERS-CoV spike protein binds wild-type rabbit DPP4 molecule that allows for attachment and infection by MERS-CoV; intranasal infection leads to mild pulmonary disease and increased viral titers (*16*)
NIAID Rocky Mountain Laboratories	Rhesus macaque	Wild-type	Acute localized to widespread pneumonia with transient clinical disease, similar to mild/moderate human MERS-CoV cases; multifocal, mild to marked interstitial pneumonia, with virus replication occurring mainly in alveolar pneumocytes was observed without evidence of systemic infection (*17*)
NIAID Rocky Mountain Laboratories	Marmoset	Wild-type	MERS-CoV spike protein binds wild-type marmoset DPP4. Multiple routes of infection used; similar to more severe human MERS-CoV cases; lethality observed (*18*)
NIAID Rocky Mountain Laboratories	Dromedaries	Wild-type	Infection studies in a small number of dromedaries underway in a large animal BSL-3 facility in the United States (*19*)

*MERS-CoV, Middle East respiratory syndrome coronavirus; DPP4, dipeptidyl peptidase-4; NIAID, National Institute of Allergy and Infectious Diseases, National Institutes of Health; BSL-3, Biosafety level 3.

of MERS-CoV infection in dromedaries, a natural host. In addition, serologic evidence of MERS-CoV infection in alpacas has been reported in Qatar (*28*). Major gaps for all animal models include a lack of consensus and availability of the optimal animal model to replicate severe human illness from MERS-CoV infection; limited availability of currently or recently circulating MERS-CoV strains; the lack of understanding of clinically relevant symptoms that can be incorporated into clinical scores or used as a signal to begin treatment in animal models; and competition for funding, laboratory space, availability of animals, and expertise with other emerging or reemerging infectious diseases, such as Ebola virus disease and Zika virus disease.

Diagnostic Devices

Critical issues for facilitating appropriate clinical management of MERS-CoV cases and for implementing infection prevention and control measures in healthcare facilities is the prompt diagnosis of MERS-CoV infection and the monitoring of prolonged viral shedding in severely ill patients and their healthcare and family contacts. Outside of the United States, several commercial and in-house academic laboratory reverse transcription PCR (RT-PCR) molecular assays are available for research, diagnostic, and viral load monitoring purposes. These assays can measure MERS-CoV RNA in samples from symptomatic patients and their asymptomatic contacts. Contributing factors to recent large clusters of MERS-CoV infection in hospitals in Saudi Arabia and South Korea may be linked to inadequate infection-control procedures and prolonged shedding of MERS-CoV. MERS-CoV RNA has been detected for 24–31 days after onset of fever in hospitalized patients (*29*,*30*).

The Secretary of the US Department of Health and Human Services declared a potential public health emergency on May 29, 2013, regarding MERS-CoV infection that could have a high potential to affect national security or the health and security of US citizens living abroad. The US Food and Drug Administration (FDA) subsequently issued an emergency use authorization to the Centers for Diseases Control and Prevention (CDC) for an in vitro molecular diagnostic test to diagnose MERS-CoV infection in multiple types of clinical specimens from symptomatic patients. The use of this test was later expanded to include the ability to test asymptomatic contacts of a person infected with MERS-CoV who traveled from Saudi Arabia to the United States. The CDC made this test available to multiple US public health laboratories, the US Department of Defense, and WHO laboratories worldwide. Although the test has been distributed extensively, it is limited in terms of the CDC's ability to scale up the supply of reagents to support a surge in MERS-CoV cases in the United States and in other countries where the test has been made available. Therefore, an emergency use authorization was issued on July 17, 2015, for the commercially developed RealStar MERS-CoV RT-PCR Kit U.S. (Altona Diagnostics GmbH, Hamburg, Germany) for use in the in vitro qualitative detection of MERS-CoV RNA in tracheal aspirate or tracheal secretion samples (*31*). Although this commercial assay is a first step in bridging the diagnostic test availability gap in case of a surge scenario, the current coverage, at least in the United States, is insufficient until alternative, FDA-cleared commercial tests are available (Table 2).

A worldwide gap exists in the lack of readily available, simple, rapid, and accurate diagnostic tests for use in outpatient and inpatient clinical settings where the ability of the facility to use currently available, higher complexity molecular tests is limited. The lack of commercial development of MERS-CoV assays may be partially related to the limited availability of clinical specimens and MERS-CoV isolates from infected patients. Availability of serum specimens from RT-PCR–confirmed MERS-CoV patients who survived can help facilitate development of serologic tests. If paired acute and convalescent serum samples are available, serologic tests can be used to confirm MERS-CoV infection when viral shedding is not detectable, and for surveillance purposes such as measuring population exposures and immunity to MERS-CoV infection.

Table 2. Diagnostics candidates for MERS-CoV*

Source	Method	Status
TIB MolBiol, Berlin, Germany	upE and ORF1a RT-PCR assays	Research use only, not for in vitro diagnostic use; company intent to pursue in vitro diagnostic use unknown (*32*)
Fast-track Diagnostics, Sliema, Malta	hCoV-EMc	In vitro diagnostic for use in the European Community (*33*)
Altona Diagnostics, Hamburg, Germany	RT-PCR Kit	In vitro diagnostic for use in the European Community, FDA EUA (*31*,*33*)
Primerdesign, Chandler's Ford, UK	Novel Coronavirus hCoV-MERS RT-PCR Kit	Research use only, not for in vitro diagnostic use; company intent to pursue in vitro diagnostic use unknown (*33*)
US Centers for Disease Control and Prevention, Atlanta, GA, USA	Real-time RT-PCR assay	Available in all US PHL/LRN laboratories and many international governmental laboratories, FDA EUA (*31*)

*MERS, Middle East respiratory syndrome; CoV, coronavirus; upE, upstream of E gene; ORF1a, open reading frame 1a polyprotein; RT-PCR, reverse transcription PCR; hCoV-EMc, Human Coronavirus–Erasmus Medical Center/2012; FDA, US Food and Drug Administration; EUA, emergency use authorization; CDC, US Centers for Disease Control and Prevention; PHL/LRN, Public Health Laboratory/Laboratory Response Network.

Therapeutic Drugs

No investigational therapeutic drugs have been evaluated for treatment of MERS-CoV patients in prospective randomized controlled clinical trials. Potential therapeutic drugs for MERS-CoV patients include available approved drugs with nonspecific properties, such as immunomodulators, small-molecule drugs with broad antiviral activity, repurposed FDA-approved small-molecule drugs that show activity against MERS-CoV in vitro (Table 3) (*34*,*35*), and newly developed monoclonal or polyclonal antibody therapies with specific activity against MERS-CoV (Table 4) (*54*).

One promising approach has been to investigate libraries of drugs approved by the FDA and the European Medicines Agency. Considering development times and manufacturing requirements for new products, repurposing of existing drugs might potentially facilitate a rapid response to outbreaks of emerging viruses (see Regulatory section for a discussion on repurposing). Other early-stage work on MERS-CoV therapeutics includes studies focusing on the essential viral replication steps of fusion, proteolysis, and RNA polymerization (Table 3) (*54*).

Immunotherapeutics under evaluation consist of convalescent plasma and monoclonal and polyclonal antibodies. Most of the monoclonal antibodies in development have specific neutralizing activity against the MERS-CoV spike protein (*55*,*56*). Platforms are being developed to rapidly discover monoclonal antibodies, either from fully human convalescent blood or from transgenic animals, which can be manufactured on a large scale and are likely to have a good safety profile. The most advanced immunotherapeutic for MERS-CoV uses a transchromosomal bovine production system to produce fully human polyclonal MERS-CoV antibodies; a phase I study of this product was recently implemented (*57*; https://clinicaltrials.gov/ct2/show/NCT02788188). Preliminary results from immunoprophylaxis or treatment studies have shown efficacy of fully human monoclonal or polyclonal antibodies in MERS-CoV-infected mice and NHPs (Table 4). Although fully human monoclonal antibodies typically have a good safety

Table 3. MERS-CoV small molecule and biologics treatment candidates*

Source	Drug	Target	Anti–MERS-CoV activity	Status
NIAID Rocky Mountain Laboratories, Hamilton, MT, USA	Ribavirin + IFN	Polymerase + Immunomodulator	Active in cell culture and NHP	Approved for hepatitis C virus, compassionate use for MERS-CoV (*36*–*38*)
University of Hong Kong, Hong Kong	Interferon B1b	Immunomodulator	Active in cell culture	Preclinical development (*24*)
Hemispherix Biopharma, Philadelphia, PA, USA	Alferon N	Immunomodulator	Active in cell culture	Approved for human papillomavirus, orphan drug designation granted by the European Medicines Agency (*39*)
Romark Laboratories, Tampa, FL, USA	Nitazoxanide	Host functions, glycosylation	Active in cell culture	Approved for cryptosporidia and giardia, in clinical trials for influenza virus (*40*)
AbbVie, North Chicago, IL, USA	Lopinavir	Protease	Active in cell culture, NHP models	Approved for HIV (*24*)
BioCryst Pharmaceuticals, Durham, NC, USA	BCX4430	Polymerase	Active in cell culture and (Ad5)-DPP4 mouse	Clinical trial for Ebola virus (*41*)
Sarafianos Laboratory, Columbia, MO, USA†	SSYA10–001	Helicase	Active in cell culture	Broadly active against coronaviruses (*42*)
Planet Biotechnology, Hayward, CA, USA	Immunoadhesin (DPP4-Fc)	Spike/binding	Active in cell culture	Preclinical development (*43*)
New York Blood Center, New York, NY, USA	HR2P-M2	Spike/fusion	Active in mouse models	Preclinical development (*44*)
Loyola University, Chicago, Stritch School of Medicine, Maywood, IL, USA	Protease inhibitors	MERS-CoV PLpro, MERS-CoV 3CLpro5	Active in cell culture	Preclinical development (*45*)
University of Maryland, College Park, MD. USA; Rega Institute, Katholieke Universiteit Leuven, Leiden, Belgium; NCATS; NIAID; University of Leiden, South Holland, the Netherlands	FDA-approved drug screens	Multiple host targets	Active in cell culture; chloroquine and chlorpromazine are promising	Multiple screening efforts (*34*,*35*)

*MERS-CoV, Middle East respiratory syndrome coronavirus; NIAID, National Institute of Allergy and Infectious Diseases, National Institutes of Health; IFN, interferon; NHP, nonhuman primate; DPP4, dipeptidyl peptidase-4; spike, MERS-CoV spike protein; PLpro, papain-like protease; 3CLpro, 3C-like protease; NCATS, National Center for Advancing Translational Sciences, NIAID; FDA, US Food and Drug Administration.
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Table 4. MERS-CoV immunotherapeutic treatment candidates*

Source	Drug	Target	Anti–MERS-CoV activity	Status
Multiple	IVIG	Spike, immune system	Unknown	Intravenous (VIG is available and has been used for the treatment of ≥1 MERS-CoV patients with unknown clinical benefit (*40*).
King Abdullah International Medical Research Center, Riyadh, Saudi Arabia	Convalescent serum	Spike, immune system	Ad5-DPP4 mouse efficacy	A pilot clinical trial of convalescent plasma treatment of MERS-CoV patients is ongoing but not recruiting in Saudi Arabia (*46*)
Sanford Applied Biosciences, Sioux Falls, SD, USA	Transgenic bovine polyclonal	Spike	Ad5-DPP4 mouse and NHP studies	Preclinical development (*47*)
National Cancer Institute, NIH, Bethesda, MD, USA	M336, M337, M338	Spike	MERS-CoV neutralization	Preclinical development (*48*)
Tsinghua University, Beijing, China	MERS-4, MERS-27	Spike	MERS-CoV neutralization	Preclinical development (*49*)
Dana Farber Institute, Boston, MA, USA	3B11, 1F8, 3A1, 80R	Spike	MERS-CoV neutralization	Preclinical development (*50*)
New York Blood Center, New York, NY, USA	Mersmab1	Spike	MERS-CoV neutralization	Preclinical development (*51*)
Regeneron Pharmaceuticals, Tarrytown, NY, USA	REGN3051, REGN3048	Spike	MERS-CoV neutralization and humanized DPP4 mouse studies	Preclinical development (*22*)
Juntendo University, Tokyo, Japan	2F9 and YS110	CD26	VLP neutralization	Preclinical development (*52*)
Humabs Biomed SA, Bellinzona, Switzerland	LCA60	Spike	Ad5-DPP4 mouse	Preclinical development (*53*)

*MERS-CoV, Middle East respiratory syndrome coronavirus; spike, MERS-CoV spike protein; MG, immunoglobulin; Ad5-DPP4, adenovirus 4 virus expressed dipeptidyl peptidase-4; NHP, nonhuman primate; DPP4, dipeptidyl peptidase-4; CD26, dipeptidyl peptidase-4; VLP, virus-like particle.

profile and a defined set of preclinical toxicology studies, challenges to development of immunotherapeutics include ensuring the absence of antibody-dependent enhancement of disease and reducing the risk for generation of escape mutant viruses that would be resistant to treatment.

Vaccines

Human Vaccination

Development of MERS-CoV candidate vaccines was initiated by the National Institute for Allergy and Infectious Diseases at the National Institutes of Health, academic investigators, and several companies (Table 5). Most candidate vaccines are still being evaluated in animal models. They have generally targeted the spike protein of MERS-CoV and are recombinant virus, subunit, DNA, or virus-like vector vaccines (*60*,*63*–*67*). One live-attenuated MERS-CoV candidate vaccine is in early development (*66*). Preliminary studies for several other MERS-CoV vaccine candidates have been initiated, and early results demonstrate immunogenicity; 2 have progressed to NHP challenge, and a phase 1 clinical study in adults of 3 different doses of a DNA plasmid vaccine that expresses the MERS-CoV spike protein was started in January 2016 (*61*). Ongoing assessment of antigenic evolution of circulating MERS-CoV strains is essential for informing vaccine development (*68*).

A concern that must be addressed in the development of MERS-CoV vaccines is the potential for causing antibody-dependent enhancement of disease upon virus challenge, such as what was observed with a SARS-CoV candidate vaccine upon SARS-CoV challenge (*69*). The lack of a precedent of coronavirus vaccines for humans poses another challenge for the evaluation of MERS-CoV vaccines for humans, although vaccines against other animal coronaviruses are safe and in use in animals.

Camel Vaccination

Considering the cultural importance of dromedaries on the Arabian Peninsula for meat, milk, and racing, prevention of camel-to-camel MERS-CoV transmission and reduction of spread from dromedaries to humans by camel vaccination is being investigated by government, academic, and commercial investigators (Table 6). Young camels appear to be at high risk for MERS-CoV infection and could be a priority group for vaccination (*73*,*74*); the loss of maternal MERS-CoV antibodies ≈5–6 months after birth suggests a short time window for vaccination (*75*). A major challenge to this approach is that dromedaries can be reinfected with MERS-CoV; a study by Farag et al. found no correlation between MERS-CoV RNA levels and neutralizing antibodies in camels (*76*), suggesting that antibodies may not be protective against infection. Because older camels can be reinfected, a camel vaccination strategy may require multiple dosing and booster vaccination to increase effectiveness over time. Experimental MERS-CoV infection studies and vaccine studies of a small number of dromedaries have been conducted in large animal Biosafety Level 3 facilities

Table 5. Human vaccine candidates for MERS-CoV targeting spike protein*

Source	Vaccine	Status
Novavax, Gaithersburg, MD, USA	Spike protein trimer in 40 nm particle; likely adjuvanted	Mouse immunogenicity shown (*58*)
NIAID/Vaccine Research Center, Bethesda, MD, USA	Two candidate vaccine approaches: DNA spike prime-S1 protein boost and S1 prime-S1 boost	Mouse and NHP immunogenicity shown; NHP[2] (macaque-radiological efficacy shown) (*59*)
GeneOne Life Science, Seoul, South Korea; Inovio Pharmaceuticals, Plymouth Meeting, PA, USA	DNA expressing spike; electroporation device	Mouse, NHP, and camel immunogenicity shown; NHP[2] (viremia, lung pathology) (*60*); Phase I study started (*61*)
Greffex, Aurora, CO, USA	Fully deleted adenovirus packaging vector	Mouse immunogenicity (*62*)
Erasmus University Rotterdam, Rotterdam, the Netherlands; University of Marburg, Marburg, Germany; Ludwig-Maximilians University, Munich, Germany	MVA vectored spike protein	Mouse immunogenicity and protection shown; clinical trials in planning stage (*63*,*64*)
New York Blood Center, New York, NY, USA; Shanghai Medical College, Shanghai, China	Spike receptor-binding domain subunit vaccine	Recombinant protein containing the 377–588-aa fragment of the S1 subunit (*65*)

*MERS-CoV, Middle East respiratory syndrome coronavirus; spike, MERS-CoV spike protein; NHP, non -human primate; MVA, modified vaccinia Ankara; S1, portion of spike protein with the receptor binding domain.

in the United States and overseas (*19*). In addition, 3 doses of a DNA vaccine containing the MERS-CoV spike protein induced humoral immunity in dromedaries (*60*). In a recent study, a modified vaccinia virus Ankara vaccine that expresses the MERS-CoV spike protein was administered intranasally and intramuscularly to dromedaries; when challenged intranasally with MERS-CoV, vaccinated dromedaries had fewer signs of respiratory infection and lower MERS-CoV titers in the upper respiratory tract compared with unvaccinated dromedaries (*77*). Alpacas (New World camelids) are being investigated as a suitable proxy for camels because of the lack of available dromedaries in the United States, the high cost of acquiring dromedaries, and the relatively smaller size of alpacas (*26*,*27*).

Regulatory Considerations for Medical Countermeasures in the United States

Regulatory considerations for MERS-CoV medical countermeasures in the United States are focused on a pathway to human clinical trials for drugs and vaccines through submission of investigational new drug applications. Investigational new drug submissions must adhere to requirements set forth in the Code of Federal Regulations, Title 21, Part 312 (21 CFR 312; http://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title21/21cfr312_main_02.tpl)._Several guidance documents exist on the FDA website related to virology, microbiology, pharmacology and toxicology, and clinical and medical considerations (*78*). The most appropriate approval pathway is likely to be product-specific and will require consideration of existing product data, proposed intended use and population for use, and validated endpoints for efficacy predictive of clinical benefit, if any. Likewise, data needed for consideration of an emergency use authorization, including dose finding and dose ranging, duration, and safety, can be obtained through sources such as investigational new drug clinical trials.

Repurposing of drugs approved by the FDA for other illnesses for a MERS-CoV indication can potentially be expedited or accelerated if 1) the mechanism of action for antiviral activity is defined, 2) there is no change to the approved final drug form and route of administration, 3) dosing does not exceed the currently approved dose and duration for the currently indicated population and adequate pharmacokinetics data support this dosing, and 4) the risk–benefit profile is acceptable for the intended population and indication. For example, the risk–benefit profile for an approved drug with an oncology indication may be unacceptable if the drug is repurposed for administration to a healthy population for MERS-CoV postexposure prophylaxis. However, data requirements to initiate human trials will depend on the characteristics of the drug product and its intended use against MERS-CoV. As such, sponsors should consider prioritizing drug development on the basis of the totality of scientific evidence and merit of the drug alone, not on whether the drug has been previously approved.

In the absence of a standardized and accepted animal model that simulates human disease from MERS-CoV infection, it is unclear how the FDA may be able to expedite licensure or approval when data are lacking. The best approach may be collection of preclinical safety data and implementation of adaptive human clinical trials. This approach was taken for medical countermeasures in response to the 2013–2016 Ebola virus disease outbreak.

For diagnostic devices, the current emergency use authorization pathway serves as a fast approach to make products available for emergency public health purposes. After an emergency has been terminated, Premarket Notifications for these products should be submitted to FDA for a more thorough evaluation as 510(k)s (http://www.fda.gov/

Table 6. Camel vaccine candidates for MERS-CoV targeting spike protein*

Source	Vaccine	Status
USG/Academic Institution Consortium	Recombinant and inactivated whole virus	Camel vaccination
NIAID Rocky Mountain Laboratories, Hamilton, MT, USA/Colorado State University, Fort Collins, CO, USA	Spike protein subunit vaccine/Advax adjuvant (baculovirus expressed)	Camel and alpaca vaccination studies (*70*,*71*)
Erasmus University Rotterdam, Rotterdam, the Netherlands; University of Marburg, Marburg, Germany; Ludwig-Maximilians University, Munich, Germany	MVA-vectored spike protein	Camel vaccination challenge studies (*71*,*72*)
Novavax AB, Uppsala, Sweden	Spike nanoparticles with adjuvant likely	In preclinical development
University of Pittsburgh, Pittsburgh, PA	Adenovirus vectored spike protein	In preclinical development (*72*)

*MERS-CoV, Middle East respiratory syndrome coronavirus; spike, MERS-CoV spike protein; USG, US government; NIAID, National Institute of Allergy and Infectious Diseases, National Institutes of Health; MVA, modified vaccinia Ankara.

MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/default.htm).

Clinical Experience and Medical Countermeasure Trials

The overarching goal for clinical research of MERS-CoV patients is to optimize clinical management and to identify effective therapies to improve survival. Although clinical data on some MERS-CoV patients have been published in case series (*58*,*79*,*80*), there is a need for much more epidemiologic, clinical, virologic, and immunologic data to improve the limited understanding of the pathogenesis of MERS-CoV infection in humans. Gaps include information on viral load and duration of viral shedding in blood, urine, respiratory, and other clinical specimens from infected persons; understanding of the innate and adaptive immune response to MERS-CoV infection; pathology data on the distribution of MERS-CoV in respiratory and extrapulmonary tissues in fatal cases; information from autopsies of persons who died of MERS-CoV; and an overall improved understanding of the pathogenesis of MERS-CoV in humans. Only 1 study has investigated MERS-CoV infection in autopsy tissues of a patient who died from the disease (*81*). Collaborations are especially needed to pool and systematically collect serial clinical specimens from MERS-CoV patients for virologic, immunologic, and biomarker analyses to correlate with clinical illness, and to conduct long-term follow-up of survivors of severe disease (*82*–*84*). Detailed understanding of host factors and cofactors associated with disease severity from asymptomatic infection to fatal illness is needed. Efforts to promote international sharing of clinical specimens and MERS-CoV isolates are needed to foster development of diagnostics, therapeutics, and vaccines.

Use of standardized clinical data collection instruments and common biologic sampling protocols for serial prospective data collection will facilitate data pooling from MERS-CoV cases and comparisons across clinical sites and countries. Global collaborations among clinical networks are also needed to implement clinical trials, preferably randomized controlled clinical trials, of MERS-CoV investigational therapeutics (*82*–*85*). Without an international agreement on protocols and systematic standardization of case reporting and data collection methods, haphazard or anecdotal reporting and analysis of disease course and outcome may continue. WHO and the International Severe Acute Respiratory and Emerging Infection Consortium are collaborating in adapting standardized protocols for controlled clinical trials for MERS-CoV (*83*).

Timelines for Clinical Trials of Medical Countermeasures

Prospective controlled clinical trials (ideally randomized clinical trials) of potential MERS-CoV therapies and vaccines in humans are needed urgently; however, there is uncertainty in estimating timelines for the development of potential MERS-CoV medical countermeasures because of the need to further characterize existing and new animal models, the unpredictability of demonstrating a favorable risk–benefit outcome during preclinical testing, and competition for resources with other emerging infectious diseases. In addition, the risk for antibody-dependent enhancement of disease may interrupt the timeline for conducting human clinical trials of MERS CoV vaccines and immunotherapeutics. Researchers of all potential MERS-CoV medical countermeasures should have preclinical toxicology data available before initiating human clinical trials. Although animal efficacy data are not technically required before implementing human clinical trials of potential countermeasures, such data are considered important for identifying the most promising medical countermeasure candidates, justifying risk in human volunteers, and informing the design of future clinical studies. Timeframes for the production of specimen panels and repositories to aid commercial diagnostic development are also contingent on obtaining adequate funding and clinical samples.

Conclusions

Although preclinical development and research on potential MERS-CoV medical countermeasures has achieved appreciable progress to date, such development is preliminary, and substantive challenges must be overcome before most potential countermeasures are ready for human

clinical trials. The only clinical trials of MERS-CoV medical countermeasures to date are phase I studies of 1 candidate vaccine and 1 immunotherapeutic that were both implemented in 2016 and are ongoing. Prioritization of animal models, standardization of representative virus strains, and establishment of clinical trial capabilities in areas where the virus is endemic among dromedaries are viewed as critical elements of effective MERS-CoV medical countermeasures development. Results of substantial progress in establishing the infrastructure and platforms for preclinical and advanced clinical development of countermeasures can serve as a model to enable more timely response to other emerging infectious diseases of global public health concern in the future.

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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 2 Oct 2015 16:54:58 +0000
To: Subbarao, Kanta (NIH/NIAID) [E]; Baric, Ralph; Munster, Vincent (NIH/NIAID) [E]; Dreier, Thomas (OS/ASPR/BARDA); Erlandson, Karl (OS/ASPR); Hensley, Lisa (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]
Cc: 'Baric, Toni C'
Subject: MERS Animal Model SAG
Attachments: MERS Model Standardization Workshop Draft Sessions 10-2-2015.docx

Hi Everyone,

Thank you for your insightful discussion during our call on the 21st. David and I have incorporated your comments in the attached document. In particular we have expanded the agenda to a rough outline of a two day workshop, and would appreciate any feedback you have on the proposed session organization and topics. One other thing we'd like to ask is for volunteers to choose a session to chair. We anticipate the session chairs will take the lead in setting the format for the session, suggesting speakers, and leading the session during the workshop.

If possible we'd like to ask for your feedback on this draft agenda and deliverables on or before Oct 14th. Please let me know If you have any questions.

Many thanks!
Erik

Erik J. Stemmy, Ph.D.
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Overarching themes and questions to be addressed by the workshop include:

1. What is the current status of the various models in development (e.g. mouse, rabbit, mink, NHP, camel)
    a. What are the biological similarities/differences, pros/cons between the models?
    b. Is there a better, or more appropriate, model for MCM development?
    c. Are different models needed for vaccine vs therapeutic development?
2. Is there a need for standardization of viral challenge, such as: viral strain; route of inoculation, etc?
3. What endpoints are currently possible/desirable?
4. What are current gaps/hurdles in advancing model development?
5. What are potential regulatory pathways for promising MCM candidates?

Deliverables from the Workshop

1. Workshop summary/journal publication
2. Establish standardization guidelines for MERS reagents
3. Determine the availability of reagents (mice, viral isolates, etc) and outline a path forward for access to reagents (What/is there a role for USG in

DRAFT Workshop Sessions

Session 1: Virology and Epidemiology (15-20 minute lectures)

A. Global status, including case study of Korean outbreak
B. Pathology update of human cases from KSA and/or ROK
C. Viral update, including differences between KSA vs ROK cases

Break

Session 2: Model Summary (20-25 minute lectures on each model; in depth science)

A. Large animal models (NHP, camel)
B. Small animal models (mice, rabbit, mink?)

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Session 3: Panel Discussion of Models (facilitated with questions for discussion)

A. Differences/Similarities
B. Pros/Cons
C. Characteristics (challenge strain, route of inoculation, etc)
D. Need for cross-model comparison, reproducibility.
E. Use of models: MCM development vs studying viral pathology
F. Potential of transmission model?

End of day 1

Recap of Session 3 Discussion (10-15 minutes)

Session 4: Lessons Learned (15-20 minute presentations)

A. Lessons Learned from SARS model development
B. Lessons Learned from SARS MCM development
C. BARDA experience licensing products under animal model

Break

Session 5: MCM Development (mix of short presentation/discussion)

A. Regulatory Questions:
    a. How to use models to advance MCMs to clinical trial

    b. What data are required (tox, efficacy, etc)
B. Public health preparedness and need for Human vs animal MCMs
C. Potential/need for broad activity against other CoVs
D. Desired vs available clinical endpoints/outcomes to advance development (e.g. Viral load reduction, weight loss, Standard lung pathology score, Mortality, Respiratory function)

Break

Summary/Path Forward

A. Gaps/hurdles
B. Goals/milestones necessary in models to advance MCM development

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 13 Oct 2015 12:58:09 +0000
To: Subbarao, Kanta (NIH/NIAID) [E]; Baric, Ralph; Munster, Vincent (NIH/NIAID) [E]; Dreier, Thomas (OS/ASPR/BARDA); Erlandson, Karl (OS/ASPR); Hensley, Lisa (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]
Cc: 'Baric, Toni C'
Subject: RE: MERS Animal Model SAG
Attachments: MERS Model Standardization Workshop Draft Sessions 10-2-2015.docx

Hi Everyone,
Just a friendly reminder soliciting your feedback on the updated agenda draft attached again here. Also, I have looked into availability of the large conference room in our Fishers Lane building and come up with some potentials dates (listed below.) Could you please let me know if there are any that should be off the table due to conflicts, any that might be good to use to piggy back on other meetings, or any other preferences you have? I would ideally like to reserve the room in the next week.

Thanks!
Erik

Current Room Availability:
January: 18-19, 20-21
February: 10-11, 15-18, 22-23, 22-25, 29-March 1
March: 9-10, 28-31

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Friday, October 02, 2015 12:55 PM
To: Subbarao, Kanta (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Munster, Vincent (NIH/NIAID) [E] (b)(6) Dreier, Thomas (OS/ASPR/BARDA) (b)(6) Erlandson, Karl (OS/ASPR) (b)(6) Hensley, Lisa (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6)
Cc: 'Baric, Toni C' (b)(6)
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Erik

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