| | |
|---|---|
| **From:** | Wojtowicz, Emma (NIH/OD) [E] |
| **To:** | Tabak, Lawrence (NIH/OD) [E] |
| **Cc:** | Chao, Brittany (NIH/NCI) [E]; Lauer, Michael (NIH/OD) [E]; Jorgenson, Lyric (NIH/OD) [E]; Tucker, Jessica (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E] |
| **Subject:** | FOR AWARENESS: Christian Science Monitor/GoF inquiry |
| **Date:** | Friday, July 9, 2021 12:28:56 PM |
| **Attachments:** | Christian Science Monitor_GoF inquiry_7.9.21.docx |

Hi Dr. Tabak-

We have been working with Christa Case Bryant with Christian Science Monitor on GoF questions. We provided a set of responses to her on 6/20 and although her story ran on 6/25, she followed up with clarifications and additional questions since she will continue to report on GoF in the coming weeks. Please see attached and below for a set of points that she asked to confirm the accuracy of and for three follow up questions. These have been vetted by OSP, OER, NIAID, and OGC and will be sent to the Department for clearance next. Moving forward, we are happy to continue sending you media responses on this issue for review/awareness, or we can go from SME review to Department clearance. Let us know your preference and if you have any questions, edits, or concerns with these responses.

Thank you-

Emma

**Christian Science Monitor Inquiry by Christa Case Bryant**

Link to 6/25 article: https://www.csmonitor.com/USA/Politics/2021/0625/How-risky-is-gain-of-function-research-Congress-scrutinizes-China

**In follow up to responses provided on 6/20 (see questions below for reference), reporter asked to confirm the accuracy of the following bolded statements:**

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**Per HHS P3CO Framework, p. 4 (Figure 1): the funding agency must consider but is not required to abide by the recommendations of the HHS department-level review of grant proposals that meet the P3CO criteria.**

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**NIH is a funding agency within HHS.**

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[redacted]

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[redacted]

**If it is decided that it does merit further review, what entity then reviews it?**

(b) (5)

[redacted]

**Who appoints the individuals to that entity?**

(b) (5)

**Is that entity accountable to NIH, or are they independent of NIH?**

(b) (5)

**Given that these grants are paid for by US taxpayers, what is the rationale for not giving the public or Congress visibility into this grant review process?**

(b) (5)

The Christian Science Monitor



# How risky is ‘gain of function’ research? Congress scrutinizes China.

Chinatopix/AP/File

Dr. Zhengli Shi works with other researchers in a lab at the Wuhan Institute of Virology in Wuhan, China, Feb. 23, 2017. Dr. Shi has adamantly denied that a leak from her lab could have led to the COVID-19 pandemic.

June 25, 2021

**Christa Case Bryant**, Staff writer

WASHINGTON

s questions mount over whether the COVID-19 pandemic could have started with a Chinese lab leak, members of Congress are shining a bright spotlight on controversial virus research often referred to as "gain of function."

Lawmakers are increasingly concerned that researchers who experiment with viruses in an effort to understand them and avert future pandemics could end up making them more lethal or transmissible to humans – potentially causing the types of outbreaks they were seeking to prevent. Members of Congress have especially focused on whether U.S. taxpayers funded such research in China.

At the center of the spotlight is Dr. Zhengli Shi at the Wuhan Institute of Virology, who collaborated on U.S.-funded grants that involved manipulating coronaviruses to understand their transmissibility to humans. She, her American colleagues, and National Institute of Health (NIH) officials have unequivocally rejected allegations that the work involved gain-of-function research or led to the outbreak of COVID-19, denouncing such claims as politicized misinformation.

## WHY WE WROTE THIS

**If a type of scientific research could prevent another pandemic, but also risk causing one if something goes wrong, is it worth it? Questions of scientific freedom, ethics, and public health are in the balance.**

Scientists don't agree on how exactly to define gain-of-function research, but generally it involves enhancing a pathogen to make it more virulent or transmissible. Critics say the NIH is using a narrow interpretation of what counts as gain of function, and has not provided ample transparency into the grant review process for such research.

Debate over gain-of-function experiments involving viruses that could cause a pandemic was once largely confined to scientific journals, workshops, and advisory boards. But now, amid heightened concerns about biosafety, lawmakers see a need

for greater oversight. A key ethical question is whether the benefits outweigh the risks, and if so, how scientific institutions and governments should best regulate it.

The issue came to a head last month when Republican senators led by Rand Paul of Kentucky grilled Dr. Anthony Fauci, director of NIH's National Institute of Allergy and Infectious Diseases, in a congressional hearing about the Wuhan lab's U.S.-funded activities. Sen. Roger Marshall of Kansas compared a U.S.-China exchange of such knowledge, which could potentially be used for bioweapons, to working with the Soviet Union on nuclear technology. Two weeks later, Democrats joined Republicans in passing an amendment proposed by Senator Paul permanently banning U.S. funding of gain-of-function research in China, after which the Senate chamber erupted in cheers.

While the House and president would need to approve the measure for it to become law, the support in the Senate indicates lawmakers' level of concern about such research and desire to establish guardrails. On June 22, Rep. Brad Wenstrup, an Ohio Republican, introduced a similar bill to ban U.S. funding of gain-of-function research in nations considered U.S. adversaries.

But scientists say it's important for their community to take the lead so that the science is not left to Congress.

"You can't expect a legislative aide in the middle of the night to define the technical features of the kinds of risks we're talking about here," says David Relman, a professor of microbiology and immunology at Stanford University.

"I'm worried that if we scientists – together with the NIH – don't get out ahead of this, we're going to have this legislated for us," he adds. "The bottom line for me is that we haven't pursued this sufficiently. Now would be a pretty good time to do this."

## "One of the most dangerous viruses you can make"

In 2011, an NIH-funded researcher in the Netherlands set off alarm bells with a paper describing how he had made, in his words, “probably one of the most dangerous viruses you can make” by enhancing an avian flu virus in a way that made it more transmissible to mammals. Together with a similar NIH-funded study in Wisconsin, it triggered a debate about the risks of conducting such experiments and what could happen if that knowledge got into the wrong hands.

Jim Lo Scalzo/AP

Republican Sen. Rand Paul of Kentucky questions Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, about gain-of-function research during a Senate hearing on May 11, 2021, on Capitol Hill in Washington. “You’re fooling with Mother Nature here. You’re allowing superviruses to be created,” said Senator Paul.

The work was eventually published, but a leaked letter from a member of the advisory board that reviewed it raised concerns that the NIH was more focused on extracting itself from controversy than resolving the underlying issues, a criticism the NIH rejected.

Several years later, a series of safety lapses involving avian flu, smallpox, and anthrax sparked fresh debate. In July 2014, the Cambridge Working Group, headed by Harvard epidemiologist Marc Lipsitch, called for experiments involving potential pandemic pathogens to be curtailed pending an assessment of the risks. A group calling themselves Scientists for Science pushed back with a statement of their own, arguing that such research was essential to preventing and treating disease, and noting that significant resources had already been devoted to ensuring safety, including special lab facilities.

Some scientists see additional restrictions as more of a hindrance than a protection, hampering academic freedom and potentially blocking scientific discoveries they say could save lives. Also, absent an international framework involving certification and inspections, any domestic limits could create a competitive disadvantage for the U.S., both intellectually and commercially.

“Whenever you talk about limiting scientific research or controlling scientific research, there are a lot of antibodies that come out,” says Andrew Weber, former assistant secretary of defense for nuclear, chemical, and biological threats under the Obama administration.

But concerns were high enough that, several months later, the U.S. government put a moratorium on funding gain-of-function research involving influenza, MERS, and SARS, subject to a review period.

The moratorium was lifted in 2017, and the Department of Health and Human Services (HHS) issued new guidelines for research involving “enhanced potential pandemic pathogens.” Under the guidelines, the funding agency is supposed to flag all grant proposals involving such research. Those flagged are then subject to an HHS-managed review process that must consider whether the project is ethically justifiable, whether there are any alternative methods that would be less risky but “equally efficacious,” and if not, whether the potential benefits outweigh the risks.

While oversight proponents see HHS’s 2017 framework as a step of progress, concerns remain.

Critics say funding agencies such as the NIH are essentially self-policing when deciding which proposals to flag for broader HHS review, and that the process is subjective and lacks transparency. Even some top experts don't know the names and number of individuals on the HHS review committee, how they are appointed, or how they arrive at their decisions about whether proposed research could be "reasonably anticipated" to create, transfer, or enhance pathogens that could cause a pandemic. There is no independent biosafety authority outside the government departments overseeing the research, which increasingly include other departments besides HHS, as well as private-sector actors.

"The fact that we have no independent body that can say, 'NIH, CDC, USDA – hey, don't do this,' is a problem," says Rocco Casagrande, managing director of Gryphon Scientific, which produced a 2015 report at the NIH's request on the risks and benefits of gain-of-function research involving influenza, MERS, and SARS in U.S. labs. "There's no one that is without conflict of interest that can stop risky experiments."

## The Wuhan Institute of Virology

Now, the debate over gain-of-function research and lab safety has gained new urgency over questions about the Wuhan Institute of Virology (WIV).

Lawmakers and others are pressing for answers on the scope of WIV's work with coronaviruses – particularly whether any of it could have enhanced their virulence or transmissibility, and if so, whether that work was funded by NIH. Growing circumstantial evidence, and particularly China's unwillingness to release relevant information, has heightened suspicions that COVID-19 could have started with a leak from the Wuhan lab. So far, no evidence has emerged to definitively prove or disprove the lab leak hypothesis, but a wide array of scientists and government officials now say it warrants investigation.

A Trump State Department fact sheet said the WIV had a track record of conducting gain-of-function research and not being transparent about its work with viruses most similar to SARS-CoV-2, which causes COVID-19. It added that the WIV "has engaged in classified research … on behalf of the Chinese military since at least 2017." The Biden administration has not walked back any of the fact sheet's key assertions.

At the May 11 congressional hearing, Senator Paul questioned the wisdom of U.S. grant money funding collaboration with Chinese scientists on such research.

"You're fooling with Mother Nature here. You're allowing superviruses to be created," said Senator Paul at the congressional hearing.

Dr. Fauci repeatedly and emphatically denied the senator's assertions. "With all due respect, you are entirely incorrect," he said. "The NIH has not ever and does not now fund gain-of-function research in that [Wuhan] institute."

Members of Congress say he is parsing words. They have requested documents that could provide more insight into the kind of work WIV was doing, such as the original grant proposal, but so far the NIH has not released them.

In a written statement to the Monitor, the NIH said that pre-funding review of grant proposals is not made public "to preserve confidentiality and to allow for candid critique and discussion."

## "Viruses do not respect borders"

Critics such as Senator Paul have focused on Dr. Shi's collaboration with two U.S. scientists: Ralph Baric of the University of North Carolina at Chapel Hill (UNC), one of the world's leading researchers on bat coronaviruses, and Peter Daszak of EcoHealth Alliance in New York, a nonprofit that seeks to prevent pandemics through its research.

In a U.S.-funded study published in 2015, Dr. Baric, using virus sequences provided by Dr. Shi, created a hybrid version of a bat coronavirus that showed the potential to infect humans. The NIH had approved the study, but it raised eyebrows among some scientists. UNC's School of Public Health said in emails to the Monitor that there was no gain of function and the hybrid virus was not sent to China.

Dr. Shi also collaborated with Dr. Daszak's nonprofit on an NIH-funded study published in 2017 that created hybrids between a virus which had previously been deemed as having the potential to infect humans – and others with unknown properties.

"To me, if you're already starting with something that is poised for human emergence, you don't go messing around with it – even if the chances of creating something bad are 1 in 100," says Stanford's Dr. Relman.

In written statements to the Monitor, EcoHealth Alliance and Dr. Baric defended their work as essential to preventing disease outbreaks and developing treatments and vaccines.

"There are many strains of viruses (including SARS-like betacoronaviruses) that exist in nature, and if we are to develop a drug that is broadly effective against all or most of these strains, we must be able to test such a drug against various strains in the laboratory setting," said Dr. Baric. He says that his team's early work enabled the U.S. to quickly find the first successful treatment for COVID-19 and contributed to the U.S. development of a vaccine.

Even with high safety standards in place, lab leaks involving viruses have led to outbreaks.

"In China, the last six known outbreaks of SARS-1 have been out of labs, including the last known outbreak, which was a pretty extensive outbreak that China initially wouldn't disclose that it came out of lab," said Scott Gottlieb, the former commissioner of the Food and Drug Administration, on CBS's "Face the Nation." He also noted that "mishaps" had occurred in U.S. labs.

From 2007-17, there were two dozen incidents and accidents at U.S. labs involving influenza, SARS, and MERS, according to documents obtained through the Freedom of Information Act by Lynn Klotz, a senior science fellow at the Center for Arms Control and Non-Proliferation, and shared with the Monitor. Ten of those occurred at UNC Chapel Hill, all involving SARS and featuring a range of scenarios, including infected mice briefly escaping from a cabinet or a researcher's hand.

In a statement to the Monitor, the School of Public Health said that the viruses were mouse-adapted strains that pose a lesser risk of infection to humans and that it notified the proper oversight agencies and took corrective action as needed.

"The University of North Carolina at Chapel Hill takes its responsibility as a leading global research institution seriously," the statement said. "Carolina's researchers are committed to safety and operate under stringent biosafety and biosecurity procedures and practices."

However imperfect the U.S. biosafety system may be, experts note, the fact that it requires such reporting and corrective actions sets it apart from China.

"That's what we're not seeing in China," notes Gregory Koblentz, director of George Mason University's Biodefense graduate program, who is working on developing an international architecture for biosafety standards, certification, and inspections. "And that legitimately feeds concerns about this type of research, because we don't see the same kind of mechanisms for reporting and accountability in the Chinese biosafety system as we see in the U.S. and other countries."

Amid criticism that U.S. scientists shouldn't be cooperating on such risky research with scientists working in China, EcoHealth Alliance stressed the need for a global approach to preventing future pandemics.

"To isolate ourselves from the rest of the world would be shortsighted," it said in its statement to the Monitor. "Viruses do not respect borders – truly effective research to identify and characterize them necessarily involves international collaboration. This is exactly the work EcoHealth Alliance does."

Dr. Fauci also defended U.S. funding of WIV's work on bat coronaviruses in a group Zoom call with reporters organized by the Nieman Foundation at Harvard, and said it would have been an abdication of responsibility for health officials not to study the place and animals where SARS originated.

"You need to study bat-human interface in the setting where it occurs. That's China. … You don't want to study bats in Fairfax, Virginia," he said on the June 8 call, while reiterating that the research NIH funded in the Wuhan lab had "nothing to do" with the outbreak of COVID-19.

"Having said that," Dr. Fauci added, "we cannot account for everything that goes on in Chinese labs."

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| **From:** | Tabak, Lawrence (NIH/OD) [E] |
| **To:** | Fine, Amanda (NIH/OD) [E] |
| **Cc:** | Chao, Brittany (NIH/NCI) [E]; Lauer, Michael (NIH/OD) [E]; Jorgenson, Lyric (NIH/OD) [E]; Tucker, Jessica (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; Wojtowicz, Emma (NIH/OD) [E] |
| **Subject:** | Re: FOR AWARENESS: Christian Science Monitor/GoF inquiry |
| **Date:** | Thursday, July 22, 2021 12:24:18 PM |

thanks

**From:** "Fine, Amanda (NIH/OD) [E]" <(b) (6)
**Date:** Thursday, July 22, 2021 at 11:03 AM
**To:** "Tabak, Lawrence (NIH/OD) [E]" <(b) (6)
**Cc:** "Chao, Brittany (NIH/NCI) [E]" <(b) (6) "Lauer, Michael (NIH/OD) [E]" <(b) (6) "Jorgenson, Lyric (NIH/OD) [E]" <(b) (6) "Tucker, Jessica (NIH/OD) [E]" <(b) (6) "Myles, Renate (NIH/OD) [E]" <(b) (6) "Wojtowicz, Emma (NIH/OD) [E]" <(b) (6)
**Subject:** RE: FOR AWARENESS: Christian Science Monitor/GoF inquiry
Apologies for missing this email on Tuesday. NIAID reviewed including Alan.
Will move forward with clearing with HHS.
Thanks!
Amanda

**From:** Tabak, Lawrence (NIH/OD) [E] <(b) (6)
**Sent:** Tuesday, July 20, 2021 2:06 PM
**To:** Fine, Amanda (NIH/OD) [E] <(b) (6)
**Cc:** Chao, Brittany (NIH/NCI) [E] <(b) (6) Lauer, Michael (NIH/OD) [E] <(b) (6) Jorgenson, Lyric (NIH/OD) [E] <(b) (6) Tucker, Jessica (NIH/OD) [E] <(b) (6) Myles, Renate (NIH/OD) [E] <(b) (6) Wojtowicz, Emma (NIH/OD) [E] <(b) (6)
**Subject:** Re: FOR AWARENESS: Christian Science Monitor/GoF inquiry
This seems accurate but I would run by NIAID please.

**From:** "Fine, Amanda (NIH/OD) [E]" <(b) (6)
**Date:** Tuesday, July 20, 2021 at 1:26 PM
**To:** "Tabak, Lawrence (NIH/OD) [E]" <(b) (6)
**Cc:** "Chao, Brittany (NIH/NCI) [E]" <(b) (6) "Lauer, Michael (NIH/OD) [E]" <(b) (6) "Jorgenson, Lyric (NIH/OD) [E]" <(b) (6) "Tucker, Jessica (NIH/OD) [E]" <(b) (6) "Myles, Renate (NIH/OD) [E]" <(b) (6) "Wojtowicz, Emma (NIH/OD) [E]" <(b) (6)
**Subject:** RE: FOR AWARENESS: Christian Science Monitor/GoF inquiry
Hi Larry-
After last Thursday's exercise, we went back to try to tighten up some responses to this inquiry in addition to providing more detail about what the review process is at the NIH IC level. The responses to which we made changes are highlighted and the additional details on the review process are in red. These have been reviewed by the same groups as before. Let us know if you have any concerns.
Thanks!
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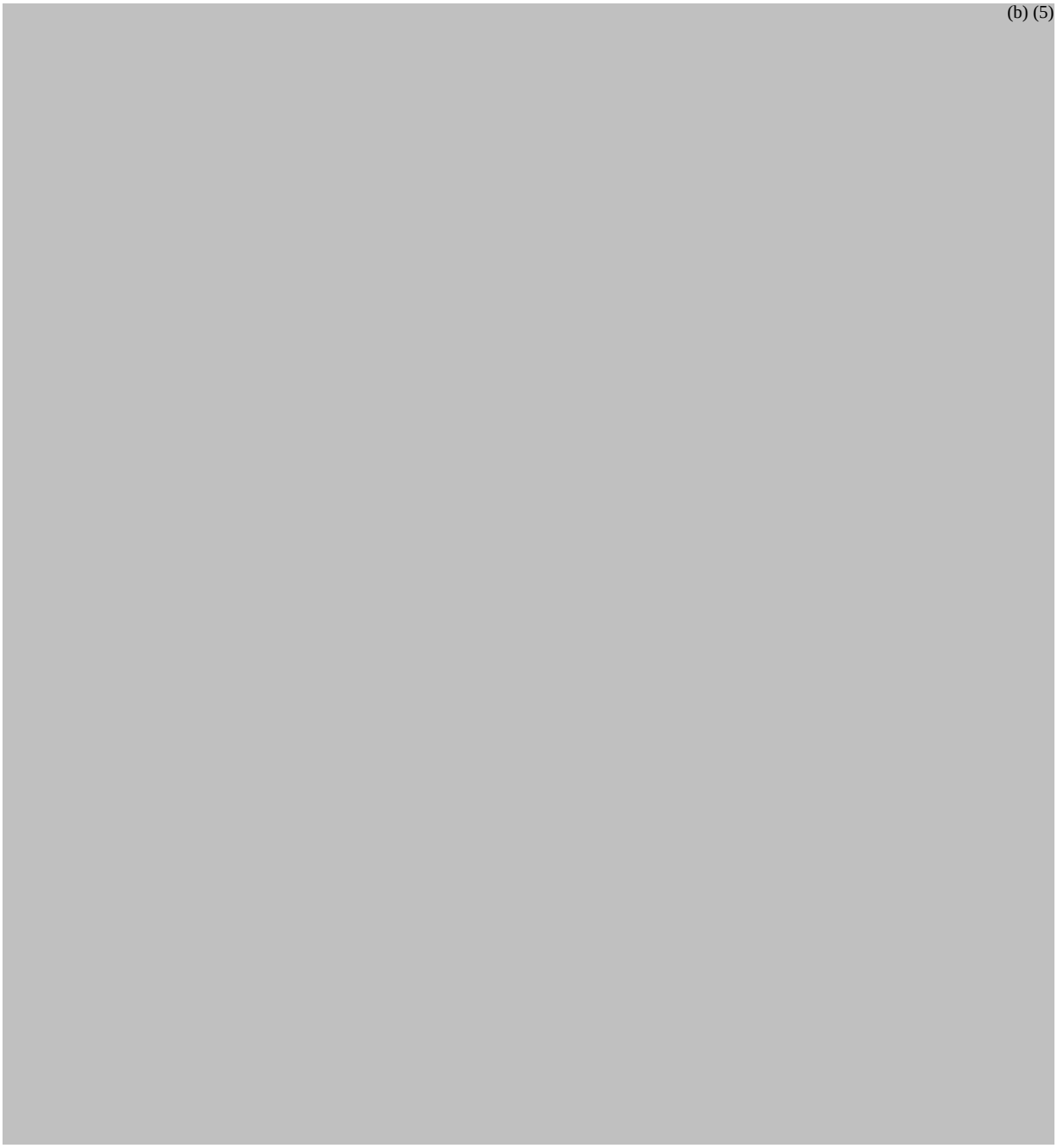

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(b) (5)

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**From:** Wojtowicz, Emma (NIH/OD) [E] <(b) (6)
**Sent:** Friday, July 9, 2021 12:40 PM
**To:** Tabak, Lawrence (NIH/OD) [E] <(b) (6)
**Cc:** Chao, Brittany (NIH/NCI) [E] <(b) (6) Lauer, Michael (NIH/OD) [E] <(b) (6) Jorgenson, Lyric (NIH/OD) [E] <(b) (6) Tucker, Jessica (NIH/OD) [E] <(b) (6) Myles, Renate (NIH/OD) [E] <(b) (6) Fine, Amanda (NIH/OD) [E] <(b) (6)
**Subject:** RE: FOR AWARENESS: Christian Science Monitor/GoF inquiry
Will do, thank you-

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**From:** Tabak, Lawrence (NIH/OD) [E] <(b) (6)
**Sent:** Friday, July 9, 2021 12:38 PM
**To:** Wojtowicz, Emma (NIH/OD) [E] <(b) (6)
**Cc:** Chao, Brittany (NIH/NCI) [E] <(b) (6) Lauer, Michael (NIH/OD) [E] <(b) (6) Jorgenson, Lyric (NIH/OD) [E] <(b) (6) Tucker, Jessica (NIH/OD) [E] <(b) (6) Myles, Renate (NIH/OD) [E] <(b) (6) Fine, Amanda (NIH/OD) [E] <(b) (6)
**Subject:** Re: FOR AWARENESS: Christian Science Monitor/GoF inquiry
Thanks Emma; please continue to keep me in the loop.
Larry

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**From:** "Wojtowicz, Emma (NIH/OD) [E]" <(b) (6)
**Date:** Friday, July 9, 2021 at 12:28 PM
**To:** "Tabak, Lawrence (NIH/OD) [E]" <(b) (6)
**Cc:** "Chao, Brittany (NIH/NCI) [E]" <(b) (6) "Lauer, Michael (NIH/OD) [E]" <(b) (6) "Jorgenson, Lyric (NIH/OD) [E]" <(b) (6) "Tucker,

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Link to 6/25 article: https://www.csmonitor.com/USA/Politics/2021/0625/How-risky-is-gain-of-function-research-Congress-scrutinizes-China

**In follow up to responses provided on 6/20 (see questions below for reference), reporter asked to confirm the accuracy of the following bolded statements:**

**The "independent expert review process" mentioned in the HHS P3CO Framework is the HHS department-level review.**

(b) (5)

**Per HHS P3CO Framework, p. 4 (Figure 1): the funding agency must consider but is not required to abide by the recommendations of the HHS department-level review of grant proposals that meet the P3CO criteria.**

(b) (5)

**NIH is a funding agency within HHS.**

(b) (5)

**The names of the members and chair appointed to the HHS-managed Review Group are not made public, nor is the number of members, the process by which they or the chair are chosen, or the terms of their service (none of the experts I asked about this could explain any of this to me).**

(b) (5)

**HHS P3CO Framework, p. 3 (Box 1, point #5) "The investigator and the institution where the research would be carried out have the demonstrated capacity and commitment to conduct it safely and securely, and have the ability to respond rapidly, mitigate potential risks and take**

**corrective actions in response to laboratory accidents, lapses in protocol and procedures, and potential security breaches;..." I am assuming that this would include any institution that carries out NIH-funded research on site, including as part of a subaward made by the primary grantee, but please correct me if I am wrong.**

(b) (5)

[redacted]

**Follow up questions to the responses provided on 6/20 (see questions below for reference):**

**Given that Dr. Fauci has been so unequivocal in stating that the NIH grants to EcoHealth Alliance and EHA's sub-awards to the Wuhan Institute of Virology did not constitute prohibited gain-of-function research, what is the rationale for not giving the public or at least members of Congress visibility into how those funds were used by providing the original grant proposal from EHA as well as interim reports?**

(b) (5)

[redacted]

**The December 2017 HHS guidelines for funding gain of function research states that it applies to proposals that are "reasonably anticipated to create, transfer, or use enhanced PPPs". How does NIAID determine what may be "reasonably anticipated," particularly when the researchers are working with a new coronavirus whose traits are unknown?**

(b) (5)

[redacted]

**When NIH grant proposals involving potential pandemic pathogens state that some of the work will be done in concert with scientists abroad, what is NIAID's process for evaluating the standards of the foreign labs in which this work will be done?**

(b) (5)

[redacted]

(b) (5)

**Responses provided to reporter on 6/20:**

**When researchers submit a grant proposal that involves potential gain of function research with potential pandemic pathogens, who decides whether it merits further review and is that individual/entity within NIH?**

(b) (5)

**If it is decided that it does merit further review, what entity then reviews it?**

(b) (5)

**Who appoints the individuals to that entity?**

(b) (5)

(b) (5)

**Is that entity accountable to NIH, or are they independent of NIH?**

(b) (5)

**Given that these grants are paid for by US taxpayers, what is the rationale for not giving the public or Congress visibility into this grant review process?**

(b) (5)

**From:** Matocha, Martha (NIH/NINR) [E]
**To:** Zardeneta, Lizeth (HHS/OS/IOS)
**Cc:** Cha, Stephen (HHS/IOS); Allen-Gifford, Patrice (NIH/OD) [E]
**Subject:** Briefing Memo_XB_July 6 2021_final documents
**Date:** Monday, July 5, 2021 10:19:00 AM
**Attachments:** Briefing Memo_XB_FINAL_July 6 2021.docx
ARPA-H Briefing Becerra_070621.pptx
Viral Origin Briefing Becerra_070621.pptx
ARPA-H Science_062221.pdf

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Hello Lizeth.

Attached please find the final documents for the 7/6/2021 briefing between the IOS and NIH.

Sincerely,

Martha Matocha, Ph.D.

Acting Deputy Director

NIH Executive Secretariat

**DATE:** July 2, 2021

**TO:** Secretary Xavier Becerra

**THROUGH:** Stephen Cha, M.D.
Counselor to the Secretary

**FROM:** Francis S. Collins, M.D., Ph.D.

**SUBJECT:** NIH High Priority Items

**Details**
**What:** Briefing for the Secretary
**Date:** July 6, 2021
**Time:** TBD
**Location:** Zoom call initiated by IOS
**Call**: Indicate if this is a phone call - TBD
**Internal or External Event:** Internal

**HHS Staff**:
The Secretary
Andrea Palm, Deputy Secretary
Sean McCluskie, Chief of Staff
Stephen Cha, Counselor to the Secretary
Francis S. Collins, M.D., Ph.D., NIH Director
Lawrence A. Tabak, D.D.S Ph.D., NIH Principal Deputy Director

**Press:** No

**Topics:**

Brief introduction to ARPA-H
SARS-CoV-2 Origins

**Objective:**

To provide the Secretary and HHS Senior Leaders an update on NIH's immediate priorities.

**Secretary's Role:**
To receive information about NIH priority topics and provide his perspective.

**List of Participants:**

Secretary Becerra
Dr. Francis Collins
Dr. Lawrence Tabak

**Agenda/Run of Show:**

11:00-11:10: ARPA-H – Dr. Collins
11:10-11:20: SARS-CoV-2 Origins – Dr. Tabak
11:20-11:30 Discussion/QA

**Background:**

The President's fiscal year 2022 budget proposes the creation of a new $6.5 billion Advanced Research Projects Agency for Health (ARPA-H) as a distinct division within NIH. If approved by Congress, ARPA-H would make bold investments leading to breakthrough technologies and approaches that have the potential to transform important areas of medicine and health in ways that cannot readily be accomplished through traditional research or commercial activity.

NIH fully supports the expert-driven investigations by the U.S. intelligence community and the World Health Organization. While both historic precedent and scientific data to date suggest SARS-CoV-2 evolved through natural transmission from animal to human, it will be important to confirm the origins of the pandemic to inform strategies needed to prevent future ones.

**Attachments:**

1. ARPA-H slides
2. SARS-CoV-2 Origins slides
3. Science article on ARPA-H

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

# ARPA-H

July 6, 2021

Science

POLICY FORUM

Cite as: F. S. Collins *et al.*, *Science*
10.1126/science.abj8547 (2021).

# ARPA-H: Accelerating biomedical breakthroughs

**Francis S. Collins[1], Tara A. Schwetz[1,2], Lawrence A. Tabak[1], Eric S. Lander[2]**

[1]National Institutes of Health; Bethesda, MD 20892, USA. [2]Office of Science and Technology Policy, Executive Office of the President; Washington, DC 20502, USA.
Email: eric.s.lander@ostp.eop.gov

**A DARPA-like culture at NIH can drive biomedical and health advances**

The biomedical research ecosystem has delivered advances that not long ago would have been inconceivable, exemplified by highly effective COVID-19 vaccines developed by global partners and approved in less than a year. The United States stands at a moment of unprecedented scientific promise and is challenged to ask: What more can we do to accelerate the pace of breakthroughs to transform medicine and health? Toward that end, President Biden recently proposed to create a new entity, the Advanced Research Projects Agency for Health (ARPA-H), within the National Institutes of Health (NIH) "to develop breakthroughs—to prevent, detect, and treat diseases like Alzheimer's, diabetes, and cancer," requesting $6.5 billion in the fiscal year 2022 budget (*1*). The idea is inspired by the Defense Advanced Research Projects Agency (DARPA), which follows a flexible and nimble strat-

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some of the m
breakthroughs,
support for scie
driven research,

**Ronald Klain** ✓
@WHCOS

I can tell you that there are few things we are doing here that matter as much, personally, to @POTUS as the effort to launch "ARPA-H"

> **Mary Jordan** ✓ @marycjordan · Jun 28
> A new health agency modeled after DARPA -- whose scientists invented the World Wide Web, GPS, and other gamechangers - could accelerate ways to defeat cancer, Alzheimer's and other diseases. @jaxalemany washingtonpost.com/politics/2021/...

5:47 PM · Jun 28, 2021 · Twitter Web App

# The Opportunity

- **Moment of unprecedented scientific promise…**
  - Cancer immunotherapies
  - Highly effective COVID-19 vaccines developed and approved in ~11 months
- **Challenges us to ask:**
  - What more can we do to accelerate the pace of breakthroughs in medicine and health?
  - How can we revolutionize prevention, treatment, or cure of cancer, infectious diseases, Alzheimer's disease, and other diseases?
  - How can we transform healthcare access, equity, quality, and reduce health disparities?

# Draft Mission

To make **pivotal investments in break-through technologies** and broadly applicable platforms, capabilities, resources, and solutions that have the potential to **transform important areas of medicine and health for the benefit of all patients** and that cannot readily be accomplished through traditional research or commercial activity

# Goals

- Build **capabilities and platforms** to revolutionize prevention, treatment, and cures in a **range of diseases**
- Convert **use-driven ideas** into tangible solutions for patients far more rapidly than previously believed possible
- Speed application and implementation of **health breakthroughs** to serve all patients
- Foster breakthroughs across various levels – from **the molecular to the societal**
- Overcome market failures through **critical solutions or incentives**

***Many areas are ripe for transformation with right support, collaboration***

# Structure

**Centered around ensuring risk tolerance, urgency, nimbleness, and innovation**

- Flat, dynamic organization
- Term-limited director with technical and leadership skills
- Creative, diverse cohort of program managers recruited for short terms with broad autonomy to drive transformational change
- Time-limited projects with goals, quantifiable metrics, and accountability
- Distinct project review and selection processes
- Equity considerations through targeted programs and inclusion in all programs
- Collaborations with performers in academia, industry, government (including ICs)

# Authorities Needed to Accomplish Mission

- **Rapid hiring outside civil service system with competitive wages**
- **Recruiting expert project managers for short, 3-5 years terms**
- **Broad, flexible funding authorities**
  - Mix and match ideas with minimal bureaucracy
  - Projects that don’t fit neatly into one-year intervals
  - Funding distribution over multiple years
  - Mechanism to challenge teams to compete
- **Exemptions from traditional review processes**

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

# Origin of SARS-CoV-2

July 6, 2021

# Importance of Studying Coronaviruses

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

[1] Cutler DM, Summers LH. JAMA. 2020

# Early Timeline of SARS-CoV-2

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

# EcoHealth Alliance Grant

- Sought to understand how animal coronaviruses evolve naturally in the environment to become transmissible to humans

- Research included:
  - Studying viral diversity in bat reservoirs
  - Surveying people with high exposure to wildlife for evidence of bat coronavirus infection
  - Characterizing viruses to predict which potentially pose a threat to human health

# EcoHealth Alliance Grant

- To support its work, EcoHealth made sub-awards to the Wuhan Institute of Virology (WIV) and other institutions based in China, where coronaviruses have emerged in the past and are prevalent

- The grant did not propose research to enhance a coronavirus to be more transmissible or virulent

- The terms of the grant were thoroughly reviewed by NIH staff, and detailed documentation shows that this grant did not meet the standards of gain of function research that would require high level oversight

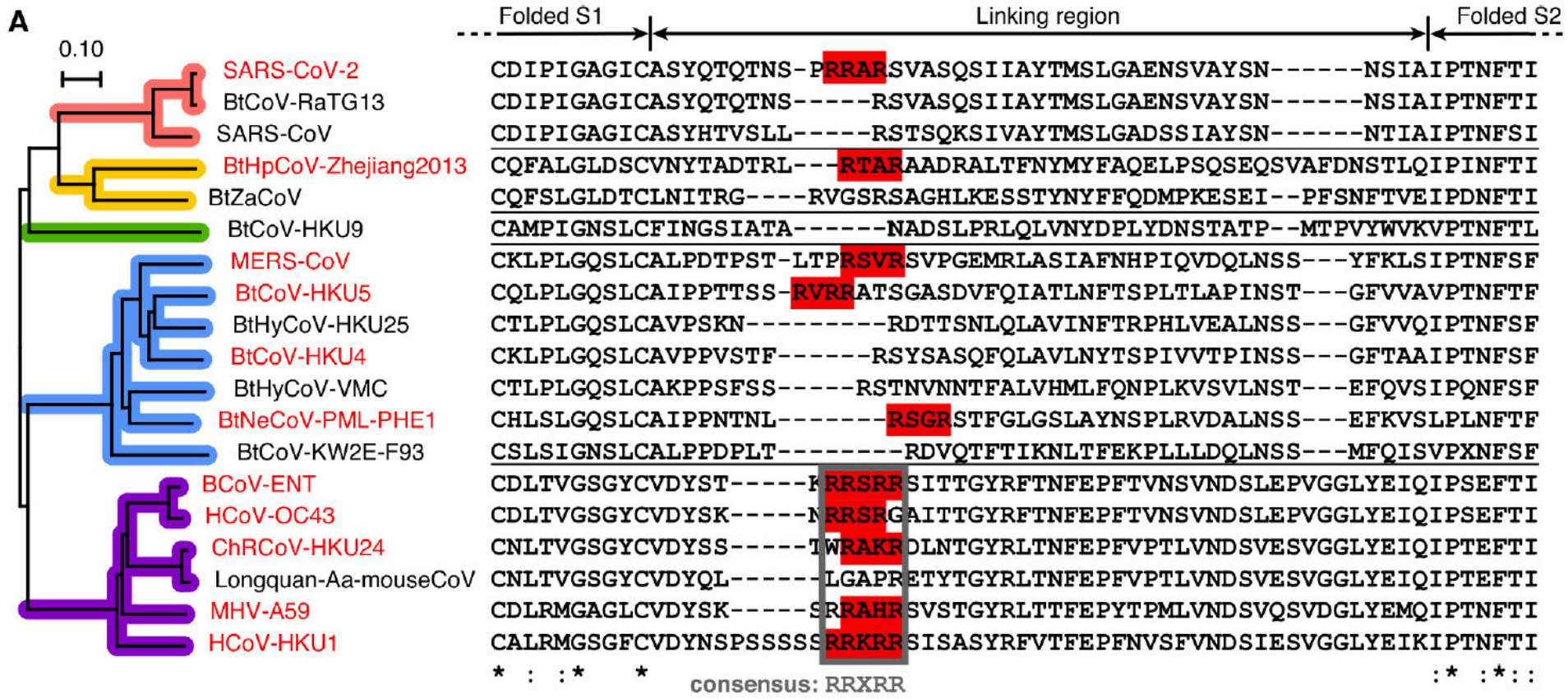
# Viruses Studied Have Only A Distant Relationship to SARS-CoV-2

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

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

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

# Furin Cleavage Sites Are Common in Betacoronavirus Spike Proteins




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

Wu and Zhao, Stem Cell Res. 2020

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

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

# Precedent for Zoonotic Origin

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

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

# Bloom Paper on “deleted” sequence

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

# Conclusions And Next Steps

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

Science

POLICY FORUM

Cite as: F. S. Collins *et al*., *Science* 10.1126/science.abj8547 (2021).

# ARPA-H: Accelerating biomedical breakthroughs

**Francis S. Collins[1], Tara A. Schwetz[1,2], Lawrence A. Tabak[1], Eric S. Lander[2]**

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**A DARPA-like culture at NIH can drive biomedical and health advances**

The biomedical research ecosystem has delivered advances that not long ago would have been inconceivable, exemplified by highly effective COVID-19 vaccines developed by global partners and approved in less than a year. The United States stands at a moment of unprecedented scientific promise and is challenged to ask: What more can we do to accelerate the pace of breakthroughs to transform medicine and health? Toward that end, President Biden recently proposed to create a new entity, the Advanced Research Projects Agency for Health (ARPA-H), within the National Institutes of Health (NIH) "to develop breakthroughs—to prevent, detect, and treat diseases like Alzheimer's, diabetes, and cancer," requesting $6.5 billion in the fiscal year 2022 budget (*1*). The idea is inspired by the Defense Advanced Research Projects Agency (DARPA), which follows a flexible and nimble strategy, undeterred by the possibility of failure, and has driven breakthrough advances for the Department of Defense (DOD) for more than 60 years. To design ARPA-H, it is critical to understand what is working well within the biomedical ecosystem, where there are crucial gaps, and the key principles of DARPA's success.

## WHEN IDEAS DON'T FIT MECHANISMS

Progress in medicine and health in recent decades has been driven by two powerful forces: pathbreaking fundamental research and a vibrant commercial biotechnology sector. Fundamental research is typically performed in university, nonprofit, and government labs. In the United States, it is mostly funded by the federal government, largely through the NIH. By steadily pursuing important fundamental questions in biology and medicine, scientists have made great progress in discovering the molecular and cellular mechanisms underlying health and disease—often suggesting new ideas for clinical treatment. Such fundamental research is what economists term a public good, in that it produces knowledge available to everyone and thus requires public investment. Some have estimated that every dollar of federal investment yields at least $8 in economic growth, and suggested that every new therapeutic approved by the US Food and Drug Administration (FDA) can be traced, in part, to fundamental discoveries supported by NIH (*2*, *3*). Given its outsized impact, robust federal investment in fundamental research remains crucial to health and to the economy.

The commercial sector is largely focused on research, development, and marketing of specific products, to bring sophisticated therapies and devices to patients. Biotechnology companies have access to abundant capital to develop products—provided they can protect their intellectual property and recoup the costs by generating sufficient profit in a short enough period of time. Currently, more than 8000 medicines are in development, including 1300 for cancer (*4*, *5*).

In many cases, these two components are all that's needed to drive progress toward clinical benefit—though subsequent regulatory approvals, reimbursement, and adoption in health care systems can also be optimized. It's becoming clear, though, that some of the most innovative project ideas, which could yield breakthroughs, don't always fit existing support mechanisms: NIH support for science traditionally favors incremental, hypothesis-driven research, whereas business plans require an expected return on investment in a reasonable time frame that is sufficient to attract investors. As a result, some of the most promising ideas may never mature, representing substantial lost opportunity.

Bold ideas may not fit existing mechanisms because (i) the risk is too high; (ii) the cost is too large; (iii) the time frame is too long; (iv) the focus is too applied for academia; (v) there is a need for complex coordination among multiple parties; (vi) the near-term market opportunity is too small to justify commercial investment, given the expected market size or challenges in adoption by the health care system; or (vii) the scope is so broad that no company can realize the full economic benefit, resulting in underinvestment relative to the potential impact. Evaluations by companies also may not consider the impact of projects on inequities that persist in our health ecosystem. In short, projects with a potentially transformative impact on the ecosystem may not yet be economically compelling or sufficiently feasible for a company to move forward. At the same time, there are no public mechanisms to propel these public goods at rapid speed.

Many such bold ideas involve creating platforms, capabilities, and resources that could be applicable across many diseases. Whereas most NIH proposals are "curiosity-driven," these ideas are largely "use-driven" research—that is, research directed at solving a practical problem.

## DARPA AS AN INSPIRATION

DARPA was launched in the wake of Sputnik with a singular mission: to make pivotal investments in breakthrough technologies for national security. DARPA has played a key role in generating

bold advances that have shaped the world—such as the internet, Global Positioning Systems, and self-driving cars—and has contributed to the development of many others, including messenger RNA vaccines. However, failure, especially failing early, and learning from that failure are also hallmarks of DARPA.

DARPA has a distinctive organization and culture that contrasts with traditional approaches in biomedical research. It is a flat and nimble organization whose work is driven by approximately 100 program managers (PMs) and office directors. The PMs are often recruited from industry or top research universities, and they come for limited terms of 3 to 5 years. They typically bring bold, risky ideas, and they are given the independence and sufficient resources to pursue them, mitigating risk through metric-driven accountability and by pursuing multiple approaches to achieve a quantifiable goal.

DARPA can support research at three stages (basic research, applied research, and advanced technology development); can fund efforts in multiple sectors (industry, university, national labs, and consortia across these sectors); can provide the critical mass of funding needed to tackle bold goals; and is empowered to promote collaboration and integration across performers. DARPA does not perform its own internal research. Although proposals are reviewed on a competitive basis, PMs have authority to select a portfolio of projects intended to achieve a particular program goal.

DARPA has long encouraged a culture that values a relentless drive for transformative technical results and a willingness to take risks. Notably, it does not focus on merely accelerating ordinary products to the market or making incremental progress, but on creating true breakthroughs. To act in this way, DARPA makes broad use of flexible hiring, procurement, and contracting authorities, provided by law.

Although DARPA is an excellent inspiration for ARPA-H, it is not a perfect model for biomedical and health research. It serves the needs of a single customer, the DOD, and its mission is focused on national security. Its projects typically involve engineered systems. By contrast, health breakthroughs (i) interact with biological systems that are much more complex and more poorly understood than engineered systems, requiring close coupling to a vast body of biomedical knowledge and experience; (ii) interact with a complex world of many customers and users—including patients, hospitals, physicians, biopharma companies, and payers; (iii) interact in complex ways with human behavior and social factors; and (iv) require navigating a complex regulatory landscape. ARPA-H can learn from DARPA, but will need to pioneer new approaches.

## DARPA-LIKE APPROACHES AT NIH

NIH has some experience with running large, complex programs using DARPA-like approaches to drive highly managed, use-inspired, breakthrough research. A classic example was the Human Genome Project, aimed at reading out the complete 3 billion–nucleotide human genetic code. When the project began in 1990, the technology to accomplish the goal hadn't been invented. By driving innovation, it was completed ahead of schedule and ultimately decreased the cost of sequencing a human genome from $3 billion at the outset to $500 today (*6*). Though estimates vary, it is clear that the overall economic return on investment has been enormous, with notable analyses estimating a nearly 180-fold return (*7*, *8*).

A very recent example is the NIH's response to the COVID-19 pandemic. Within weeks, NIH created two programs. The Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) program is an unprecedented partnership with government, industry, nonprofits, and academia to drive preclinical and clinical therapeutics, developing master protocols for testing prioritized compounds in rigorous randomized clinical trials. These efforts accelerated the development and testing of several of the vaccines that are now being widely used. The Rapid Acceleration of Diagnostics (RADx) program used an "innovation funnel" approach to identify promising ideas for COVID-19 tests and support 32 new technology platforms that collectively are contributing 2 million tests per day, mostly at point of care (*9*).

Although these programs have been successful, they required bespoke solutions and herculean efforts to get them off the ground. Because NIH lacks a regular framework for such projects, many bold ideas are hard to realize. That's where ARPA-H can help.

## ARPA-H MISSION

ARPA-H should have a clear mission. Building on DARPA's mission statement, an initial mission could be: "To make pivotal investments in breakthrough technologies and broadly applicable platforms, capabilities, resources, and solutions that have the potential to transform important areas of medicine and health for the benefit of all patients and that cannot readily be accomplished through traditional research or commercial activity."

Notably, ARPA-H's focus should be broad—ranging from molecular to societal—because breakthrough technologies are needed and are possible at many levels (see the box). When President Biden challenges researchers to "end cancer as we know it," many basic scientists naturally think about solutions at the laboratory bench: powerful ways to enlist DNA and RNA readouts, genetic regulation, novel chemistry, and the immune system to prevent, detect, and treat cancers. Technologists think about new sensors and artificial intelligence–assisted medical decision-making. As importantly, though, there are also opportunities for highly impactful breakthroughs at the macro level to ensure equity in health care access and health outcomes for all patients. Equity considerations (including race, ethnicity, gender/gender identity, sexual orientation, disability, and income level) must be woven throughout the ARPA-H mission—with some projects

focused directly on addressing equity and all projects considering equity in their design. Breakthroughs aimed at the most vulnerable groups are not only just and necessary, they will likely improve care for all patients.

ARPA-H's mission will clearly be different from the mission of the existing NIH Institute and Centers (ICs). For example, the name and mission of the National Center for Advancing Translational Sciences (NCATS), an NIH institute created in 2011, might suggest some overlap. However, NCATS' primary focus is to support a national network of clinical research centers and a drug screening hub. These two programs account for nearly 90% of its resources. A modestly sized component within NCATS, the Cures Acceleration Network, is aligned with the general directions of ARPA-H.

Similarly, the NIH Common Fund, a program created by law in 2007, is aimed at a different goal than ARPA-H's use-driven objective: It supports programs to explore new areas of foundational research that cut across multiple ICs—for example, the human microbiome effort. ARPA-H would also be distinct from other existing agencies, such as the Biomedical Advanced Research and Development Authority (BARDA), which focuses on medical countermeasures for public health security threats.

## DESIGNING ARPA-H: A DISTINCT DIVISION, CULTURE, AND ORGANIZATION AT NIH

ARPA-H should be housed as a division within NIH, rather than being a stand-alone entity, for two reasons. First, the goals of ARPA-H fall squarely within NIH's mission ("to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability"). Second, ARPA-H will need to draw on the vast range of biomedical and health knowledge, expertise, and activities at NIH. Setting up ARPA-H within NIH will ensure scientific collaboration and productivity and avoid unproductive duplication of scientific and administrative effort.

It is important to acknowledge, however, that a DARPA-like approach is radically different from NIH's standard mechanisms of operation and will require a new way of thinking. The creation of ARPA-H will benefit from transparency, accountability, and a healthy skepticism to ensure that the entity does not become a typical NIH institute.

Taking many features from the DARPA model, ARPA-H needs to have a distinctive culture, organization, authorities, leadership, and autonomy (*10*, *11*). ARPA-H's organization should be flat, lean, and nimble. The culture should value bold goals with big potential impact over incremental progress. The organization should lure a diverse cohort of extraordinary PMs from industry or leading universities, for limited terms, with the chance to make a huge impact. They should be empowered to take risks, assemble portfolios of projects, make connections across organizations, help clear roadblocks, establish aggressive milestones, monitor progress closely, and take responsibility for the project's progress and outcomes. Projects should be bounded in time, typically a few years, with longer periods allowed for efforts that are highly complex. ARPA-H should expect that a sizable fraction of its efforts will fail; if not, the organization is being too risk-averse. The best approach is to fail early in the process, by addressing key risks upfront. To determine which risks should be taken and to evaluate proposed programs and projects, ARPA-H should adopt an approach similar to DARPA's "Heilmeier Catechism," a set of principles that assesses the challenge, approach, relevance, risk, duration, and metrics of success (*12*).

The ARPA-H director should have substantial authority and independence to act. To keep the entity vibrant, the director should typically serve a single term of 5 years, with the possibility of a single extension in rare cases. For ARPA-H to accomplish its goals, it will need to be provided by Congress with certain authorities parallel to those provided to DARPA, including the authority to recruit, attract with competitive pay, and quickly hire for a set term extraordinary PMs.

Unlike DARPA's focus on a single customer, ARPA-H will need to create breakthrough innovations that serve an entire ecosystem and all populations. ARPA-H should have a senior leader responsible for ensuring that issues of equity are considered in all aspects of ARPA-H's work—from scientific program development to staff recruitment and hiring.

Within the Department of Health and Human Services, it will be important for ARPA-H to collaborate with other key agencies such as the FDA, the Centers for Disease Control and Prevention, BARDA, and the Centers for Medicare and Medicaid Services—to identify critical needs and opportunities and to partner on complex projects that interact, for example, with public health infrastructure or medical regulation.

DARPA should also play a role in advising ARPA-H on its experiences in driving breakthrough innovation and collaborating on specific projects of shared interest. And, it would be valuable to engage science-based agencies and departments, such as the National Science Foundation, the National Institute of Standards and Technology, and the Department of Energy.

It will be critical for ARPA-H to engage with the broader biomedical community, including patients and their care-givers, researchers, industry, and others, to understand the full range of problems and the practical considerations that need to be addressed for all groups and populations.

The potential opportunity is extraordinary. Through bold, ambitious ideas and approaches, ARPA-H can help shape the future of health and medicine by transforming the seemingly impossible into reality. The time to do this is now.

### REFERENCES AND NOTES

1. Remarks by President Biden in Address to a Joint Session of Congress (2021), www.whitehouse.gov/briefing-room/speeches-remarks/2021/04/29/remarks-by-president-biden-in-address-to-a-joint-session-of-congress/.

2. A. A. Toole, Does Public Scientific Research Complement Private Investment in Research and Development in the Pharmaceutical Industry? *J. Law Econ.* **50**, 81–104 (2007). doi:10.1086/508314
3. E. Galkina Cleary, J. M. Beierlein, N. S. Khanuja, L. M. McNamee, F. D. Ledley, Contribution of NIH funding to new drug approvals 2010-2016. *Proc. Natl. Acad. Sci. U.S.A.* **115**, 2329–2334 (2018). doi:10.1073/pnas.1715368115 Medline
4. G. Long, "The Biopharmaceutical Pipeline: Innovative Therapies in Clinical Development" (The Pharmaceutical Research and Manufacturers of America, 2017).
5. "Medicines in Development for Cancer 2020 Report" (The Pharmaceutical Research and Manufacturers of America, 2020).
6. DNA Sequencing Costs: Data (2020), www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data.
7. S. Tripp, M. Grueber, "The Economic Impact and Functional Applications of Human Genetics and Genomics" (American Society of Human Genetics, 2021).
8. "The Impact of Genomics on the U.S. Economy" (Batelle Technology Partnership Practice, for United for Medical Research 2013).
9. "RADx diversifies COVID-19 test portfolio with four new contracts, including one to detect variants" (2021), www.nibib.nih.gov/news-events/newsroom/radx-diversifies-covid-19-test-portfolio-four-new-contracts-including-one-detect-variants.
10. A. Prabhakar, "How to Unlock the Potential of the Advanced Research Projects Agency Model" (Day One Project 2021).
11. R. E. Dugan, K. J. Gabriel, in *Harvard Business Review* (Harvard Business Publishing, 2013).
12. "The Heilmeier Catechism" (2021), www.darpa.mil/work-with-us/heilmeier-catechism.

**ACKNOWLEDGMENTS**

The authors thank R. Fleurence and A. Hallett for their helpful input in preparation of the manuscript.

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10.1126/science.abj8547

## Examples of potential projects that ARPA-H could drive

The Advanced Research Projects Agency for Health (ARPA-H) will have a broad focus, and these projects are meant to illustrate the breadth of potential projects that it could support.

**Cancer and other chronic diseases**

- Vaccines that can prevent most cancers. Use messenger RNA vaccines to teach the immune system to recognize 50 common genetic mutations that drive cancers, so that the body will wipe out cancer cells when they first arise.
- New manufacturing processes to create patient-specific T cells to search and destroy malignant cells, decreasing costs from $100,000s to $1000s to make these therapies widely available.
- Molecular "zip codes" that target a drug or gene therapy vector to any specific tissue and cell type, to make treatments much more effective by treating diseases at their source and eliminating side effects due to impacts on other tissues or cells.
- Small, highly accurate, inexpensive, nonintrusive, wearable 24/7 monitors (e.g., smart watches) for blood pressure and blood sugar.
- New approaches to accelerate discovery of brain imaging and blood biomarkers capable of measuring synaptic loss, neuronal death, and glial inflammatory pathways, as a means of tracking responses to potential Alzheimer's disease therapies.

**Infectious diseases**

- Ability to design, test, and approve a vaccine against any newly emerging human virus in 100 days.
- Ability to administer vaccines through a skin patch or oral spray, to allow rapid, massive vaccination campaigns.

**Health care access, equity, and quality**

- Platforms to reduce health disparities in maternal morbidity and mortality, which are among the highest in the world, by identifying those at highest risk for pregnancy complications and providing ethically integrated, regular virtual house calls by nurses and midwives, from early in pregnancy through at least 6 months postpartum.
- Platforms to promote better health outcomes through substantially improving how medication is taken, as recommended, on a regular basis or over a standard course (e.g., for hypertension, diabetes, or infections), by engaging community health workers aided by privacy-preserving smart devices and telehealth.

**From:** Collins, Francis (NIH/OD) [E]
**To:** Tabak, Lawrence (NIH/OD) [E]
**Cc:** Burklow, John (NIH/OD) [E]
**Subject:** RE: Help requested
**Date:** Saturday, July 3, 2021 11:06:27 AM
**Attachments:** Viral Origin Briefing Becerra_070621.pptx

---

Hi guys,
The slides from Alan are good. At first I thought it was a bit weedy to get into furin cleavage sites, and we might skip over those for time, but they tell an important story.
I made a few edits, here marked in red font. Please note especially the additions to the conclusion slide. If you're OK with this, then just convert the red type back to black and it's ready to go – along with the short set on ARPA-H from Rachael.
John, do we have the rest of the template completed for this meeting? Can I have a quick look at that?
FC

---

**From:** Tabak, Lawrence (NIH/OD) [E] <(b) (6)
**Sent:** Friday, July 2, 2021 10:42 PM
**To:** Collins, Francis (NIH/OD) [E] <(b) (6)
**Cc:** Burklow, John (NIH/OD) [E] <(b) (6)
**Subject:** FW: Help requested
Francis,
Here are the slides from NIAID.
Larry

---

**From:** "Embry, Alan (NIH/NIAID) [E]" <(b) (6)
**Date:** Friday, July 2, 2021 at 10:28 PM
**To:** "Tabak, Lawrence (NIH/OD) [E]" <(b) (6)
**Cc:** Anthony Fauci <(b) (6)
**Subject:** RE: Help requested
Larry,
Attached is a draft slide deck to help with your upcoming briefing. I included a few slides as background, knowing that you likely won't include in the final presentation.
Please let me know if you have any questions or need more information.
Thanks,
Alan

---

**From:** Tabak, Lawrence (NIH/OD) [E] <(b) (6)
**Sent:** Thursday, July 1, 2021 11:18 AM
**To:** Embry, Alan (NIH/NIAID) [E] <(b) (6)
**Cc:** Fauci, Anthony (NIH/NIAID) [E] <(b) (6)
**Subject:** Help requested
**Importance:** High
Alan,
Using these materials from Renate (which no doubt had a great deal of input from you and your team) and the slides Elodie provided –

Could you draft a short (<10 slides) slide deck on the origins of SARS-CoV-2 pitched out the smart-lay-person's level. Francis and I have to brief Secretary on this (and other topics) on Tuesday and materials need to be sent way ahead.
If I could have by something by cob Friday, that would be ideal.
Very sorry for the HW assignment.
Larry

# Importance of Studying Coronaviruses

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

[1] Cutler DM, Summers LH. JAMA. 2020

# Early Timeline of SARS-CoV-2

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

# EcoHealth Alliance Grant

- Sought to understand how animal coronaviruses evolve naturally in the environment to become transmissible to humans

- Research included:
  - Studying viral diversity in bat reservoirs
  - Surveying people with high exposure to wildlife for evidence of bat coronavirus infection
  - Characterizing viruses to predict which potentially pose a threat to human health

# EcoHealth Alliance Grant

- To support its work, EcoHealth made sub-awards to the Wuhan Institute of Virology (WIV) and other institutions based in China, where coronaviruses have emerged in the past and are prevalent

- The grant did not propose research to enhance a coronavirus to be more transmissible or virulent

- The terms of the grant were thoroughly reviewed by NIH staff, and detailed documentation shows that this grant did not meet the standards of gain of function research that would require high level oversight

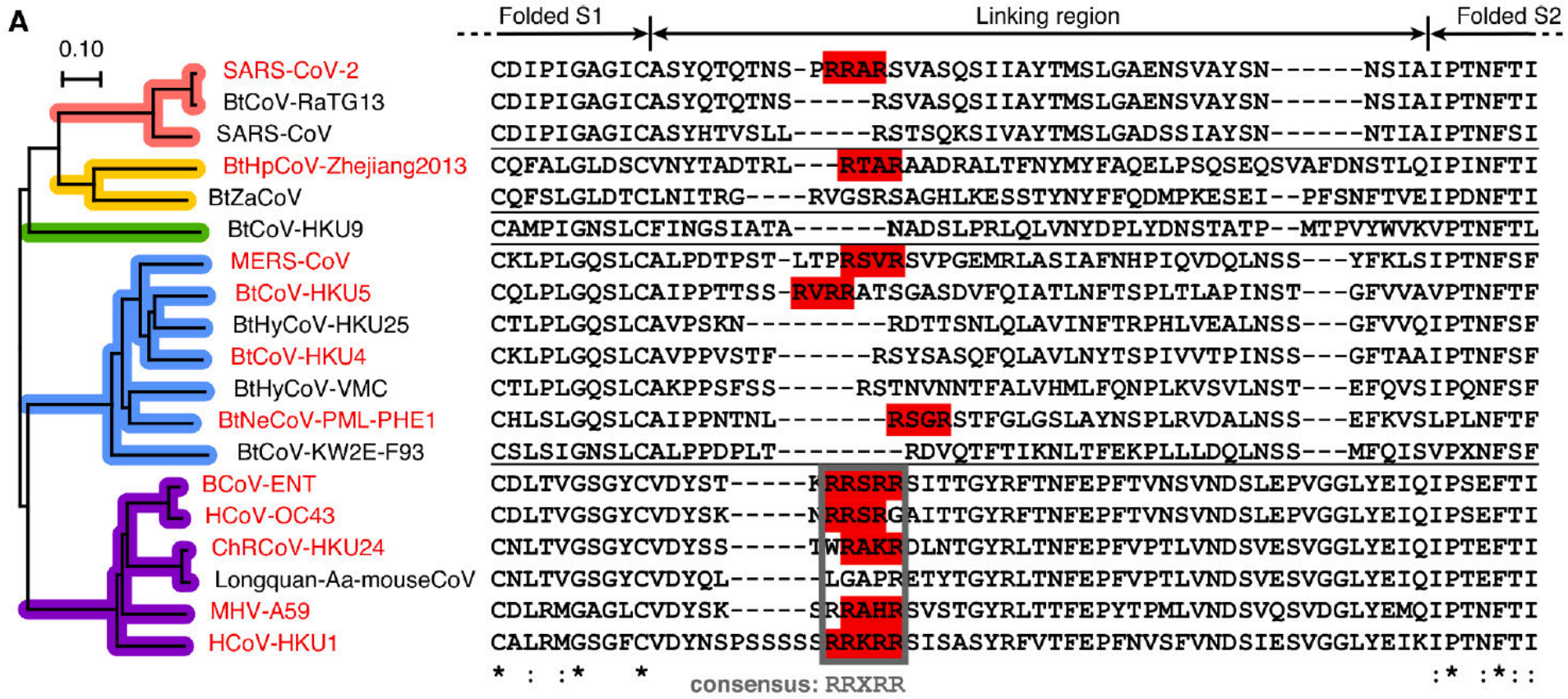
# Viruses Studied Have Only A Distant Relationship to SARS-CoV-2

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

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

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

# Furin Cleavage Sites Are Common in Betacoronavirus Spike Proteins




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

Wu and Zhao, Stem Cell Res. 2020

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

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

# Precedent for Zoonotic Origin

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

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

# Bloom Paper on "deleted" sequence

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

# Conclusions And Next Steps

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

**From:** Burklow, John (NIH/OD) [E]
**To:** Myles, Renate (NIH/OD) [E]
**Cc:** Collins, Francis (NIH/OD) [E]
**Subject:** Re: Siegel
**Date:** Friday, July 16, 2021 1:09:08 PM

---

Good to hear!

Sent from my iPhone

> On Jul 16, 2021, at 1:04 PM, Myles, Renate (NIH/OD) [E] < (b) (6) wrote:
>
> Phew! Thanks for the summary; glad to hear it went well and he stuck to the important topics. Will keep you posted on what we hear from Marc on where and how it will be used.
>
> **From:** Collins, Francis (NIH/OD) [E] < (b) (6)
> **Sent:** Friday, July 16, 2021 1:01 PM
> **To:** Burklow, John (NIH/OD) [E] < (b) (6) Myles, Renate (NIH/OD) [E] < (b) (6)
> **Subject:** Siegel
> Just finished, went 22 minutes. Marc was generally quite cordial. Never asked about the Wuhan grant! Wanted to know about genome evidence for natural vs. lab accident, whether a new WHO investigation would help, pandemic preparedness. Did ask about the general area of gain of function, but didn't call it that, I talked about influenza. I pivoted to vaccine hesitancy, and advocated for looking at the facts, talked about unnecessary deaths. I did a bit of a riff on our country's long history of relying on facts and knowledge to make decisions that allow us to flourish, and my concern that we've lost some of that here.
> He asked whether I had any concerns about the scientific trustworthiness of Peter Daszak or Peter Palese, I basically said no.
> He wants a video of the ARRA band, just for fun. I might send him one, but only if the band agrees.
> All in all, seemed pretty benign. Maybe even helpful.
> FC

**From:** Myles, Renate (NIH/OD) [E]
**To:** Conrad, Patricia (NIH/NIAID) [E]
**Cc:** Collins, Francis (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; Wood, Gretchen (NIH/OD) [E]; McManus, Ayanna (NIH/OD) [E]; Fauci, Anthony (NIH/NIAID) [E]; Billet, Courtney (NIH/NIAID) [E]; Embry, Alan (NIH/NIAID) [E]; Burklow, John (NIH/OD) [E]; Wojtowicz, Emma (NIH/OD) [E]; Roberts, Jacqueline (NIH/OD) [E]; Jorgenson, Lyric (NIH/OD) [E]; Tucker, Jessica (NIH/OD) [E]; Barasch, Kimberly (NIH/NIAID) [E]
**Subject:** RE: MATERIALS: Interview Request for Dr. Collins: David Willman/WaPo on GoF
**Date:** Friday, July 2, 2021 7:24:26 AM

---

Thanks, Patty.

**1:00 p.m. ET Pre-call:**

(b) (6)

Leader: (b) (6) (Renate to activate)

Participant: (b) (6)

**1:-15 p.m. ET Call with David Willman:**

(b) (6)

Leader: (b) (6) (Renate to activate)

Participant Code: (b) (6)

Thanks,

Renate

---

**From:** Conrad, Patricia (NIH/NIAID) [E] < (b) (6)

**Sent:** Friday, July 2, 2021 6:12 AM

**To:** Myles, Renate (NIH/OD) [E] < (b) (6)

**Cc:** Collins, Francis (NIH/OD) [E] < (b) (6) Fine, Amanda (NIH/OD) [E] < (b) (6) Wood, Gretchen (NIH/OD) [E] < (b) (6) McManus, Ayanna (NIH/OD) [E] < (b) (6) Fauci, Anthony (NIH/NIAID) [E] < (b) (6) Billet, Courtney (NIH/NIAID) [E] < (b) (6) Embry, Alan (NIH/NIAID) [E] < (b) (6) Burklow, John (NIH/OD) [E] < (b) (6) Wojtowicz, Emma (NIH/OD) [E] < (b) (6) Roberts, Jacqueline (NIH/OD) [E] < (b) (6) Jorgenson, Lyric (NIH/OD) [E] < (b) (6) Tucker, Jessica (NIH/OD) [E] < (b) (6) Barasch, Kimberly (NIH/NIAID) [E] < (b) (6)

**Subject:** Re: MATERIALS: Interview Request for Dr. Collins: David Willman/WaPo on GoF

We can make 1 pm work for Dr Fauci. Will you send new zoom info?

Sent from my iPhone

> On Jul 1, 2021, at 11:29 PM, Myles, Renate (NIH/OD) [E] < (b) (6) wrote:
>
> Thanks, Francis. Adding Patty and Kim from NIAID to check Tony's schedule.
>
> ---
>
> **From:** Collins, Francis (NIH/OD) [E] < (b) (6)
>
> **Sent:** Thursday, July 1, 2021 10:42 PM
>
> **To:** Myles, Renate (NIH/OD) [E] < (b) (6) Fine, Amanda (NIH/OD) [E] < (b) (6) Wood, Gretchen (NIH/OD) [E] < (b) (6) McManus, Ayanna (NIH/OD) [E] < (b) (6) Fauci, Anthony

(NIH/NIAID) [E] < (b) (6) Billet, Courtney (NIH/NIAID) [E]
< (b) (6) Embry, Alan (NIH/NIAID) [E] < (b) (6)
**Cc:** Burklow, John (NIH/OD) [E] < (b) (6) Wojtowicz, Emma (NIH/OD) [E]
< (b) (6) Roberts, Jacqueline (NIH/OD) [E]
< (b) (6) Jorgenson, Lyric (NIH/OD) [E] < (b) (6)
Tucker, Jessica (NIH/OD) [E] < (b) (6)
**Subject:** RE: MATERIALS: Interview Request for Dr. Collins: David Willman/WaPo on GoF

Thanks, Renate. If it's helpful, I could join a pre-call at 1 pm. That should be on a different phone line than the 1:15 pm call with Willman.

FC

---

**From:** Myles, Renate (NIH/OD) [E] < (b) (6)
**Sent:** Thursday, July 1, 2021 10:23 PM
**To:** Collins, Francis (NIH/OD) [E] < (b) (6) Fine, Amanda (NIH/OD) [E]
< (b) (6) Wood, Gretchen (NIH/OD) [E] < (b) (6)
McManus, Ayanna (NIH/OD) [E] < (b) (6) Fauci, Anthony
(NIH/NIAID) [E] < (b) (6) Billet, Courtney (NIH/NIAID) [E]
< (b) (6) Embry, Alan (NIH/NIAID) [E] < (b) (6)
**Cc:** Burklow, John (NIH/OD) [E] < (b) (6) Wojtowicz, Emma (NIH/OD) [E]
< (b) (6) Roberts, Jacqueline (NIH/OD) [E]
< (b) (6) Jorgenson, Lyric (NIH/OD) [E] < (b) (6)
Tucker, Jessica (NIH/OD) [E] < (b) (6)
**Subject:** MATERIALS: Interview Request for Dr. Collins: David Willman/WaPo on GoF

Good evening:

I'm attaching relevant documents for tomorrow's call with David Willman so you have them all in one place. Also, we think it would be helpful if we could find 20 minutes for a pre-call, if possible.

Thanks,

Renate

---

**From:** Myles, Renate (NIH/OD) [E] < (b) (6)
**Sent:** Thursday, July 1, 2021 7:21 PM
**To:** Collins, Francis (NIH/OD) [E] < (b) (6) Fine, Amanda (NIH/OD) [E]
< (b) (6) Wood, Gretchen (NIH/OD) [E] < (b) (6)
McManus, Ayanna (NIH/OD) [E] < (b) (6) Fauci, Anthony
(NIH/NIAID) [E] < (b) (6) Billet, Courtney (NIH/NIAID) [E]
< (b) (6) Embry, Alan (NIH/NIAID) [E] < (b) (6)
**Cc:** Burklow, John (NIH/OD) [E] < (b) (6) Wojtowicz, Emma (NIH/OD) [E]
< (b) (6) Roberts, Jacqueline (NIH/OD) [E]
< (b) (6) Jorgenson, Lyric (NIH/OD) [E] < (b) (6)
Tucker, Jessica (NIH/OD) [E] < (b) (6)
**Subject:** Re: Interview Request for Dr. Collins: David Willman/WaPo on GoF

Adding Dr. Fauci and others. Possible to add 20 minutes for a pre-call to talk through David's questions?

---

**From:** Collins, Francis (NIH/OD) [E] < (b) (6)

**Sent:** Thursday, July 1, 2021 6:22:07 PM
**To:** Fine, Amanda (NIH/OD) [E] < (b) (6) Wood, Gretchen (NIH/OD) [E] < (b) (6) McManus, Ayanna (NIH/OD) [E] < (b) (6)
**Cc:** Burklow, John (NIH/OD) [E] < (b) (6) Myles, Renate (NIH/OD) [E] < (b) (6) Wojtowicz, Emma (NIH/OD) [E] < (b) (6) Roberts, Jacqueline (NIH/OD) [E] < (b) (6) Jorgenson, Lyric (NIH/OD) [E] < (b) (6) Tucker, Jessica (NIH/OD) [E] < (b) (6)
**Subject:** RE: Interview Request for Dr. Collins: David Willman/WaPo on GoF

Tony Fauci is available to join also.

---

**From:** Fine, Amanda (NIH/OD) [E] < (b) (6)
**Sent:** Thursday, July 1, 2021 5:03 PM
**To:** Collins, Francis (NIH/OD) [E] < (b) (6) Wood, Gretchen (NIH/OD) [E] < (b) (6) McManus, Ayanna (NIH/OD) [E] < (b) (6)
**Cc:** Burklow, John (NIH/OD) [E] < (b) (6) Myles, Renate (NIH/OD) [E] < (b) (6) Wojtowicz, Emma (NIH/OD) [E] < (b) (6) Roberts, Jacqueline (NIH/OD) [E] < (b) (6) Jorgenson, Lyric (NIH/OD) [E] < (b) (6) Tucker, Jessica (NIH/OD) [E] < (b) (6)
**Subject:** RE: Interview Request for Dr. Collins: David Willman/WaPo on GoF

Hello-
I understand we are moving forward with setting up this interview. If it is still available, I will offer the July 2 at 1:15pm ET time to David. Lyric is able to join at this time.
We'll send a Zoom link for the call once David confirms.
Thanks,
Amanda

---

**From:** Collins, Francis (NIH/OD) [E] < (b) (6)
**Sent:** Thursday, July 1, 2021 1:26 PM
**To:** Wood, Gretchen (NIH/OD) [E] < (b) (6) Fine, Amanda (NIH/OD) [E] < (b) (6) McManus, Ayanna (NIH/OD) [E] < (b) (6)
**Cc:** Burklow, John (NIH/OD) [E] < (b) (6) Myles, Renate (NIH/OD) [E] < (b) (6) Wojtowicz, Emma (NIH/OD) [E] < (b) (6) Roberts, Jacqueline (NIH/OD) [E] < (b) (6) Jorgenson, Lyric (NIH/OD) [E] < (b) (6) Tucker, Jessica (NIH/OD) [E] < (b) (6)
**Subject:** RE: Interview Request for Dr. Collins: David Willman/WaPo on GoF

Please hold, I'm not sure I want to do this. May need to answer questions by e-mail instead.

---

**From:** Wood, Gretchen (NIH/OD) [E] < (b) (6)
**Sent:** Thursday, July 1, 2021 1:08 PM
**To:** Fine, Amanda (NIH/OD) [E] < (b) (6) Collins, Francis (NIH/OD) [E] < (b) (6) McManus, Ayanna (NIH/OD) [E] < (b) (6)
**Cc:** Burklow, John (NIH/OD) [E] < (b) (6) Myles, Renate (NIH/OD) [E] < (b) (6) Wojtowicz, Emma (NIH/OD) [E] < (b) (6) Roberts, Jacqueline (NIH/OD) [E] < (b) (6) Jorgenson, Lyric (NIH/OD) [E] < (b) (6) Tucker, Jessica (NIH/OD) [E] < (b) (6)
**Subject:** Re: Interview Request for Dr. Collins: David Willman/WaPo on GoF

Hi Amanda,
Please offer 1:15 PM tomorrow, July 2.
Thank you,
Gretchen

---

**From:** Amanda Fine <(b) (6)
**Date:** Thursday, July 1, 2021 at 12:57 PM
**To:** Francis Collins <(b) (6) Gretchen Wood <(b) (6) "McManus, Ayanna (NIH/OD) [E]" <(b) (6)
**Cc:** John Burklow <(b) (6) Renate Myles <(b) (6) "Wojtowicz, Emma (NIH/OD) [E]" <(b) (6) Jacqueline Roberts <(b) (6) "Jorgenson, Lyric (NIH/OD) [E]" <(b) (6) Jessica Tucker <(b) (6)
**Subject:** RE: Interview Request for Dr. Collins: David Willman/WaPo on GoF

Hi All-
Circling back on this one. David Willman was able to extend his deadline to speak with Francis. Are there times we can offer for this week?
Note, David shared the below question he specifically wants to ask about the following language that was not included in the Framework:

1. On January 9, 2017, the White House issued guidance for judging gain-of-function research: "**To the maximum extent possible," the "review mechanisms should provide transparency to the public**." The Framework policy put in place on Dec. 19, 2017, did not include this language. Were Drs. Collins or Fauci or their aides aware of this? If so, what was their position regarding omitting the call for this level of transparency?
2. From February 2013 until December 2017, HHS policy said this about the HHS-level review committee's authority: **``The Department-level review will also identify any additional risk mitigation measures that are required, and determine whether a given proposal is acceptable for HHS funding. For proposals that are deemed acceptable for HHS funding, the funding agency within HHS will make the final funding decision. Proposals that have been determined to be unacceptable for HHS funding through Department-level review are not eligible for funding agency support.''** The Framework policy put in place as of December 2017 did not include the aforementioned language – and says only that the HHS-level committee may make recommendations. Were Drs. Collins and Fauci aware that this change was being made? What was their rationale for supporting or opposing it? More broadly, why was the change made?

Thanks,
Amanda

---

**From:** Collins, Francis (NIH/OD) [E] <(b) (6)
**Sent:** Tuesday, June 29, 2021 4:50 PM
**To:** Fine, Amanda (NIH/OD) [E] <(b) (6) Wood, Gretchen (NIH/OD) [E] <(b) (6) McManus, Ayanna (NIH/OD) [E] <(b) (6)
**Cc:** Burklow, John (NIH/OD) [E] <(b) (6) Myles, Renate (NIH/OD) [E]

< (b) (6) Wojtowicz, Emma (NIH/OD) [E] < (b) (6)
Roberts, Jacqueline (NIH/OD) [E] < (b) (6) Jorgenson, Lyric (NIH/OD)
[E] < (b) (6) Tucker, Jessica (NIH/OD) [E] < (b) (6)
**Subject:** RE: Interview Request for Dr. Collins: David Willman/WaPo on GoF

Wow, these are very weedy questions. I'll need help from OSP (Jessica and Lyric) on both questions, as my memory is not very clear.

FC

---

**From:** Fine, Amanda (NIH/OD) [E] < (b) (6)
**Sent:** Tuesday, June 29, 2021 10:50 AM
**To:** Collins, Francis (NIH/OD) [E] < (b) (6) Wood, Gretchen (NIH/OD) [E]
< (b) (6) McManus, Ayanna (NIH/OD) [E] < (b) (6)
**Cc:** Burklow, John (NIH/OD) [E] < (b) (6) Myles, Renate (NIH/OD) [E]
< (b) (6) Wojtowicz, Emma (NIH/OD) [E] < (b) (6)
Roberts, Jacqueline (NIH/OD) [E] < (b) (6) Jorgenson, Lyric (NIH/OD)
[E] < (b) (6) Tucker, Jessica (NIH/OD) [E] < (b) (6)
**Subject:** RE: Interview Request for Dr. Collins: David Willman/WaPo on GoF

Hi Francis-

David just got back with his specific topics/questions for you and Dr. Fauci. From David: I'd be interested in Drs. Collins and Fauci's overarching thoughts about their stewardship of gain of function research with potential pandemic pathogens, spanning the past decade. To what extent do they think decisions affecting these research proposals should be open to public view? Has adequate transparency been achieved? I'd also welcome their response(s) to questions I sent yesterday, particularly:

- During the pause on gain of function research, from October 2014 to late 2017, did Director Collins have the sole authority to grant exceptions for particular projects? During roughly the same timeframe, as a revision to federal policy guiding the research – the Framework – was developed, what role did Dr. Collins, his chief of staff and other aides take in shaping the revisions?
- Regarding the Framework that was issued in December 2017: From the time of the pause in October 2014, the policy had required NIH's referral to the HHS committee of grants for which certain flu and coronaviruses would generate pathogens ``transmissible among mammals,'' broadly, which might infect humans. The final policy elided the reference, instead specifying altered pathogens ``likely capable of wide and uncontrollable spread in human populations.'' What was Dr. Collins's position regarding this revision? And regarding this, what was Dr. Fauci's position?

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**From:** Fine, Amanda (NIH/OD) [E]
**Sent:** Tuesday, June 29, 2021 10:38 AM
**To:** Collins, Francis (NIH/OD) [E] < (b) (6) Wood, Gretchen (NIH/OD) [E]
< (b) (6) McManus, Ayanna (NIH/OD) [E] < (b) (6)
**Cc:** Burklow, John (NIH/OD) [E] < (b) (6) Myles, Renate (NIH/OD) [E]
< (b) (6) 'Wojtowicz, Emma (NIH/OD) [E] ( (b) (6)
< (b) (6) Roberts, Jacqueline (NIH/OD) [E]
< (b) (6) Jorgenson, Lyric (NIH/OD) [E] < (b) (6)

Tucker, Jessica (NIH/OD) [E] <(b) (6)

**Subject:** Interview Request for Dr. Collins: David Willman/WaPo on GoF

**Interview Request for Dr. Collins**

***June 29, 2021***

**Request: Topic –** NIH-funded research involving potential pandemic pathogens
**Deadline:** COB today, Tuesday, June 29, 2021
**Additional information:**
David has been working on an article that will focus on NIH-funded research involving potential pandemic pathogens. The article will reconstruct events beginning with the 2011/2012 controversy over research conducted by Yoshihiro Kawaoka and Ron Fouchier on H5N1, and will look at related iterations of federal policy guiding the awarding of grants and the administration of this research.
We've responded to previous inquiries from David for this article, but as a last-minute request he has asked to speak with Drs. Collins and Fauci. We've requested the specific questions that David has for Drs. Collins and Fauci.
In the same request, he also shared a list of technical questions, below for context, for which OSP is working on developing responses:

- Does NIH maintain a list of gain of function projects with potential pandemic pathogens that were funded from 2012 through January 2021?
- As was demonstrated by Christian Hassell's remarks at a January 2020 meeting of the National Biosecurity Advisory Board, there are doubts as to whether NIH has referred all gain of function projects with potential pandemic pathogens for review by the HHS-level committee. How many total such projects have been referred by NIH to the HHS committee from 2012-2020? What does NIH say in response to what Dr. Hassell voiced?
- Regarding the original Fouchier/Kawaoka experiments with H5N1, some present and former federal officials say that the details should have been discussed publicly before NIH agreed to fund the work. NIH's view?
- During the pause on gain of function research, from October 2014 to late 2017, did Director Collins have the sole authority to grant exceptions for particular projects? During roughly the same timeframe, as a revision to federal policy guiding the research – the Framework – was developed, what role did Dr. Collins, his chief of staff and other aides take in shaping the revisions?
- Regarding the Framework that was issued in December 2017: From the time of the pause in October 2014, the policy had required NIH's referral to the HHS committee of grants for which certain flu and coronaviruses would generate pathogens "transmissible among mammals," broadly, which might infect humans. The final policy elided the reference, instead specifying altered pathogens "likely capable of wide and uncontrollable spread in human populations." What was Dr. Collins's position regarding this revision?

**Recommendation:**
OCPL recommends Dr. Collins participate with Dr. Lyric Jorgenson on the call in case Dr. Collins would like to defer to her on a technical question.
**Submitted by:**
Amanda Fine, (b) (6)

NIH News Media Branch
**Contact information:**
David Willman
Washington Post
301-656-3401 –direct
david.willman@washpost.com
**Other important notes:**
**Accept: ____**
**Decline: ____**
**Need more information: ____**

**David Willman's articles on this topic:**

# Washington Post

Politics

# Renewed focus on Wuhan lab scrambles the politics of the pandemic

By Annie Linskey, Shane Harrisand David Willman

May 27, 2021 at 10:01 p.m. EDT

Senate Democrats lined up alongside Sen. Josh Hawley (Mo.), one of their least-favorite Republicans, to support a measure urging the Biden administration to declassify intelligence on whether the novel coronavirus originated in a Chinese lab. A Democratic-led House subcommittee is pledging an investigation into the virus's origins, including the lab's safety record.

And President Biden, in an unusual public statement, directed U.S. intelligence agencies to "redouble their efforts" to determine the cause of the pandemic, suggesting that while the virus could have jumped from animals to humans, it also could have escaped from the lab.

The rapid developments mark a new effort by Democrats to show they are pushing to figure out how the pandemic started and, in the process, considering a theory that some initially attributed to conspiracy theorists: that the pandemic that has cost about 3.5 million lives worldwide stemmed from human error at the Wuhan Institute of Virology.

How the lab leak theory suddenly became credible

That thesis is far from conclusive; no significant new evidence has emerged to support it, and the pandemic's origins may never be definitively known. Many still believe the virus jumped naturally from animals to humans. But some scientists who dismissed the theory early on have begun reassessing their views, and new evaluations have been recently aired in a recent piece in the Bulletin of the Atomic Scientists.

Republicans, saying they feel vindicated because some pointed to the lab early on, have been pushing the lab-leak theory more aggressively at congressional hearings and in conservative media outlets. And Democrats say the departure of former president Donald Trump, who often talked about the pandemic in racially charged terms, makes it easier to consider the theory without potentially offensive undertones.

The shifting terrain highlights how much of the early debate on the virus's origins was colored by America's tribal politics, as Trump and his supporters insisted on China's responsibility and many

Democrats dismissed the idea out of hand — when the origins of the virus were in fact wrapped in uncertainty.

The polarization, which left many feeling they had to embrace one theory or the other, was exacerbated by the tendency of some on the right to conflate the lab-leak theory with more easily dismissible ideas like the notion that the coronavirus was part of a Chinese biological weapon.

“Like everything else, it became politicized very early on,” said Rep. Jamie B. Raskin (D-Md.), a member of the House select subcommittee on the coronavirus crisis.

Biden has enjoyed high approval ratings, at least among Democrats and independents, for his handling of the pandemic. He passed a $1.9 trillion stimulus package, ramped up a vaccination program that began under the Trump administration, and has begun steering the country toward normalcy in the aftermath of nearly 600,000 American deaths.

During much of this effort Democrats have focused less — publicly at least — on the need to determine the origin of the pandemic that engulfed the world a year ago. That is now prompting a Republican effort to reclaim the “follow the science” mantra that Democrats used effectively in 2020 to position themselves as the party better equipped to end the pandemic.

Republicans are also seeking to use the episode to sow doubt about Biden’s ability to confront China, with some saying Biden’s ostensible reluctance to focus on the Wuhan lab shows he is soft on the rising superpower.

After Biden on Wednesday announced he had given intelligence officials 90 days to come up with a clearer picture of the virus’s origins, Republicans wasted little time claiming vindication.

“The only reason that Biden’s doing this is it’s becoming untenable not to look into whether or not the virus originated in a Chinese lab,” Sen. Lindsey O. Graham (R-S.C.) said in a statement.

Sen. Ted Cruz (R-Tex.) called on the Senate Commerce Committee to “appoint an independent commission with investigative authority, with credibility to get to the bottom of what happened.” He noted that a bill to form such a commission was voted down by Democratic senators.

Democrats dismiss the GOP statements as posturing, noting that Republicans did little to challenge some of Trump’s more far-fetched theories on the virus, such as the idea that injecting bleach could cure it or his efforts to ridicule mask-wearing.

Some Democratic lawmakers also said they had never ruled out the Wuhan lab theory, and that they have simply become more receptive to it as scientists and epidemiologists have done the same.

“The researchers themselves were skeptical about the possibility of the lab,” said Rep. Diana DeGette (D-Colo.), who chairs a powerful oversight panel on the House Energy and Commerce Committee.

DeGette said that in recent days she’s been in talks with the top Republican on her subcommittee to determine how to best investigate the origins of the virus. She said that her panel so far focused on emergency matters like getting Americans vaccinated.

“We haven’t really had the luxury to sit back and say, ‘Okay, now what happened in that lab?’ ” DeGette said. “But I do think we need to get to that issue.”

Some Democrats argued that Republicans’ renewed emphasis on the lab theory was an effort to change the focus from the Trump administration’s fumbling of the pandemic.

“Democrats have been interested from the beginning,” Raskin said, “But we also recognized the way in which that question could be used as a distraction from the Trump administration’s own miserable failures in addressing the virus.”

Biden’s decision to roil the waters this week by publicly disclosing a division within the intelligence agencies may reflect his frustration that they have yet to produce a consensus on the virus’s origins, according to some former intelligence officials.

Biden initially asked the intelligence community to examine the origins of the pandemic in March. About two weeks ago he received the results of that inquiry in his presidential daily briefing, according to a White House official, who spoke on the condition of anonymity to discuss sensitive material.

As Biden and his top aides digested the results of the initial intelligence review, senior White House officials realized there were more questions they could try to answer. And two former senior officials told The Washington Post that they believed the intelligence community under Trump hadn’t sufficiently examined all of the material that may shed light on the origins of the pandemic.

Biden then requested a declassification of at least some of the initial results, which showed the intelligence community was split on whether the virus came from nature or the Wuhan lab.

The president said Wednesday that two “elements” of the intelligence community “lean toward” the hypothesis that the outbreak began when an animal infected a human, while another leans toward the notion of a lab escape, “each with low or moderate confidence.”

The president decided to take the unusual step of revealing an inconclusive debate among the intelligence agencies because of the public interest in understanding the origins of the virus, but also because of the “swirl around the issue,” said the White House official, referring to the renewed public conversation around the lab theory.

Another factor, the official said, was China’s decision to signal at a World Health Assembly meeting that it would not support the next steps in an international investigation into the origins.

“China’s part has been completed,” a delegate from China said at the meeting.

That dismissal “accelerated and intensified our desire to declassify what we knew from our own investigation, and share it as quickly as possible,” the White House official said.

Experts who have pushed for more scrutiny of the lab-leak hypothesis applauded Biden’s call for more investigation. Jamie Metzl, a National Security Council staffer in the Clinton administration and a member of a World Health Organization advisory panel called the statement “solid and reasonable.”

Still, Metzl, who helped organize an open letter calling for more scrutiny of the Wuhan lab unrestricted by Chinese authorities, said the statement "does not go far enough" in calling on the World Health Assembly to mandate a full investigation before its annual gathering ends Monday.

Biden's statement came after congressional Republicans had been pressing the lab theory with renewed vigor for several months.

Sen. Rand Paul (R-Ky.) pressed Anthony S. Fauci, the government's top infectious-disease expert, when he appeared before a Senate panel earlier this month, saying that government officials have been unequivocal about insisting the virus was not man-made.

"I'm fully in favor of any further investigation of what went on in China," Fauci responded.

Sen. John Neely Kennedy (R-La.) pressed Fauci at a different hearing, quizzing him about why the United States provided funding via a subcontract to the Wuhan lab. Fauci responded that China is a logical place to get funding to study coronaviruses, since that is where they have emerged.

About two months ago, Republican leaders of the House Energy and Commerce Committee began seeking details about the pandemic's origin from federal agencies and U.S.-funded scientists who have collaborated with Chinese researchers.

They wrote an 11-page letter posing more than 30 questions and requesting a range of documents from the National Institutes of Health, largely regarding work done by recipients of NIH funding that have collaborated with the Wuhan lab.

The lab has experimented with many species of bats and the multiple strains of coronaviruses they carry, and the first covid-19 cases were reported in late 2019 in and around the city of Wuhan.

Although aides to the House Republicans sought over a period of weeks to enlist bipartisan support for an inquiry into the cause of the pandemic, none of the Democrats stepped forward. But on May 14, one Democrat, Rep. Anna G. Eshoo (Calif.), who is chairwoman of the Energy and Commerce panel's health subcommittee, broke ranks.

Eshoo issued a statement applauding a group of 18 scientists who had just written, in the journal Science, that a "transparent, objective, data-driven'' investigation is needed to determine the pandemic's origin. "If you take partisan politics and mix them with science it's a toxic combination," Eshoo said in an interview. "One doesn't go with the other."

Yasmeen Abutaleb, Adam Taylor, Katerina Ang and Erin Cunningham contributed to this report.



# Washington Post

**Politics**

# Biden asks intelligence community to redouble efforts to determine definitive origin of the coronavirus

President Biden speaks about the state of vaccinations as Vice President Harris listens during a coronavirus disease response event March 18. (Carlos Barria/Reuters)

By
Annie Linskey,
Yasmeen Abutaleb,
Shane Harris
and
David Willman

**May 26, 2021 at 8:06 p.m. EDT**

President Biden said Wednesday he had asked U.S. intelligence agencies to "redouble their efforts" to determine the origin of the coronavirus, an abrupt departure from the previous White House position of relying on the World Health Organization to uncover how the contagion started.

The new message reflects a notable shift in some prominent scientists' assessments that the virus all but certainly jumped from an animal species to humans. The theory that has more recently gained traction is that the pandemic — which has killed more than 3.4 million people worldwide — may have accidentally escaped from the Wuhan Institute of Virology in China, though that is far from conclusive. Biden ordered intelligence officials to deliver a report within 90 days "that could bring us closer to a definitive conclusion."

*Timeline: How the Wuhan lab-leak theory suddenly became credible*

Some Republicans pushed the idea early on that the Wuhan lab, rather than a natural transmission from animals to humans, was at fault. Among them was former president Donald Trump, who often used inflammatory language to describe the virus's origins in China.

But that notion was dismissed by Democrats and many scientists, who viewed the focus on the lab as part of a larger attack on China that fueled an increase in hate crimes against Asian Americans.

"There was so much inaccurate information flowing from the White House that many viewed this as just another thing that was not true and a way for the White House to divert attention from a fledgling covid response," said Chris Meekins, a former Health and Human Services official who is now an analyst at Raymond James, a financial services firm.

But in recent weeks, some notable researchers have begun arguing more pointedly that the lab theory should remain on the table until more is known, including some who made the case in an article in the journal Science. A series of reports in the Wall Street Journal, including one highlighting how several Wuhan lab employees became sick in fall 2019 with covid-like symptoms, have boosted the reexamination.

The origin of the deadliest pandemic in recent memory carries enormous implications for public health — and beyond. If investigators point to China, one of the most powerful and sensitive countries in the world, it could ignite a global diplomatic firestorm.

Health officials complain that China has hampered investigations into the matter, and a definitive finding could remain elusive despite Biden's directive. But Wednesday's movesuggests he is growing more concerned about China's possible role.

Some scientists cautioned that despite the renewed interest, no significant new information has emerged in recent weeks. They urged Biden to ensure that intelligence officials provide clear evidence in their upcoming report, which they are typically reluctant to do.

"The only way this will be useful is if Biden can get some concrete information on the supposed infections in Wuhan Institute of Virology lab workers in fall 2019," said Angela Rasmussen, a virologist at the Vaccine and Infectious Disease Organization at the University of Saskatchewan.

She cautioned that the mere fact that several people from the lab were ill shortly before the outbreak is hardly proof. "There's nothing remarkable about three people seeking medical care during cold [and] flu season in a city of 11 million people," Rasmussen added. "It's not proof they had covid."

The White House shift also signals less deference to the WHO, which Biden had been seeking to bolster as part of his effort to restore global institutions after the Trump administration. Biden made rejoining the WHO one of his first moves as president.

As recently as Tuesday, the Biden administration had stressed that the WHO should lead efforts to uncover the cause. Biden "believes there needs to be an independent investigation, one that's run by the international community," White House press secretary Jen Psaki said Tuesday.

But the WHO has struggled in the past to reach a definitive conclusion on the origin of the virus, partly due to what officials say is China's unwillingness to cooperate with investigators.

After Biden's announcement, White House spokeswoman Karine Jean-Pierre declined to give a specific reason for the shift. "This is just a continuation of what the president has been focused on," she said. The president's statement did provide an unusual window into a debate within U.S. intelligence agencies on the virus's origins.

Biden disclosed that he asked for an initial review in March, and that "one element" of the intelligence community "leans" toward the view that the novel coronavirus came from a laboratory accident. Two other components, he said, believe the virus came from animal-to-human contact.

A person familiar with the White House deliberations, who spoke on the condition of anonymity to discuss the talks, said Biden had not been satisfied with the initial report that he'd assigned in March, adding, "It was clear to all we could and must do more beyond existing efforts."

Wednesday's announcement "took some time to declassify," the person said, acknowledging that it's "a very rare step" to reveal debate within the intelligence community.

Biden's statement disclosing that internal split may have been a way to signal his displeasure with the initial report. "It is very unusual for a president to issue such a public statement, which some would consider a not-so-mild rebuke of the intelligence community's work," said a former senior intelligence officer, who spoke on the condition of anonymity to candidly describe the president's remarks.

The person familiar with the White House deliberations also noted that China had “made clear” at a WHO meeting Tuesday that it “had no intention” of participating in the next steps of the investigation. That “ignited heightened interest to take additional steps from the United States to investigate the origins using the resources of our intelligence team and our health experts,” the person said.

Current and former intelligence officials who favor the lab leak hypothesis have pointed to what they see as two pieces of what they call compelling evidence in the intelligence that has been gathered so far. The first is that staff members at the Wuhan Institute of Virology became sick in the fall of 2019 with symptoms that resembled covid-19, the disease caused by the coronavirus, as well as seasonal illnesses. David Asher, a former State Department official who led the department’s investigation into the pandemic’s origins, described the sick lab workers as “the first known cluster that we’re aware of, of victims of [what] we believe to be covid-19.”

Asher added, “There is a possibility it was influenza, but I’m very doubtful that three people in highly protected circumstances in a level-three laboratory working on coronaviruses would all get sick with influenza that put them in a hospital or in severe conditions all in the same week, and it didn’t have anything with the coronavirus. That’s highly hard to believe.”

A second piece of evidence is the Chinese military’s alleged involvement in bioweapons programs and its connection to the Wuhan lab. Those who suspect the lab say that helps explain the Chinese government’s refusal to allow close inspection of the lab and its records.

Trump has seized on the developments to contend he was right all along in blaming China and that his critics have been proved wrong. Biden sought to frame the matter differently, suggesting it was Trump’s negligence in the first place that cost the United States the opportunity to know more.

“Back in early 2020, when covid-19 emerged, I called for the [Centers for Disease Control and Prevention] to get access to China to learn about the virus so we could fight it more effectively,” Biden 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.”

In early 2020, Trump praised China repeatedly for its handling of the virus. “China has been working very hard to contain the Coronavirus,” he tweeted in January 2020. “The United States greatly appreciates their efforts and transparency.”

Soon afterward, however, Trump reversed course and threatened to pull the United States out of the WHO and accused the organization of being too deferential to China. He made official moves to do so in July 2020.

*Fact-checking the Paul-Fauci dispute over Wuhan lab funding*

Other Democrats also took a tougher tone Wednesday. Rep. Diana DeGette (D-Colo.) agreed that the lab theory should be investigated. “It’s very important that we find — that we investigate particularly if the virus escaped from some lab,” she said.

Some Republicans, meanwhile, are suggesting that their early suspicions of the Wuhan lab were dismissed prematurely.

“The common-sense case for a lab leak is the same as it was in January 2020, when I first mentioned the possibility,” Sen. Tom Cotton (R-Ark.) tweeted this week. “The United States & the world must demand a full, impartial investigation into COVID-19 origins, with a special focus on the Wuhan labs.”

But when the debate first heated up in early 2020, discussions of the lab were often conflated with conspiracy theories and unsupported claims that China had deliberately engineered the virus to harm the United States.

Scott Gottlieb, who headed the Food and Drug Administration under Trump, said it is crucial to distinguish between the conspiracy theories involving sinister plots and legitimate questions about the lab’s procedures.

“We can’t let the more politically fanciful narrative obscure the more likely but equally epochal reality that this could have been the result of tragically poor lab practices,” Gottlieb said.

The debate has now flared up again in Congress, with Sen. Rand Paul (R-Ky.) and other Republicans criticizing a subcontract that the Wuhan Institute received under a grant from the National Institutes of Health. The Senate on Tuesday approved Paul’s proposal to permanently ban all funding of “gain-of-function” research, which can involve enhancing a virus’s strength, in China.

NIH Director Francis Collins has repeatedly said the Wuhan lab was not authorized under the NIH grant to conduct that research.

Meanwhile, Trump has been trying to frame the fresh examination of the lab theory as a victory.
In an interview with Newsmax on Tuesday night, Trump stressed his early suspicions that the lab was the source of the virus. “I said right at the beginning that’s where it came from,” Trump said. “It was obvious to smart people that’s where it came from. I have no doubt about it.”
*John Wagner contributed to this report.*

# Gain-of-Function Oversight - Key Activity Timeline

- **2011:** Two NIH-funded studies (conducted at the University of Wisconsin and Erasmus Medical Center) confirmed H5N1 had the potential to become mammalian transmissible but raise biosafety and biosecurity concerns
    - Identified genetic determinants associated with mammalian-transmissibility of HPAI H5N1
    - Generated HPAI H5N1 viruses that were transmissible by respiratory droplets between ferrets (animal model)
- **2011 – 2012: NSABB tasked to review manuscripts**
    - March 2012: Recommends publication of revised version of one manuscript in full (unanimously); and that the data, methods, and conclusions presented in the other revised manuscript be communicated after appropriate further scientific review and revision (12-6 split vote). This was after initial consideration of publication of redacted versions (Apr. 2012 NIH director statement).
    - May and June 2012: H5N1 papers published in Science and Nature
- **Jan. 2012 – Jan. 2013:** Flu researchers impose voluntary pause on GOF studies (initially 60 days; extended through Jan. 2013) (Jan. 2012 NIH director statement on H5N1 Research)
- **Dec. 2012: USG hosted International Consultative Workshop on GOF Research with HPAI H5N1 (Archived recording)**
    - Shared multidisciplinary international perspectives on research that increases transmissibility in mammals (by respiratory droplets), pathogenicity, and/or alters host range
    - HHS solicited stakeholder perspectives on proposed framework for guiding HHS funding decisions on certain HPAI H5N1 GOF research
- **Feb. 2013: HHS *Framework for Guiding Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory Droplets*** ensures a robust review of research proposals—prior to making a funding decision—that considers the scientific and public health benefits, biosafety and biosecurity risks, and appropriate risk mitigation measures to guide HHS funding decisions
    - Scope: Proposals reasonably anticipated to confer GOF attributes that enable influenza viruses expressing the virulent form of the hemagglutinin (HA) gene from highly pathogenic H5N1 to be transmissible among mammals by respiratory droplets. The scope does not include routine characterization studies of naturally occurring H5N1 viruses.
    - **Aug. 2013: Framework expanded** to cover certain GOF experiments involving H7N9 influenza virus
- **Oct. 2014: *USG Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses*** allows comprehensive assessment of GOF research to inform development of new federal policy to help guide future investments in this important area of research
    - **Oct. 22, 2014: USG tasked NSABB** with providing recommendations on a conceptual approach for evaluating proposed GOF research (meeting summary)

  - Independent risk/benefit and ethics assessments commissioned (See OSP GOF page)
  - **Dec. 15-16, 2014: 1st National Academies symposium** on potential risks and benefits of GOF research (meeting summary)
  - **Mar. 10-11, 2016: 2nd National Academies symposium** on potential U.S. government policies for the oversight of GOF research (meeting summary)
  - 21 NIH projects affected by the pause

- **2014 – 2017: NIH grants 10 exceptions under the Pause**
  - "An exception from the research pause may be obtained if the head of the USG funding agency determines that the research is urgently necessary to protect the public health or national security"
  - 5 Influenza; 5 MERS (letters included)
  - 7 extramural requests submitted by NIAID division director; approved by NIAID director (or designee) and NIH director (or designee)
  - 3 intramural requests submitted by NIAID investigator, approved by NIAID scientific director, NIAID director (or designee), and NIH director (or designee

- **May 2015: NSABB issues *Framework for Conducting Risk and Benefit Assessments of Gain-of-Function Research***
  - Recommendations to guide assessment of potential risks and benefits associated with gain-of-function research involving pathogens with pandemic potential

- **May 2016: NSABB issues *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research***
  - Recommends additional, multidisciplinary review, prior to determining whether they are acceptable for funding

- **Jan. 2017**: **OSTP *Recommended Policy Guidance for Departmental Development of Review Mechanism for Potential Pandemic Pathogen Care and Oversight* (P3CO Policy Guidance)**
  - Instructs USG D/As to implement Department-level review to inform funding decisions for studies anticipated to involve creation, transfer, or use of enhanced PPP
  - Scope: A potential pandemic pathogen (PPP) is one that satisfies both of the following: [1] It is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations; and [2] It is likely highly virulent and likely to cause significant morbidity and/or mortality in humans. An enhanced PPP is a PPP resulting from the enhancement of a pathogen's transmissibility and/or virulence. Wild-type pathogens that are circulating in or have been recovered from nature are not enhanced PPPs, regardless of their pandemic potential.

- **Dec. 2017: *HHS Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens* (HHS P3CO Framework);**
  - HHS P3CO Framework requires multidisciplinary Department-level review of proposed enhanced PPP research to guide HHS funding decisions and oversight
  - Scope: A potential pandemic pathogen (PPP) is a pathogen that satisfies both of the following: [1] It is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations; and [2] It is likely highly virulent and likely to cause significant morbidity

and/or mortality in humans. An enhanced PPP is defined as a PPP resulting from the enhancement of the transmissibility and/or virulence of a pathogen. Enhanced PPPs do not include naturally occurring pathogens that are circulating in or have been recovered from nature, regardless of their pandemic potential.

To the extent that transmissibility and/or virulence of PPPs are modified in the following categories of studies, the resulting pathogens are not considered to be enhanced PPPs for the purposes of this Framework: [1] Surveillance activities, including sampling and sequencing; and [2] Activities associated with developing and producing vaccines, such as generation of high growth strains.

- **Dec. 2017: NIH lifts funding pause**
  - If a Scientific Review Group (SRG) identifies research that may create, transfer, or use enhanced PPPs as described above, the Scientific Review Officer will record this as an administrative note and instruct the SRG members that the presence of such research in the application will not affect their impact scores.
  - Following completion of the SRG review, Program officials will review all proposed research being considered for funding to determine if the research meets the scope of the HHS P3CO Framework, and if it does, will work with the applicant, institution, and funding agency staff, as appropriate, to comply with the HHS P3CO Framework.
- **2018: NIH refers two projects for review to HHS P3CO Review Group**
  - Evaluated through NIH peer review process in 2013; found to be scientifically meritorious but subject to GoF Research Funding Pause resulting in the funds being redirected within the awards to support other non-GoF research
  - HHS P3CO Review Group determined that both are acceptable for HHS funding with recommended changes to increase the potential benefits while decreasing risks
    - Suggested changes were included as terms and conditions of the awards
    - It was determined that there are no feasible, equally efficacious alternative methods to address the same question in a manner that poses less risk than the proposed approaches
    - Grant award: NIH Reporter – Transmissibility of Avian Influenza Viruses in Mammals
    - Contract award – NIH Reporter – Centers of Excellence for Influenza Research and Surveillance (CEIRS): Universal Influenza Research Efforts
- **2019: NIH Director issues Statement** on NIH commitment to transparency on research involving potential pandemic pathogens

(b) (5)

**PRE-DECISIONAL TPs for WSJ and WaPo Interviews on GOF**

**Likely focus** - What GoF is, benefits and drawbacks of this type of research, including a discussion of whether there should be different limits now.

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**High Level Points**

*[topic relationship to NIH]*

- NIH is a biomedical research agency and our only interest is to advance science to improve human health and reduce disease NIH takes the safety, security, and responsible conduct of the research we support very seriously.
- Research on pathogens is critical to public health and national security
  Predicting and preparing for next flu strain
- Pathogens have the potential to spill over to humans and cause widespread disease; sometimes NIH has to supports research in other countries with the best models for these systems

*[SARS-COV2]*

- Important questions have been raised about the origins of SARS-CoV-2 and NIH fully supports the need for expert-driven investigations by the U.S. Intelligence community and the World Health Organization.
- However, there has been mischaracterization of, and misinformation reported about, NIH support of specific GOF research.
- There are even allegations that NIH might have approved a grant that permitted research at the Wuhan Institute of Virology (WIV) to perform GOF research on coronaviruses that would have increased their transmissibility or lethality for humans.
- Neither NIH nor NIAID approved any grant that would have supported GOF research on coronaviruses that would have increased their transmissibility or lethality for humans.
- On May 19, 2019, the NIH Director issued a statement to correct the misinformation.

**QAs on GOF research and benefits**

1. **What is GOF research?**
   - The term "gain-of-function" (GOF) can describe a wide swath of research approaches that are commonly used and don't involve risks that deserve special oversight. Some scientists use the term GOF research broadly to refer to any modification of a biological agent that confers new or enhanced activity to that agent.
   - In some cases, this research is performed to give new properties to agents to allow them to grow and be studied in the lab; for example, the agent may be modified so that it can be studied in research animals.
   - However, not all research that some label as GOF research entails the same level of risk.
   - The subset of GOF research that is anticipated to enhance the *transmissibility* and/or *virulence* of potential pandemic pathogens (PPP), which could make them more dangerous to humans, has been the subject of substantial scrutiny and deliberation.
   - Such research is important to public health/national security but biosafety/biosecurity risks must be mitigated.

2. **What are the benefits of GOF research involving PPP?**
    - Genetic changes or mutations in pathogens, especially viruses that have ribonucleic acid as its genetic material, regularly occur in nature.
    - Some mutations in nature can cause pathogens to gain new functions or enhance existing characteristics such as fitness or pathogenicity (ability to cause disease). We have seen many examples of that with SARS-CoV-2.
    - GOF research studies are commonly employed to help us:
        - understand the fundamental nature of human-pathogen interactions
        - elucidate molecular mechanisms underlying pathogenesis
        - assess the pandemic potential of emerging infectious agents
        - inform public health and preparedness efforts, including surveillance and the development of vaccines and medical countermeasures
    - As such, GOF studies are a critically important tool to help prepare for and respond to pandemics.
    - **IF NEEDED – Specific benefits example**
        - The molecular basis for avian versus mammalian influenza virus receptor binding has been elucidated largely through GOF experiments.
        - Earlier GOF experiments with HPAI H5 viruses helped quickly identify similar mutations in the emerging 2013 LPAI H7N9.
        - Early detection of these molecular markers in H7N9 viruses isolated from humans was evidence that these viruses posed a significant pandemic threat.
        - Development of a candidate vaccine virus (CVV) began within a day using synthetic biology; and
        - NIH launched clinical trials testing H7N9 avian influenza vaccine candidate.
        - Since 2013 HHS has stockpiled tens of millions of doses of H7N9 vaccine as part of U.S. pandemic preparedness.
        - Since its emergence, there have been multiple epidemics of human infections with Asian H7N9 viruses resulting in 1,568 confirmed human cases and 616 deaths

**<u>QAs on GOF oversight and HHS P3CO Framework</u>**

3. **What oversight systems are in place for such GOF research that could enhance PPPs?**
    - NIH takes the safety, security, and responsible conduct of the research we support very seriously.
    - For example, NIH-supported research involving high-consequence agents/toxins is carried out in accordance with the biosafety practices outlined in the manual Biosafety in Microbiological and Biomedical Laboratories (BMBL) and may additionally be subject to another biosafety policy, the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*.
    - The possession, use, and transfer of Biological Select Agents and Toxins, which have the potential to pose a severe threat to public, animal, or plant health, are subject to oversight under the Select Agent Regulations and additionally may be subject to USG policies for the oversight of Dual Use Research of Concern.
    - NIH requires compliance with relevant guidelines, policies, and regulations through terms and conditions of awards.

- Under many of these policies, research is regularly reviewed at the institutional and federal levels to ensure safety and security, as well as proper adherence to approved risk mitigation plans.
- As for GOF research involving enhanced PPP specifically, several of these policies would apply to GOF research, depending on the specific experiments proposed and performed.
- HHS additionally established, in 2017, its *Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens*. The HHS P3CO Framework ensures a multidisciplinary, HHS department-level pre-funding review and evaluation of proposed research that is reasonably anticipated to create, transfer, or use enhanced PPPs.
- When supported with NIH funds, this subset of GOF research is only conducted in laboratories with stringent oversight and appropriate biosafety and biosecurity controls to help protect researchers from infection and prevent the release of microorganisms into the environment.

**4. What is the purpose of the HHS P3CO Framework and this additional oversight?**

- The HHS P3CO Framework is intended to guide HHS funding decisions on proposed research that is reasonably anticipated to create, transfer, or use PPPs resulting from the enhancement of a pathogen's transmissibility or virulence in humans (enhanced PPP) and seeks to preserve the benefits of life sciences research involving enhanced PPPs while minimizing potential biosafety and biosecurity risks.
- Under the HHS P3CO Framework, HHS funding agencies are responsible for conducting standard scientific merit review and referring proposed research that meets the scope of the Framework and is being considered for funding for HHS department-level review.
- The multidisciplinary HHS review group critically evaluates the proposed research, including a risk/benefit assessment and proposed risk mitigation plan.
- This Department-level review results in recommendations to the funding agency on whether the proposed research is acceptable for HHS funding and what, if any, additional risk mitigation measures should be incorporated into the terms and conditions of award, if the research is funded.
- The thoughtful review process laid out by the HHS P3CO Framework helps to facilitate the safe, secure, and responsible conduct of this type of research in a manner that maximizes the benefits to public health.

**5. What is the scope of the HHS P3CO Framework?**

- Proposed intramural and extramural life sciences research that is being considered for funding and that has been determined by the funding agency as reasonably anticipated to create, transfer, or use enhanced PPPs is subject to additional HHS department-level review.
- A PPP is one that satisfies both of the following:
    - It is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations, and
    - It is likely highly virulent and likely to cause significant morbidity and/or mortality in humans.
- An enhanced PPP is a PPP resulting from the experimental enhancement of a pathogen's transmissibility and/or virulence.

6. **What is required of researchers who submit research proposals that falls under the scope of the HHS P3CO Framework?**
    - The HHS P3CO Framework is intended to guide HHS funding decisions. The responsibilities of the funding agency and the HHS review group are articulated in the Framework. The funding agency contacts investigators/institutions whose research proposals are determined to involve enhanced PPP research and works with them to gather material necessary for submission to the HHS review group.
    - If funded, investigators are required to adhere to the terms and conditions of award, which includes adherence to the approved risk mitigation plan along with any other relevant terms, guidelines, policies, and regulations.

7. **What material is reviewed by the HHS review group?**
    - The funding agency also briefs the HHS P3CO Review Group on the proposed research and provides material for review including a description of the proposed research, a risk/benefit analysis – including a short description of the potential value of the research, and a risk mitigation plan developed by the institution and reviewed by the funding agency.

8. **What criteria does HHS use to guide funding recommendations under the P3CO policy?**
    - The HHS department-level review is guided by eight criteria listed in the HHS P3CO Framework, which include that:
        - The pathogen that is anticipated to be created, transferred, or used by the research must be reasonably judged to be a credible source of a potential future human pandemic;
        - There are no feasible, equally efficacious alternative methods to address the same question in a manner that poses less risk;
        - The investigator and the institution where the research would be carried out have the demonstrated capacity and commitment to conduct it safely and securely; and
        - The potential risks as compared to the potential benefits to society are justified.

9. **What expertise do the members of the HHS review group have?**
    - The HHS review group includes members with expertise in scientific research, biosafety, biosecurity, MCM development and availability, law, ethics, public health preparedness and response, biodefense, select agent regulations, and public health policy, as well as the funding agency perspectives and other relevant areas.

10. **What are the possible results of the department-level review?**
    - The Department-level review may result in recommendations that the research is acceptable for HHS funding; research is not acceptable for HHS funding; research is acceptable for HHS funding on the condition that certain experiments are modified; research is acceptable for HHS funding on the condition that certain risk mitigation measures are employed at the federal and/or institutional level; or other recommendations, as deemed appropriate.

11. **What mechanisms are there to facilitate public transparency in funding decisions around P3CO research?**

- The pre-funding review of individual proposals is not public to protect sensitive and/or preliminary data or intellectual property, to preserve confidentiality, and to allow for candid critique and discussion.
- However, information about the review process, including the material evaluated and criteria considered, is provided in the Framework.
- If funded, information about the projects that NIH supports is made available via NIH Reporter – an online, publicly accessible database. This information is also posted on HHS's Science, Safety, Security website.

**12. How many projects have been funded under the HHS P3CO Framework?**

- NIH has funded two projects involving influenza virus subsequent to review by the HHS P3CO review committee; both projects have since ended. Information about these funded projects is publicly available on NIH Reporter and on HHS's Science, Safety, Security website.

(b) (5)

[redacted]

**QAs on GOF Deliberative Process**

**13. Why did the USG pause funding for certain GOF studies?**

- The pause allowed the USG to conduct a comprehensive assessment of GOF research with the goal of developing new federal policy to help guide future investments in this important area of research.
    - **IF NEEDED**- The pause was partly in response to biosafety incidents at Federal research facilities around that time.

**14. What is the history of the development of P3CO policies?**

- Oct. 2014: GOF deliberative process to reassess risks/benefits and USG funding pause for certain studies involving influenza, MERS, or SARS.
    - **i.** Independent risk/benefit assessment commissioned
    - **ii.** NSABB and NASEM meetings facilitated broad public discussions
    - **iii.** May 2016 NSABB report recommends multidisciplinary, Department-level review to inform agency funding decisions
- Jan. 2017: OSTP Recommended Policy Guidance for Departmental Development of Review Mechanism for Potential Pandemic Pathogen Care and Oversight (P3CO Policy Guidance) instructs USG D/As to implement Department-level review to inform funding decisions for studies anticipated to involve creation, transfer, or use of enhanced PPP, i.e., PPP resulting from enhancement of a pathogen's transmissibility and/or virulence
- Dec. 2017: HHS Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens (HHS P3CO Framework) requires multidisciplinary Department-level review of proposed enhanced PPP research to guide HHS funding decisions and oversight; NIH lifts funding pause.

**15. IF PRESSED - How many NIH-supported projects were affected by the 2014 USG funding pause?**

- Exceptions to the pause were allowable if they were determined to be urgently necessary to protect public health or national security.
- I'd need to get back to you on specific numbers if desired.
- **[THERE IS SOME CONFLICTING INFO IN PRESS, SO BEST TO DEFER ON SPECIFIC NUMBERS]**- A total of 21 NIH-supported projects were affected by the USG funding pause (Science has quoted these numbers as 18 projects or 21 projects at different times). Of these, 10 exceptions from the pause were granted (5 MERS, 5 influenza) for projects or experiments that were determined to be urgently necessary to protect public health, in accordance with the pause statement.

**Tough QAs**

**16. Should there be further restrictions on GOF research that could enhance PPP?**

- The U.S. has a comprehensive biosafety and biosecurity oversight system that is predicated on identifying and assessing benefits and risks, and appropriately mitigating risks, from both the Federal and institutional levels.
- The HHS P3CO Framework and OSTP P3CO Policy Guidance provide additional scrutiny of proposed research and help to facilitate the safe, secure, and responsible conduct of important research in a manner that maximizes the benefits to public health.
- Of course, we are always considering how to ensure our policies strike the right balance of allowing potential benefits to be realized while managing potential risks, and we will consider to do so.

**17. Should the NIH be supporting GOF research in foreign countries?**

- NIH supports research in other countries to learn more about viruses lurking in bats and other mammals that have the potential to spill over to humans and cause widespread disease. Our support ensures that the information will be shared. It would be irresponsible for us not to do this work.
- This has helped us to assess the pandemic potential of emerging infectious pathogens, including coronaviruses that have caused SARS and MERS. This is our best path to inform the development of medical countermeasures such as vaccines.

**18. What are the protocols for collaboration with other countries related to GOF research that a researcher must go through in order to get approval?**

- All research proposals subject to the scope of the HHS P3CO Framework undergo review as outlined in the Framework.
- Both foreign and domestic institutions are required to adhere to the terms and conditions of award issued by the funding agency subsequent to HHS P3CO review.
- In addition, research involving foreign institutions require NIAID advisory Council approval as standard NIAID procedure and must undergo State Department clearance.

**19. Has NIH issued funding for enhanced PPP research conducted in a foreign country?**

- NIH has funded two projects involving influenza virus subsequent to review by the HHS P3CO review committee; both awards were to domestic institutions (University of Wisconsin-Madison and the Icahn School of Medicine at Mt. Sinai) and both projects have since ended. (b) (5)

**20. Did NIH funds support coronavirus research conducted at WIV and did this work involve any GOF or enhanced PPP research?**

- As has been publicly stated, NIH awarded a grant to EcoHealth Alliance Inc., a research organization based in New York City, in June 2014. The research proposed in the grant application sought to understand how bat coronaviruses evolve naturally in the environment to become transmissible to the human population. This included studying viral diversity in bat reservoirs, surveying people who work in live animal markets or other jobs 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.
- The application did not propose research to enhance any coronavirus to be more transmissible or virulent.
- The application was subjected to rigorous peer review and was judged to be very high priority, given how SARS-CoV had already emerged in this bat population.
- To support its work, EcoHealth made sub-awards to the Wuhan Institute of Virology and other institutions based in East Asia where coronaviruses tend to emerge and are prevalent.
- Following the initiation of the funding pause, this grant was reviewed again and determined by experts to fall outside the scope of the funding pause.

**From:** Tabak, Lawrence (NIH/OD) [E]
**To:** Collins, Francis (NIH/OD) [E]
**Cc:** Hallett, Adrienne (NIH/OD) [E]
**Subject:** Update on Status of Congressional Inquiries
**Date:** Thursday, July 1, 2021 6:02:19 PM
**Attachments:** GoF Table_Status_6.30.21.docx

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The attached table provides the current status of the recent Congressional letters related to EcoHealth, Gain of Function, and/or SARS-CoV-2 origins.

| From | Incoming Date | Subject | Status |
|---|---|---|---|
| Sen. Grassley (399541) | 3/8/21 | Writes to Acting Secretary Cochran and Avril Haines (National Intelligence) regarding the work the government has done to determine the origins of the coronavirus. Question 9 in the letter was regarding the NIH grant to EcoHealth Alliance and "gain of function" research. | **Completed on 5/21/2021** (signed by Dr. Tabak) |
| Rep. Reschenthaler +12 (399706) | 3/15/21 | Write to Acting Secretary Cochran regarding a grant awarded by NIAID to EcoHealth Alliance Inc. with a history of collaborating with the Wuhan Institute of Virology (WIV). | **Completed on 5/21/2021** (signed by Dr. Tabak) |
| Reps. McMorris Rodgers, Guthrie, and Griffith (398508) | 3/18/21 | Write to Dr. Collins requesting information to advance an independent, scientific investigation into the origins of the COVID-19 pandemic. | **Completed on 5/21/2021** (signed by Dr. Tabak) |
| Rep. Mike Gallagher (399431) | 5/5/21 | Writes to Dr. Fauci requesting answers to specific questions regarding the cause of the COVID-19 pandemic | **Completed on 6/25/2021** (signed by Dr. Fauci) |
| Sens. Ron Johnson, Tom Cotton, Mike Gallagher, James Lankford, Roger Marshall, Rand Paul, and Rick Scott (399802) | 5/20/2021 | Sen. Ron Johnson +6 write to Dr. Collins regarding the origins of COVID-19 (SARS-CoV-2) and information regarding gain of function research. | OLPA sent to HHS for their review and White House review on 6/23/2021. OLPA, OSP, OER, and NIAID have already reviewed. Once approved by HHS and the WH, the letter will be ready for review by LAT, ASF, and FC, followed by signature. |
| Reps. Richard Burr, Rand Paul, and Roger Marshall (399882) | 5/25/2021 | Writes Dr. Fauci regarding the status of the federal efforts to combat COVID-19 and any information regarding NIAID and GoF research of concern. | OLPA sent to HHS for their review and White House review on 6/23/2021. OLPA, OSP, OER, and NIAID have already reviewed. Once approved by HHS and the WH, the letter will be ready for review by LAT, ASF, and FC, followed by signature. |
| Sen. Charles Grassley, follow up | 5/26/2021 | Writes Sec. Becerra and Dr. Collins requesting a more detailed response to his March 8 letter seeing | OLPA sent to HHS for their review and White House review on 6/23/2021. OLPA, OSP, OER, and NIAID have |

| | | | |
|---|---|---|---|
| | | information on grants funded to EcoHealth Alliance. | already reviewed. Once approved by HHS and the WH, the letter will be ready for review by LAT, ASF, and FC, followed by signature. |
| Sen. Ron Johnson (399931) | 5/27/2021 | Writes Dr. Fauci seeking clarification on his comments relating to the origins of COVID-19. Senator Johnson seeks answers to specific questions by June 10, 2021. | OLPA is managing and working with ASL. |
| Reps. James Comer and Jim Jordan (399943) | 5/28/2021 | Writes Drs. Collins and Fauci regarding the origins of COVID-19 and to seek information on NIH funding to the Wuhan Institute of Virology. | OLPA is managing and working with ASL. |
| Rep. Marjorie Taylor Greene (400088) | 6/4/21 | Writes President Biden requesting answers to several questions regarding the origins of COVID-19 by June 30, 2021. | This draft went into NIH IMOD clearance on 6/28/2021, which OLPA is managing. Once complete, the draft will then go to HHS and the WH for review. |
| Reps. James Comer and Jim Jordan (400193) | 6/9/21 | Write Dr. Fauci regarding the origins of COVID-19. | OLPA is managing and working with ASL. |
| Reps. Upton and McMorris Rodgers +24 (400207) | 6/10/21 | Write Dr. Collins regarding the origins of COVID-19 and poses questions they would like NIH to address at a briefing. Also requests written answers to several questions. | OLPA is managing and working with ASL. |
| Rep. Johnson +4 (400264) | 6/11/21 | Write to Sec. Becerra and Dr. Collins regarding NIH's handling of the COVID-19 pandemic and provide five questions for NIH response. | OLPA is managing and working with ASL. |
| Sen. John Kennedy (400351) | 6/15/21 | Requests NIH issue a report to Congress detailing all grants NIH awarded to Dr. Daszak. | OLPA is managing and working with ASL. |
| Sens. Blackburn, Grassley, and Marshall (400559) | 6/28/21 | Write to Dr. Collins requesting responses to seven inquiries regarding report on Chinese researchers “directing” NIH to delete gene sequences of early COVID-19 cases. | Assigned to OLPA to draft a response with input from NLM. The draft is due to ES by COB 7/7/21 to begin the clearance process. An FYI was provided to NIAID, OSP, ADEPD, DEPD, and OGC. |

**From:** Tabak, Lawrence (NIH/OD) [E]
**To:** Collins, Francis (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
**Cc:** Jorgenson, Lyric (NIH/OD) [E]
**Subject:** Re: seeking an analogy
**Date:** Wednesday, June 30, 2021 3:40:35 PM

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We run NSABB on behalf of HHS; I imagine we would need to ask ASPR (and now that one is in place that has or can be done). Lyric must weigh in.
Larry

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**From:** Francis Collins < (b) (6)
**Date:** Wednesday, June 30, 2021 at 3:38 PM
**To:** "Myles, Renate (NIH/OD) [E]" < (b) (6) "Burklow, John (NIH/OD) [E]" < (b) (6)
**Cc:** "Tabak, Lawrence (NIH/OD) [E]" < (b) (6) "Jorgenson, Lyric (NIH/OD) [E]" < (b) (6)
**Subject:** RE: seeking an analogy
That's helpful. So are we actually tasking NSABB to review P3CO?

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**From:** Myles, Renate (NIH/OD) [E] < (b) (6)
**Sent:** Wednesday, June 30, 2021 3:10 PM
**To:** Collins, Francis (NIH/OD) [E] < (b) (6) Burklow, John (NIH/OD) [E] < (b) (6)
**Cc:** Tabak, Lawrence (NIH/OD) [E] < (b) (6) Jorgenson, Lyric (NIH/OD) [E] < (b) (6)
**Subject:** RE: seeking an analogy
+ Lyric
Hi Francis:
We are thinking about this. It's a bit of a challenge because the analogy you provided is essentially saying GOF (the bridge) didn't cause the car crash (the pandemic), but we didn't approve GoF in Wuhan and the scientific evidence suggests the virus wasn't human engineered, so not sure if an analogy confuses that issue. We'll continue to think through it.
In the meantime, I've framed a response to the question. Also, attached is OSP's backgrounder on GoF, which includes examples of the benefits.

**Should we be conducting GOF research; is there enough oversight to ensure it can be conducted safely?**

- NIH takes this topic very seriously.
- But before we delve into this, I'd like to separate the discussion about specific GOF research involving potential pandemic pathogens and the SARS-CoV-2 origins
- First, NIH has never approved any grant supporting "gain-of-function" research on coronaviruses that would have increased their transmissibility or lethality for humans.
- More importantly, the preponderance of scientific research to date continues to support early analysis by experts in the field of evolutionary virology that the virus does not have the characteristics of being human engineered.
- We should be very careful not to make that leap without the evidence to support it. As Carl Sagan has said, extraordinary claims require extraordinary evidence. We continue to follow the science on this.
- So, back to gain of function. Between 2014 and 2017, the U.S. Government initiated a four-year review in a publicly open deliberative process to consider such research and to weigh the benefits and risks. That effort resulted in what I believe has proven to be a robust framework for guiding this research.

- And just to be clear, the research we are talking about is specifically that which increases the transmissibility or virulence of a pathogen in humans.
- Importantly, NIH and other USG agencies regularly review our policies against evolving information and technologies to determine if they need to change.
- NIH will task the independent National Science Advisory Board for Biosecurity to evaluate the state of the science against the existing policies.

Thanks,
Renate

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**From:** Collins, Francis (NIH/OD) [E] <(b) (6)
**Sent:** Wednesday, June 30, 2021 7:50 AM
**To:** Burklow, John (NIH/OD) [E] <(b) (6) Myles, Renate (NIH/OD) [E] <(b) (6)
**Cc:** Tabak, Lawrence (NIH/OD) [E] <(b) (6)
**Subject:** seeking an analogy

Hi John and Renate,

With the focus on the 2014 funding pause and the 2017 P3CO coming more to the forefront (Willman in WaPo, upcoming WSJ, MIT Tech), I think NIH needs to be prepared to explain how these oversight policies were developed, and we need to be non-defensive and open to rational recommendations about how details of these policies might need to be reconsidered.

But we must vigorously resist the connecting of dots now being done on the right, that says our funding of WIV to study bat viruses (judged not to require P3CO) was a direct contributor to COVID-19.

This gets woolly. I need an analogy to explain this.

Here's one – connecting these dots is like trying to say a terrible car crash on the east side of the city was because of some bridgework being done on the west side.

Can you do better?

Francis

**From:** Jorgenson, Lyric (NIH/OD) [E]
**To:** Collins, Francis (NIH/OD) [E]
**Cc:** Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]
**Subject:** Re: seeking an analogy
**Date:** Wednesday, June 30, 2021 8:10:40 PM

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Hi Francis-

I think that we could restart at any time but may wish to consider the availability of the members tasked with the charge.

There are a few other considerations and groups to consult if we wanted to modify the charge, especially given the NSABB's service to the interagency.

Happy to discuss further if helpful.

Lyric Jorgenson, PhD
Acting Associate Director for Science Policy &
Acting Director of the Office of Science Policy
National Institutes of Health

> On Jun 30, 2021, at 4:19 PM, Collins, Francis (NIH/OD) [E] < (b) (6) wrote:
>
> Interesting. Given the passage of time since January 2020, would you consider revising this? Who has to weigh in on this? When might the restart of actual work happen?
> FC
>
> **From:** Jorgenson, Lyric (NIH/OD) [E] < (b) (6)
> **Sent:** Wednesday, June 30, 2021 3:45 PM
> **To:** Myles, Renate (NIH/OD) [E] < (b) (6) Collins, Francis (NIH/OD) [E] < (b) (6) Burklow, John (NIH/OD) [E] < (b) (6)
> **Cc:** Tabak, Lawrence (NIH/OD) [E] < (b) (6)
> **Subject:** RE: seeking an analogy
> We tasked the NSABB in January of 2020 with the following, but this charge as been on hold due to the experts involved tied up in the pandemic response:
> Charge to the NSABB Carrie D. Wolinetz, Ph.D., Associate Director for Science Policy, NIH Dr. Wolinetz reviewed the new NSABB charge, which is divided into three phases. In Phase 1 the NSABB will provide recommendations regarding the balance between security and public transparency when sharing information about enhanced PPP research. During Phase 2A the NSABB will evaluate and analyze U.S. DURC policies including their scope, implementation, effectiveness, and impacts on stakeholders; as well as the effectiveness of the pathogen list and experiment type construct. Finally, in Phase 2B the NSABB will evaluate the "Future Commitments" outlined in the OSTP

policy guidance and provide recommendation on incorporation of the P3CO policy into the DURC policy framework. The anticipated timeline involves the NSABB forming a working group focused on Phase 1 activities in February. By the spring or early summer of 2020, the NSABB will develop recommendations on the Phase 1 charge and shortly thereafter, form working groups to address Phases 2a and 2b. with a goal to deliver recommendation on Phase 2 in spring 2021.

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**From:** Myles, Renate (NIH/OD) [E] < (b) (6)
**Sent:** Wednesday, June 30, 2021 3:42 PM
**To:** Collins, Francis (NIH/OD) [E] < (b) (6) Burklow, John (NIH/OD) [E] < (b) (6)
**Cc:** Tabak, Lawrence (NIH/OD) [E] < (b) (6) Jorgenson, Lyric (NIH/OD) [E] < (b) (6)
**Subject:** RE: seeking an analogy

Good question. I defer to Lyric. I think you suggested as much to WSJ.

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**From:** Collins, Francis (NIH/OD) [E] < (b) (6)
**Sent:** Wednesday, June 30, 2021 3:39 PM
**To:** Myles, Renate (NIH/OD) [E] < (b) (6) Burklow, John (NIH/OD) [E] < (b) (6)
**Cc:** Tabak, Lawrence (NIH/OD) [E] < (b) (6) Jorgenson, Lyric (NIH/OD) [E] < (b) (6)
**Subject:** RE: seeking an analogy

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**From:** Myles, Renate (NIH/OD) [E] < (b) (6)
**Sent:** Wednesday, June 30, 2021 3:10 PM
**To:** Collins, Francis (NIH/OD) [E] < (b) (6) Burklow, John (NIH/OD) [E] < (b) (6)
**Cc:** Tabak, Lawrence (NIH/OD) [E] < (b) (6) Jorgenson, Lyric (NIH/OD) [E] < (b) (6)
**Subject:** RE: seeking an analogy

+ Lyric

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- So, back to gain of function. Between 2014 and 2017, the U.S. Government initiated a four-year review in a publicly open deliberative process to consider such research and to weigh the benefits and risks. That effort resulted in what I believe has proven to be a robust framework for guiding this research.
- And just to be clear, the research we are talking about is specifically that which increases the transmissibility or virulence of a pathogen in humans.
- Importantly, NIH and other USG agencies regularly review our policies against evolving information and technologies to determine if they need to change.
- NIH will task the independent National Science Advisory Board for Biosecurity to evaluate the state of the science against the existing policies.

Thanks,
Renate

---

**From:** Collins, Francis (NIH/OD) [E] <(b) (6)
**Sent:** Wednesday, June 30, 2021 7:50 AM
**To:** Burklow, John (NIH/OD) [E] <(b) (6) Myles, Renate (NIH/OD) [E] <(b) (6)
**Cc:** Tabak, Lawrence (NIH/OD) [E] <(b) (6)
**Subject:** seeking an analogy

Hi John and Renate,

With the focus on the 2014 funding pause and the 2017 P3CO coming more to the forefront (Willman in WaPo, upcoming WSJ, MIT Tech), I think NIH needs to be prepared to explain how these oversight policies were developed, and we need to be non-defensive and open to rational recommendations about how details of these policies might need to be reconsidered.

But we must vigorously resist the connecting of dots now being done on the right, that says our funding of WIV to study bat viruses (judged not to require P3CO) was a direct contributor to COVID-19.

This gets woolly. I need an analogy to explain this.

Here's one – connecting these dots is like trying to say a terrible car crash on the east side of the city was because of some bridgework being done on the west side.

Can you do better?

Francis

*Weekly reports should be Arial, size 14 font; additional information, if necessary, may be included in the appendix*

# WEEKLY REPORT

Month DD, YYYY

MEMORANDUM FOR THE CABINET SECRETARY

FROM: [FIRST LAST], [DEPARTMENT], [PHONE NUMBER]

SUBJECT: [Agency] Weekly Report | Week ending (Month DD, YYYY)

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## AMERICAN RESCUE PLAN (ARP) / AMERICAN JOBS PLAN (AJP) / ECONOMY

The American Rescue Plan and American Jobs Plan are cross-cutting priorities among many agencies. Please list in bullet form how your agency is working to implement ARP, to bring AJP across the finish line, as well as broader efforts supporting the economy.

In the below sub-sections, be sure to include significant progress and/or setbacks towards high priority agency goals, progress on implementing Executive Orders / policy agenda, and principal-level activity.

Note: Please order bullets by priority in all sections

Sections are:

- **Significant activity for consideration to raise to the attention of POTUS:**
  - 0-3 bullets as needed
  - Please begin each point with a short 2-5 word **bolded descriptive subject line**
    - Ex: "**State and Local Funding:** On May 10th, the Department of the Treasury launched the portal to process applications for the $350 billion State and Local Fiscal Recovery Fund. Over 1,200 entities have successfully completed their submissions.

- Do NOT bold any other words or phrases in the bullet outside of the sections, sub-sections, and subject lines. Do NOT bold agency names.
- Make sure all bullets in this section can be read as standalone bullets without needing additional context.
- Include date of action, hard numbers and data wherever possible
  - Example: "**COVID-19 Home Tests:** On February 1st, Department of Defense (DOD) and Department of Health and Human Services (HHS) awarded $231.8 million to increase onshore production capacity of the Ellume COVID-19 Home Test for the United States, improving production capacity to 640,000 tests per day by December 2021."
- Include bullets only with concrete actions, announcements, meetings, etc. Avoid generalities as much as possible.
  - Ex: Do NOT say "[Agency] continued to implement COVID-19 work safety plan."
- Do not use acronyms. Spell out a name then put acronym in parentheses.
  - Ex: "Federal Emergency Management Agency (FEMA)"
- Do not include year and do not superscript dates.
  - Ex: "On February 1st" - (not "On February 1st")

- **Past Week Accomplishments and Setbacks/Obstacles:**
  - 0-5 bullets as needed
  - Remove sub-section if leaving blank. Put "N/A" if zero entries for the entire section (i.e. no points for anything in ARP)

- **Requests for White House Collaboration:**
  - 0-1 bullets as needed

- **Next Week – Upcoming Events / Tasks / Developments:**
  - 0-5 bullets as needed

## COVID-19

Tackling COVID-19 is a cross-cutting priority among many agencies. Please list in bullet form how your agency is working to fulfill the administration's mandate in addressing the pandemic.

In the below sub-sections, be sure to include significant progress and/or setbacks towards high priority agency goals, progress on implementing Executive Orders / policy agenda, and principal-level activity.

Same sections:

- **Significant activity for consideration to raise to the attention of POTUS:**
    - 0-3 bullets as needed

- **Past Week Accomplishments and Setbacks/Obstacles:**
    - 0-5 bullets as needed

- **Requests for White House Collaboration:**
    - 0-1 bullets as needed

- **Next Week – Upcoming Events / Tasks / Developments:**
    - 0-5 bullets as needed

**CLIMATE**

Addressing the climate crisis is a cross-cutting priority among many agencies. Please list in bullet form how your agency is working to advance the goals of the administration's climate agenda.

In the below sub-sections, be sure to include significant progress and/or setbacks towards high priority agency goals, progress on implementing Executive Orders / policy agenda, and principal-level activity.

Same sections:

- **Significant activity for consideration to raise to the attention of POTUS:**
    - 0-3 bullets as needed

- **Past Week Accomplishments and Setbacks/Obstacles:**
    - 0-5 bullets as needed

- **Requests for White House Collaboration:**
  - 0-1 bullets as needed

- **Next Week – Upcoming Events / Tasks / Developments:**
  - 0-5 bullets as needed

## EQUITY FOR UNDERSERVED COMMUNITIES

Please list in bullet form how your agency is working to advance the Administration's goals of ensuring that equity for underserved communities is rooted in all agency activity.

In the below sub-sections, be sure to include significant progress and/or setbacks towards high priority agency goals, progress on implementing Executive Orders / policy agenda, and principal-level activity.

Same sections:

- **Significant activity for consideration to raise to the attention of POTUS:**
  - 0-3 bullets as needed

- **Past Week Accomplishments and Setbacks/Obstacles:**
  - 0-5 bullets as needed

- **Requests for White House Collaboration:**
  - 0-1 bullets as needed

- **Next Week – Upcoming Events / Tasks / Developments:**
  - 0-5 bullets as needed

## SIGNIFICANT EXECUTIVE ORDER (EO) & AGENCY ACTIVITY

Please list any significant agency activity, including activities related to executive orders, important agency initiatives, announcements, and actions that do not fall into the above priority buckets. Please pay special attention to actions which may have significant interest in particular geographic regions.

If you have an item that fits into more than one of the issue areas above, you're also welcome to include it in this section.

In the below sub-sections, as needed, you may include significant progress and/or setbacks towards additional high priority agency goals, progress on implementing Executive Orders / policy agenda, and principal-level activity.

Sections are:

- **Significant activity for consideration to raise to the attention of POTUS:**
    - 0-3 bullets as needed

- **Past Week Accomplishments and Setbacks/Obstacles:**
    - 0-5 bullets as needed
    - Remove sub-section if leaving blank. Put "N/A" if zero entries for the entire section (i.e. no points for anything in ARP)
    - Order bullets by priority in all sections

- **Requests for White House Collaboration:**
    - 0-1 bullets as needed

- **Next Week – Upcoming Events / Tasks / Developments:**
    - 0-5 bullets as needed

## APPENDIX

In the below sub-sections please be as comprehensive and detailed as possible. Please list details for the previous week and a look-ahead at least 4 weeks out in all sections where possible, and particularly for Travel, Speeches, and Media appearances. And where applicable, please indicate if an engagement was specific to ARP, AJP, AFP, or another priority.

Sections are:

- **Week ahead messaging:**
    - Please include 3-5 bullet points about what your agency's top messaging priorities are for the next week

        - Please also flag any upcoming activity you think White House Comms should be aware of

- **Travel:**
    - List travel in the following format:
        - **Date** – Location(s): Topline event description, including type of event (roundtable, tour, etc.)
        - Key attendees: Members of Congress, key local elected officials and/or business/non-profit/community/faith leaders
        - When event will be noticed publicly
        - Please label if supporting AJP, ARP, and/or AFP, or if another priority
            - *Example*: **May 31st** – Ford Plant in Dearborn, Michigan: Secretary Granholm will participate in a roundtable with Ford executives and United Auto Workers (UAW) members to discuss electric vehicles and how both AJP and AFP will support U.S. competitiveness, create good-paying jobs and help us reach climate goals. Senators Gary Peters (D-MI) and Debbie Stabenow (D-MI) and Governor Gretchen Whitmer (D-MI) have been invited. We expect to notice this event on May 28th.

    - Recent (previous week) and upcoming (4 weeks minimum)
    - Include TBD date and tentative travel as well, indicating so

- **Speeches:**
    - Recent (previous week) and upcoming (4 weeks minimum)

- **Media:**
    - Principal-level interviews
    - Recent (previous week) and upcoming (4 weeks minimum)

- **Principal level meetings or calls with Governors, Mayors, or other elected officials of note:**
    - Include any relevant meetings you would like to flag for White House Intergovernmental Affairs. These will vary by agency

and could include but are not limited to Attorneys General, Education Commissioners, Health Secretaries, etc.
    - Recent (previous week) and upcoming (4 weeks minimum)
    - Include purpose, agenda/topics covered

- **Noteworthy public engagement:**
    - Noteworthy public engagement could include but is not limited to meetings with unions, business leaders, faith and community leaders, constituency groups, etc.
    - Principal-level engagement
    - Recent (previous week) and upcoming (4 weeks minimum)

- **Principal level meetings or calls with Members of Congress:**
    - Recent (previous week) and upcoming (4 weeks minimum)
    - Include purpose, agenda/topics covered

- **Noteworthy inquiries from Congressional committees or Members of Congress; scheduled testimony by Secretary or Deputy Secretary:**
    - These should be letters, requests for briefings, meetings, and hearings.

- **Noteworthy rulemaking in the Federal Register:**
    - Recent (previous week) and upcoming anticipated

- **Funding Announcements:**
    - Recent (previous week) and upcoming (4 weeks minimum)

- **Grant Notices (NOFA/NOFOs):**
    - Recent (previous week) and upcoming (4 weeks minimum)

**From:** McGarey, Barbara (HHS/OGC)
**To:** Tabak, Lawrence (NIH/OD) [E]
**Subject:** Documents transmitted to ODNI
**Date:** Friday, July 23, 2021 7:42:45 AM
**Attachments:** RPPR 4 12 17.pdf
RPPR 9 16 20.pdf
RPPR 5 13 16.pdf
RPPR 5 1 15.pdf

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This is what was sent to ODNI, via Les Holly.

Barb

Barbara M. McGarey

Deputy General Counsel

HHS Office of the General Counsel

She/her/hers

(b) (6)

(b) (6) (cell)

## A. COVER PAGE

| | |
|---|---|
| **Project Title:** Understanding the Risk of Bat Coronavirus Emergence | |
| **Grant Number:** 5R01AI110964-02 | **Project/Grant Period:** 06/01/2014 - 05/31/2019 |
| **Reporting Period:** 06/01/2014 - 05/31/2015 | **Requested Budget Period:** 06/01/2015 - 05/31/2016 |
| **Report Term Frequency:** Annual | **Date Submitted:** 05/01/2015 |
| **Program Director/Principal Investigator Information:**<br><br>PETER DASZAK , PHD BS<br><br>**Phone number:** (b) (6)<br>**Email:** (b) (6) | **Recipient Organization:**<br><br>ECOHEALTH ALLIANCE, INC.<br>ECOHEALTH ALLIANCE, INC.<br>460 W 34TH ST<br>17TH FLOOR<br>NEW YORK, NY 100012320<br><br>**DUNS:** 077090066<br>**EIN:** 1311726494A1<br><br>**RECIPIENT ID:** 07-049-7012 |
| **Change of Contact PD/PI:** No | |
| **Administrative Official:**<br><br>ALEKSEI CHMURA<br>460 W 34th St., 17th Floor<br>New York, NY 10001<br><br>**Phone number:** (b) (6)<br>**Email:** (b) (6) | **Signing Official:**<br><br>ALEKSEI CHMURA<br>460 W 34th St., 17th Floor<br>New York, NY 10001<br><br>**Phone number:** (b) (6)<br>**Email:** (b) (6) |
| **Human Subjects:** Yes<br>HS Exempt: No<br>Exemption Number:<br>Phase III Clinical Trial: | **Vertebrate Animals:** Yes |
| **hESC:** No | **Inventions/Patents:** No |

## B. ACCOMPLISHMENTS

### B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Zoonotic coronaviruses are a significant threat to global health, as demonstrated with the emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, and the recent emergence Middle East Respiratory Syndrome (MERS-CoV). The wildlife reservoirs of SARS-CoV were identified by our group as bat species, and since then hundreds of novel bat-CoVs have been discovered (including >260 by our group). These, and other wildlife species, are hunted, traded, butchered and consumed across Asia, creating a largescale human-wildlife interface, and high risk of future emergence of novel CoVs.
To understand the risk of zoonotic CoV emergence, we propose to examine 1) the transmission dynamics of bat-CoVs across the human-wildlife interface, and 2) how this process is affected by CoV evolutionary potential, and how it might force CoV evolution. We will assess the nature and frequency of contact among animals and people in two critical human-animal interfaces: live animal markets in China and people who are highly exposed to bats in rural China. In the markets we hypothesize that viral emergence may be accelerated by heightened mixing of host species leading to viral evolution, and high potential for contact with humans. In this study, we propose three specific aims and will screen free ranging and captive bats in China for known and novel coronaviruses; screen people who have high occupational exposure to bats and other wildlife; and examine the genetics and receptor binding properties of novel bat-CoVs we have already identified and those we will discover. We will then use ecological and evolutionary analyses and predictive mathematical models to examine the risk of future bat-CoV spillover to humans. This work will follow 3 specific aims:

Specific Aim 1: Assessment of CoV spillover potential at high risk human-wildlife interfaces. We will examine if: 1) wildlife markets in China provide enhanced capacity for bat-CoVs to infect other hosts, either via evolutionary adaptation or recombination; 2) the import of animals from throughout Southeast Asia introduces a higher genetic diversity of mammalian CoVs in market systems compared to within intact ecosystems of China and Southeast Asia; We will interview people about the nature and frequency of contact with bats and other wildlife; collect blood samples from people highly exposed to wildlife; and collect a full range of clinical samples from bats and other mammals in the wild and in wetmarkets; and screen these for CoVs using serological and molecular assays.

Specific Aim 2: Receptor evolution, host range and predictive modeling of bat-CoV emergence risk. We propose two competing hypotheses: 1) CoV host-range in bats and other mammals is limited by the
phylogenetic relatedness of bats and evolutionary conservation of CoV receptors; 2) CoV host-range is limited by geographic and ecological opportunity for contact between species so that the wildlife trade disrupts the 'natural' co-phylogeny, facilitates spillover and promotes viral evolution. We will develop CoV phylogenies from sequence data collected previously by our group, and in the proposed study, as well as from Genbank. We will examine co-evolutionary congruence of bat-CoVs and their hosts using both functional (receptor) and neutral genes. We will predict host-range in unsampled species using a generalizable model of host and viral ecological and phylogenetic traits to explain patterns of viral sharing between species. We will test for positive selection in market vs. wild-sampled viruses, and use data to parameterize mathematical models that predict CoV evolutionary and transmission dynamics. We will then examine scenarios of how CoVs with different transmissibility would likely emerge in wildlife markets.



Specific Aim 3: Testing p edict ons of CoV inter-species transmission. We will test our models of host range ( e. emergence potent al) experimentally using reverse genetics, pseudovirus and receptor binding assays, and virus infection experiments in cell culture and humanized mice. With bat-CoVs that we've isolated or sequenced, and using live virus or pseudovirus infection in cells of different origin or expressing different receptor molecules, we will assess potential for each isolated virus and those with receptor binding site sequence, to spill over. We will do this by sequencing the spike (or other receptor binding/fusion) protein genes from all our bat-CoVs, creating mutants to identify how significantly each would need to evolve to use ACE2, CD26/DPP4 (MERS-CoV receptor) or other potential CoV receptors. We will then use receptor-mutant pseudovirus binding assays, in vitro studies in bat, primate, human and other species' cell lines, and with humanized mice where particularly interesting viruses are identified phylogenetically, or isolated. These tests will provide public health-relevant data, and also iteratively improve our predictive model to better target bat species and CoVs during our field studies to obtain bat-CoV strains of the greatest interest for understanding the mechanisms of cross-species transmission.

### B.1.a Have the major goals changed since the initial competing award or previous report?

No

### B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: Accomplishments.pdf

### B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

**For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?**

No

### B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

File uploaded: Professional Development.pdf

**B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?**

1) Conference and University lectures
• PI Daszak, and Co-investigators Olival and Shi gave >10 invited University lectures that included specific discussion of the current project and results.

2) Agency and other USG briefings
• NRC, 2015: Invited speaker, IOM Forum on public health preparedness, Interagency meeting on Medical Countermeasures. PI Daszak specifically reported on the findings from Year 1 of this project and the risk of SARS-like viruses causing future pandemics
• World Health Summit, Berlin 2014: PI Daszak was an invited panelist at a session on pandemic risk, and specifically reported the results and aims of this project
• International bat virus conference, Colorado, 2014: PI Daszak and Co-investigator Olival presented results from this study
• National Academies, Division of Earth & Life Studies, Spring Advisory Committee Meeting, DC. PI Daszak presented results from this study as part of an invited talk.
• Consortium of Universities for Global Health Conf., Washington DC, 2014. PI Daszak presented data from this study in a session on disease ecology

3) Public outreach
• PI Daszak reported on this project at an EcoHealth Alliance meeting hosted by the Cosmos Club, 2014

**B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?**

Specific Aim 1: Assessment of CoV spillover potential at high risk human-wildlife interfaces. Early in Year 2 of the study, it is anticipated that all of the qualitative research (i.e, 5-7 focus groups and ~100 ethnographic interviews) will be completed, transcribed and translated. It is anticipated that a total of approximately 100 ethnographic interviews and five to seven focus groups will be conducted in targeted areas with known bat populations in Yunnan, Guangxi, Guangdong and Fujian over the next few months. At least one of the focus groups and an estimated 35-40% of the interviews and surveys will be conducted with women. Subjects are enrolled in this study without regard to ethnicity.
Preliminary analyses will be conducted and will focus on the factors least understood, but crucial to the development of a behavioral risk survey that captures relevant behaviors and practices. Factors include specific human-animal interactions, experiences of unusual illness in both humans and animals, and an assessment of the context within which these activities occur. Because of the unique dataset and the expected richness of the data, additional research questions will be developed and explored using grounded theory, as well as more recently developed methods such as narrative analysis and case oriented understanding.

Results from preliminary analyses will contribute to the development of the behavioral risk survey. A behavioral survey sampling frame and recruitment materials are currently being developed. After pilot testing the behavioral survey, we will begin concurrent biologic specimen collection from bats, other wildlife and humans to compare circulating CoV strains in the bat population with serological exposure in human populations. The behavioral risk survey will facilitate the identification of explicit behavioral risks and practices that are found among study participants seropositive for SARS-like corona virus. These findings will be used to develop better risk mitigation policies and targeted intervention strategies.



Specific Aim 2: Receptor evolution, host range and predictive modeling of bat-CoV emergence risk.
Future steps to optimize the model of role of species diversity in CoV emergence risk will include:
1. Parameterizing with actual data on species diversity and abundance of animals from Southern China markets.
2. Parameterizing with species-specific data on CoV prevalence and strain variation in different bat species from field surveillance, e.g. if Rhinolopus spp. represent the highest risk for SARS-related CoV emergence, these species will be given a higher weight.
3. Incorporation of CoV lineage specific probabilities for inter-host spillover based on receptor binding data.

We will also conduct further modeling activities, including:
1. Comparative cophylogenetic analyses of bat host and CoV RdRp and Spike gene phylogenies, to assess patterns of evolutionary congruence and frequency of cross-species transmission.
a. Using previously published data from literature and Genbank
b. Using sequence data from our S. China surveillance
2. Calculate CoV divergence times using Spike RBD sequences for S. China.
3. Construct initial generalized linear mixed model to predict CoV diversity using S. China data and bat host-specific trait data. Update model regularly with new data from CoV screening in different bat species.

Specific Aim 3: Testing predictions of CoV inter-species transmission.
The following experiments will be undertaken in Year 2:
1. Animal infection experiment with SARS-like CoV
Option 1. Virus infection through ACE2 humanized mouse. Human ACE2 promotor (9-10 kb) and ACE2 will be inserted into a expressing vector and sent to a commercial company to generate transgenic mice. The stably expressed human ACE2 mice will be used for virus infection.
Option 2. Virus infection through SARS-CoV susceptible animals such as ferrets.
All above animal infection experiment will be performed under the containment of BSL3.
2. Continued surveillances of SARS-like CoVs in Yunnan and Guangdong provinces and isolation of novel virus strains.
3. Surveillance of infection in human populations by SARS-like CoVs. This work will be performed at two locations, one each in Yunnan and Guangdong provinces. PCR and ELISA will be used, respectively, for detection of viral replicase gene and antibody against the viral

nucleocapsid protein.

**Year 1 Report for Understanding the Risk of Bat Coronavirus Emergence**

**Award Number: 1R01AI110964-01**

**B2: What was accomplished under these goals?**

**Specific Aim 1: Assessment of CoV spillover potential at high risk human-wildlife interfaces.**

In the first year of this R01, we have:

1) Designed a behavioral risk study using an iterative approach that begins with rapid and focused qualitative research at or near biological surveillance sites in China where bats have previously been captured, sampled and found to contain novel CoVs. The study design includes: 1) structured observation and mapping of public spaces, 2) focus groups and 3) ethnographic interviews. The primary enrollment criteria are related to occupational exposure to bats and residence near bats. This research is conducted with two groups of individuals: those involved in the bat value chain (from hunter through market to consumer) and those highly exposed to bats (e.g., cave dwellers). The qualitative data will be used to inform a behavioral risk survey, as well as to contextualize findings from behavioral surveillance analyses.

2) Conducted observational research and mapping in: ***Yunnan***: In and around Xiang Yun village (two clinics and one wildlife restaurant); in and around the remote Lu Feng village (1 wildlife farm, 1 wildlife butcher and 1 wildlife restaurant) and at the An Ning communicable disease hospital complex; ***Guangxi***: In and around LiPu, (two markets, 3 wildlife farms, 1 wildlife restaurant ; and ***Guangdong***: Guangzhou wildlife market, Foshon wildlife market (this market is whe e the first cases of SARS were traced back to in 2003).



3) Secured local IRB approval in November 2014 from Wuhan University School of Public Health, Hubei Province, to conduct qualitative research, to administer behavioral surveys and to collect biological data including blood (no more than 550ml), sputum, and stool samples from humans. We secured US IRB approval through Hummingbird IRB (2014-23 approval letter sent to NIH) in November 2014 for qualitative, quantitative and biological specimen data collection.

4) Drafted protocols, guides, and training modules for Observational Research, Focus Groups, and Ethnographic Interviews and pilot tested these. The Observational Guide and Ethnographic Interview materials were pilot tested in live animal markets in Queens, New York City. Consistent with the original proposal, we have trained interviewers and identified key informants. Key informants include community health workers from three different administrative level CDCs, Barefoot Doctors, public health clinicians, local wildlife farmers and wildlife restaurant owners, as well as market vendors and workers. Ethnographic and Focus Group Interviews to be conducted pending NIH approval of IRB approval letter.

**Specific Aim 2: Receptor evolution, host range and predictive modeling of bat-CoV emergence risk.**

***1)*** *Collation and preliminary analysis of published bat Coronavirus data to optimized specimen collection and taxonomic targets for surveillance.*

Over the last decade a large number of bat viral discovery studies have been published globally (including a large number focused on CoVs). In year 1, we conducted the first ever systematic analysis of these data. We collated literature from over 100 viral discovery studies in bats, to examine patterns of host range and known viral diversity in different bat taxa (Young and Olival, In Review). We found that Coronavirus diversity has been most thoroughly characterized in a few bat families, including the Vespertillionidae and 5 other families, but several bat taxa remain under-represented in global virus surveillance efforts (**Fig 1**). Identification of these surveillance gaps allows us to better target our field surveillance towards bat taxa where CoV diversity is largely unknown (blue and light colored cells, **Fig 1**). These analyses were completed at various taxonomic levels, including by bat subfamily and genera (Family level analysis only shown).

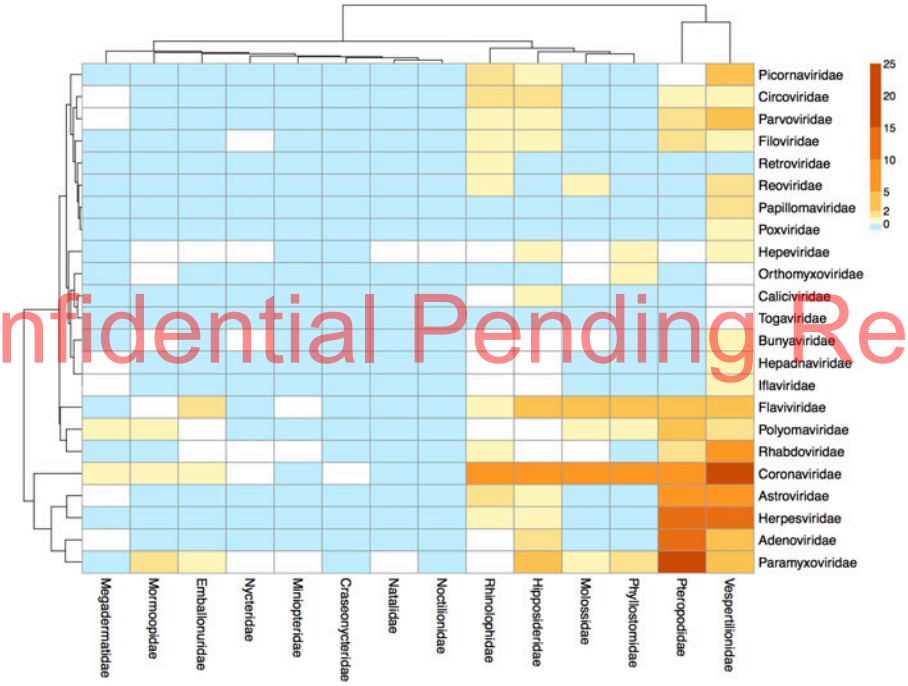





**Figure 1.** Heat map of viral richness by bat host and viral family, clustered by similarity in viral richness across host and viral families.

To maximize our chances of discovering CoVs, we need to define the number of specimens required for our bat surveillance work and the bat taxonomic groups on which to focus our surveillance. We used generalized linear mixed models (GLMM) and applied this to a subset of our collated data for CoVs alone. We found that sample type screened (feces), collection methods, and the number of specimens tested best explains the probability of finding an individual CoV positive sample. We will now use these

approaches to increase the likelihood of getting positive samples in our fieldwork in China.

**2)** *Preliminary 'What-if' Model: Role of species diversity in CoV emergence risk.* We built a mathematical model to analyze different scenarios of CoV spillover. We began with an assessment of how the diversity of wildlife (and other factors) in wet markets may affect the probability of CoV zoonotic spillover. We modeled evolution of CoVs within wildlife in a market following the initial introduction of a novel virus in one specific host. We assume this initial virus is a single genotype that does not yet have a great enough rate of spread to create an epidemic, but has a rate of spread close to this threshold. When this virus infects a new host, a new genotype is generated, based on random drift from the infecting genotype. We use Neutral Theory of Species Diversity to specify the species distribution in the market, for a given total number of species and total abundance of animals. We assume 500 animals in the market, and alter the species diversity from 3 to over 40. These numbers are easily attained in a small to medium market in Southern China (and in year 2 we will groundtruth these assumptions)

As the number of species present in a market increases from 3 to 20, the percent of simulations where zoonotic spillover occurred from any of the animals into humans increases (**Fig 2**). However, the risk remains fairly level if wildlife biodiversity increases above that level. The probability of epidemic failure is inverse to the probability of a zoonotic spillover taking hold and decreases with increasing species diversity (**Fig 2**). Therefore our null model shows that reducing the diversity of species in live animal markets could reduce the risk of zoonotic spillover, including of potentially pandemic CoVs.



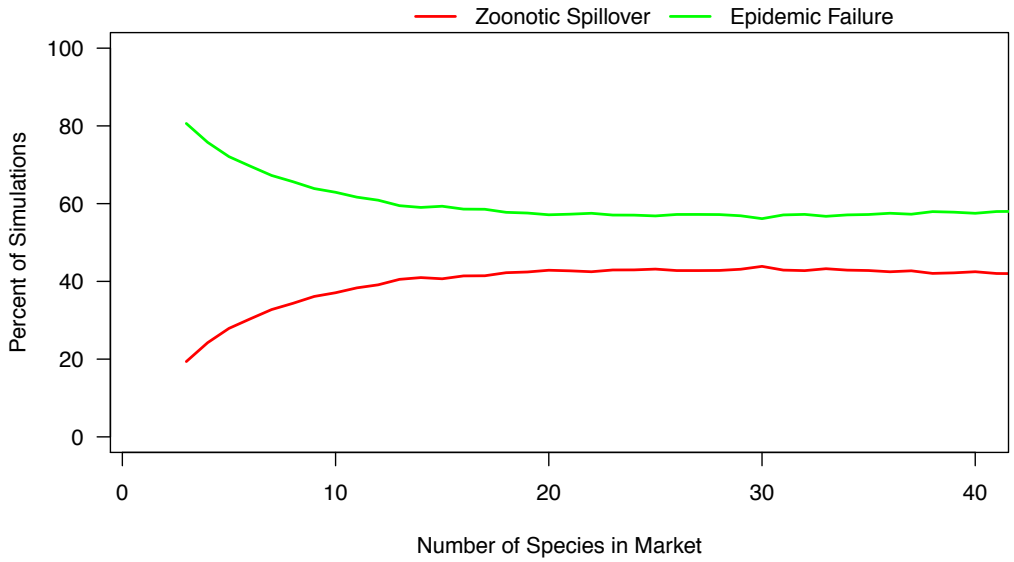



**Figure 2**. 'What-if' scenario model based on the Neutral Theory of Species Diversity to examine the role of wildlife species diversity for CoV spillover in markets.

**Specific Aim 3: Testing predictions of CoV inter-species transmission.**

*1) Bat Coronavirus Surveillance in 2014*

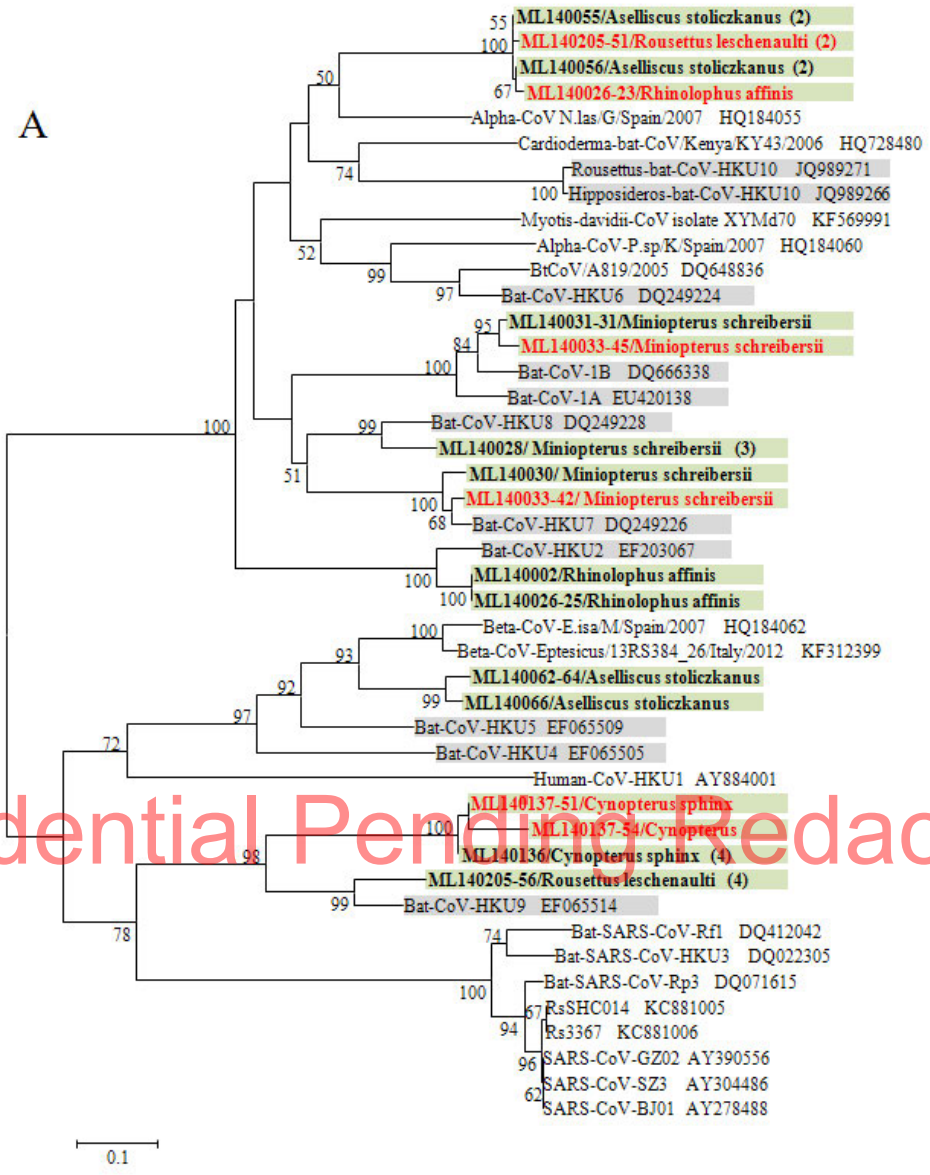
We collected 1555 anal swab samples, 1357 fecal samples, 461 blood samples, 469 serum samples and 24 tissue samples from > 14 bat genera in 5 provinces and in Laos (**Table 1**).

**Table 1** Bat Samples collected for CoV surveillance in 2014

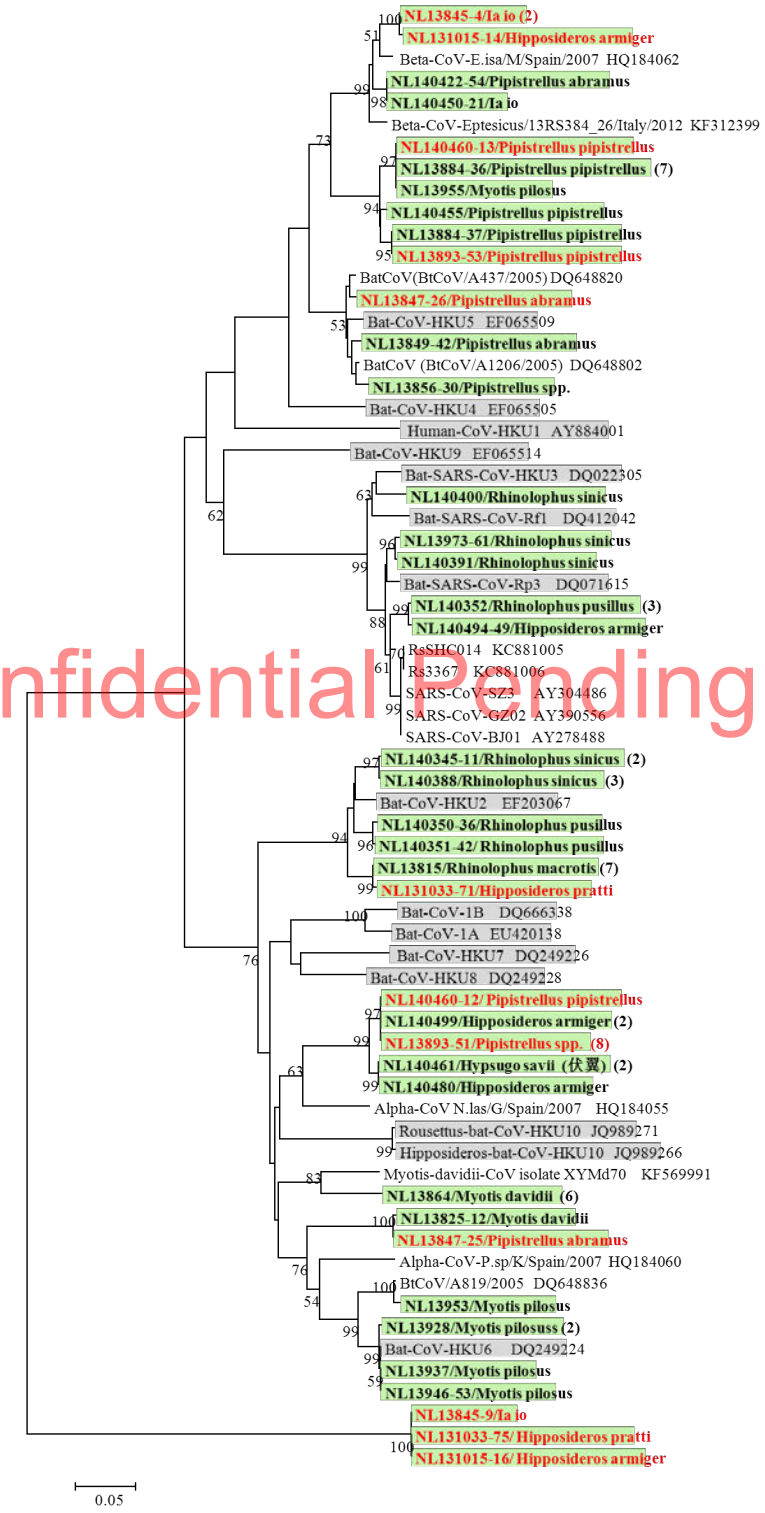
| | | Anal | Oral | Fecal | Blood | Serum | tissue |
|---|---|---|---|---|---|---|---|
| Jan. 2014 | Mengla, Yunnan | 164 | -- | -- | -- | -- | -- |
| Mar. 2014 | Beihai, Guangxi | 30 | -- | -- | -- | -- | -- |
| Apirl 2014 | Shenzhen | 77 | -- | -- | -- | -- | -- |
| May 2014 | Ruyuan, Guangdong | 167 | -- | -- | -- | -- | -- |
| | Chuxiong, Yunnan | 52 | 52 | 103 | -- | 8 | 16 |
| | Jinning, Yunnan | -- | -- | 131 | -- | -- | -- |
| | Mojiang, Yunnan | 25 | 25 | 103 | -- | -- | 3 |
| May-Sep. 2014 | Xianning, Hubei | -- | -- | 583 | -- | -- | -- |
| Jun. 2014 | Guangdong | 77 | -- | -- | -- | -- | -- |
| Jul. 2014 | Hainan | 460 | -- | -- | -- | -- | -- |
| Aug. 2014 | Yichang, Hubei | -- | -- | 114 | -- | -- | -- |
| Sep. 2014 | Guilin,Guangxi | 121 | 122 | -- | 122 | 122 | -- |
| | Guangdong | 335 | 337 | -- | 335 | 335 | -- |
| Jul.--Sep. 2014 | Mojiang, Yunan | -- | -- | 96 | -- | -- | -- |
| Oct. 2014 | Jinning, Yunan | 13 | 13 | 6 | 3 | 3 | 4 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Mojiang, Yunan | 34 | 34 | 100 | 1 | 1 | 1 |
| | Laos | | | 121 | | | |
| | Total | 1555 | 583 | 1357 | 461 | 469 | 24 |

CoV was detected in 14% (336/2329) samples (**Table 2**). Diverse alphacoronaviruses were identified, including isolates closely related to Bat CoV 1A, 1B, HKU2, HKU6, HKU7, HKU8 and HKU10. Groups of novel alphacoronaviruses were discovered in a variety of bat species (**Fig 3**). **Novel SARS-like coronaviruses were detected in *Rhinolophus* bats collected in different regions of Guangdong province.** Diverse novel betacoronaviruses related to HKU5 were detected in *Pipistrellus* bats and *Ia io* in Guangdong and in *Aselliscus stoliczkanus* in Mengla, Yunnan. Novel coronaviruses related to HKU9 were found in *Cynopterus sphinx* and *Rousettus leschenaulti* in Mengla (**Fig 3A**). In addition, sequences significantly divergent to other CoV were obtained from three samples of *Ia io* and *Hipposideros* bats.



B



C

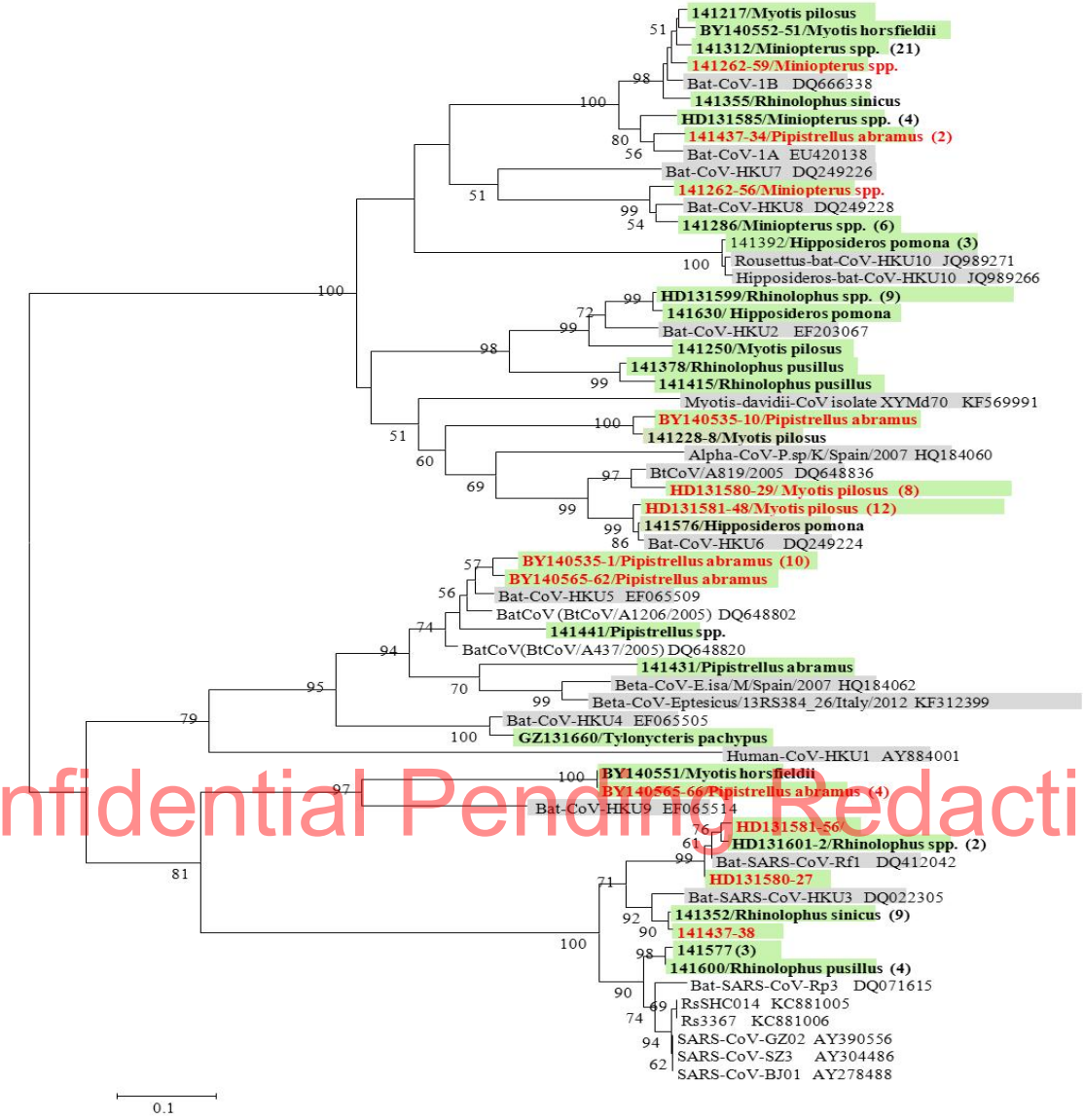





**Figure 3:** Phylogenetic analysis of partial RdRp gene of CoV. CoVs identified in this study are in bold and named by the sample numbers. Sequence amplified from samples co-infected with two CoV strains are indicated in red. (A) CoVs detected in Mengla, Yunnan. (B) CoVs detected in Ruyuan, Guangdong. (C) CoVs detected in other regions in Guangdong.

*2) Complete S gene sequencing and recombination analysis of novel SARS-like CoV*

We amplified the full-length S gene of the novel SL-CoV detected in a *Rhinolophus sinicus* colony in Yunnan Province. In addition to our previously reported Rs3367 and RsSHC014, we now have 24 new full-length S gene sequences from 22 samples. Phylogenetic analysis showed that these SL-CoV are diverse, **and identified two strains of novel SL-CoV more closely related to SARS-CoV than Rs3367** (**Fig 4A**). Our new strains named Rs4841 and Rs4874 share the highest homology to SARS-CoV than any other known SL-CoV, including those we published previously in *Nature*. These viruses are highly similar to SARS-CoV in receptor-binding domain (RBD) sequence but also in N-terminal domain (NTD) (**Figure 4B**). Analysis of the complete S protein shows > 97% amino acid identify to that of SARS-CoV isolates.



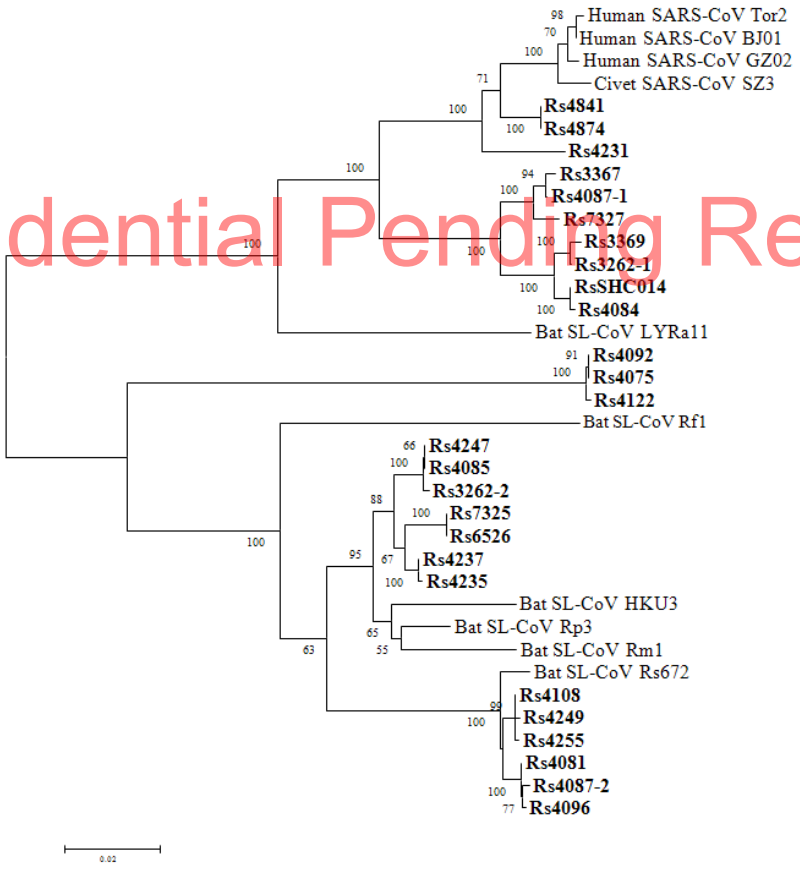



**Figure 4A** Phylogenetic analysis of novel SL-CoVs discovered in Year 1 of this project (**Bold**), based on amino acid sequences of complete S gene.

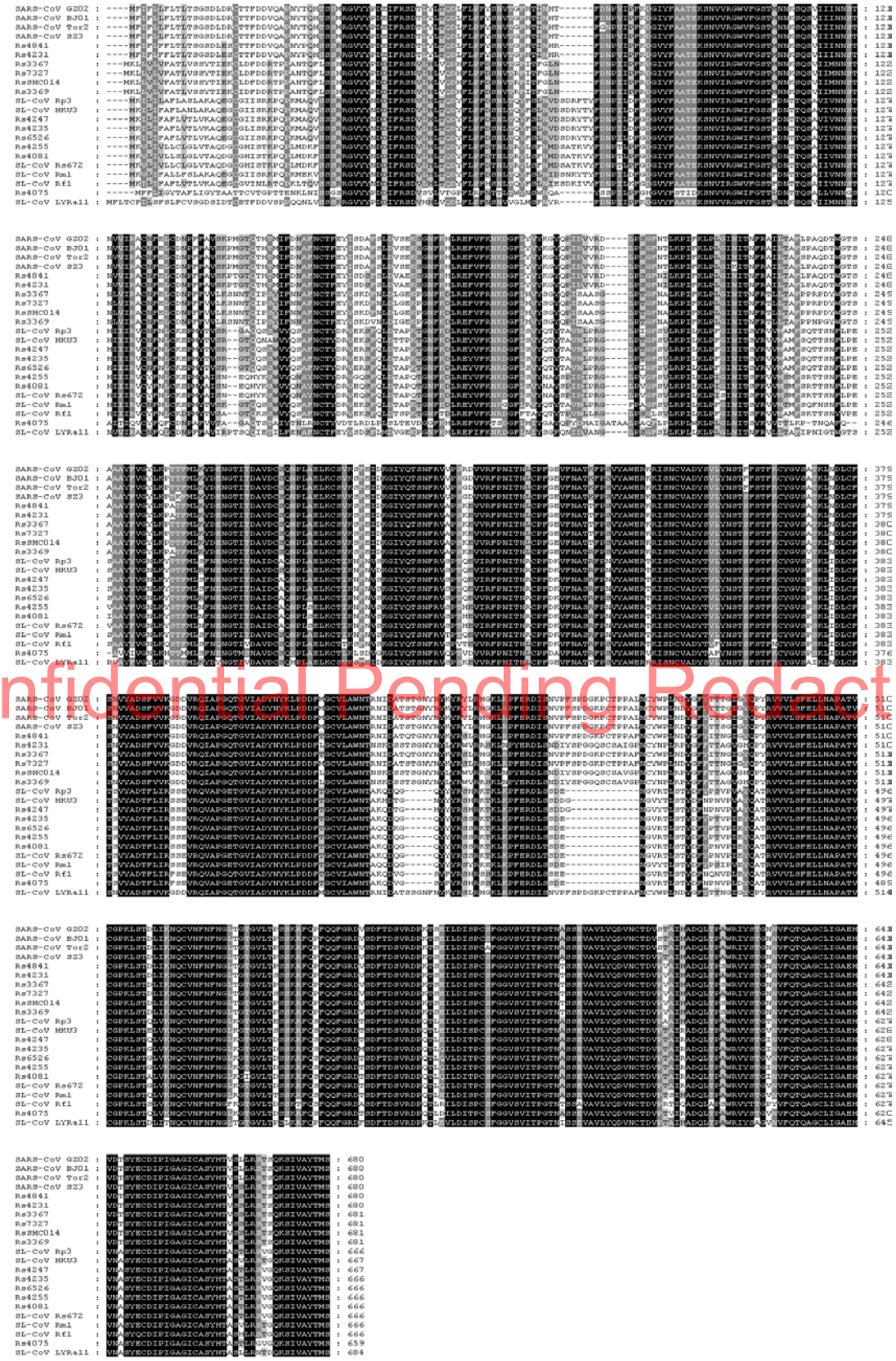


**Figure 4B** Alignment of amino acid sequences of S1 (aa1-680) of SARS-CoV and bat SL-CoVs.

We performed recombination analysis and detected potential recombination events in S genes of multiple SL-CoV strains suggesting that that the region around nt1000 in RBD is a recombination hotspot. In addition, a novel SL-CoV strain (Rs4075) with an NTD sequence distinct from all other SL-CoVs was identified (**Figure 4**). The results suggest that the high genetic diversity of SL-CoV in this colony is related to the frequent recombination.

*3) Virus isolation and characterization*

Isolation on Vero E6 cells was conducted on all CoV PCR-positive samples using an optimized protocol. Repoducible CPE was observed for Rs4841 (the strain closely related to SARS-CoV in both the RBD and NTD region of the S protein). Purified virions displayed typical coronavirus morphology under electron microscopy, and this novel isolate was named SL-CoV-WIV16.

We conducted virus infectivity studies (using HeLa cells expressing or not expressing ACE2 from humans, civets or Chinese horseshoe bats) to determine whether SL-CoV WIV16 can use ACE2 as a cellular entry receptor **(Figure 5).** We found that WIV16 is able to use ACE2 of different origins as an entry receptor.



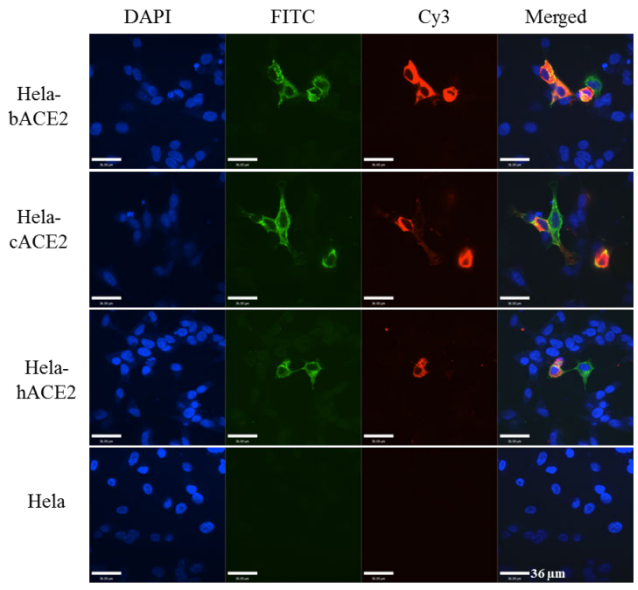


**Figure 5.** Analysis of receptor usage of SL-WIV16 determined by immunofluorescence assay. Determination of virus infectivity in Hela cells without the expression of ACE2. b, bat; c, civet; h, human. Nuclei are stained with DAPI. The columns (from left to right) show staining of nuclei (blue), ACE2 expression (green), virus replication (red) and merged triple-stained images.

To assess its cross-species transmission potential, we conducted infectivity assays in cell lines from a range of species. Our results (**Figure 6)** show that SL-CoV-WIV16 can grow in human alveolar basal epithelial (A549), pig kidney-15 (PK15), *Rhinolophus sinicus* kidney (RSKT), *Macaca mulatta* Kidney cell lines (MK2) and human lung carcinoma (NCI-H292), but not in human cervix (HeLa), Syrian golden hamster kidney (BHK21), *Myotis davidii* kidney (BK), *Myotis davidii* intestine (MDI), *Rousettus leschenaulti* kidney (RLK), *Rhinolophus sinicus* brain (RSBT), *Rhinolophus sinicus* heart (RSHT), *Rhinolophus sinicus* Lung (RSLuT), *Rhinolophus sinicus* intestine (RSI) or *Pteropus alecto* kidney (PaKi) lines.

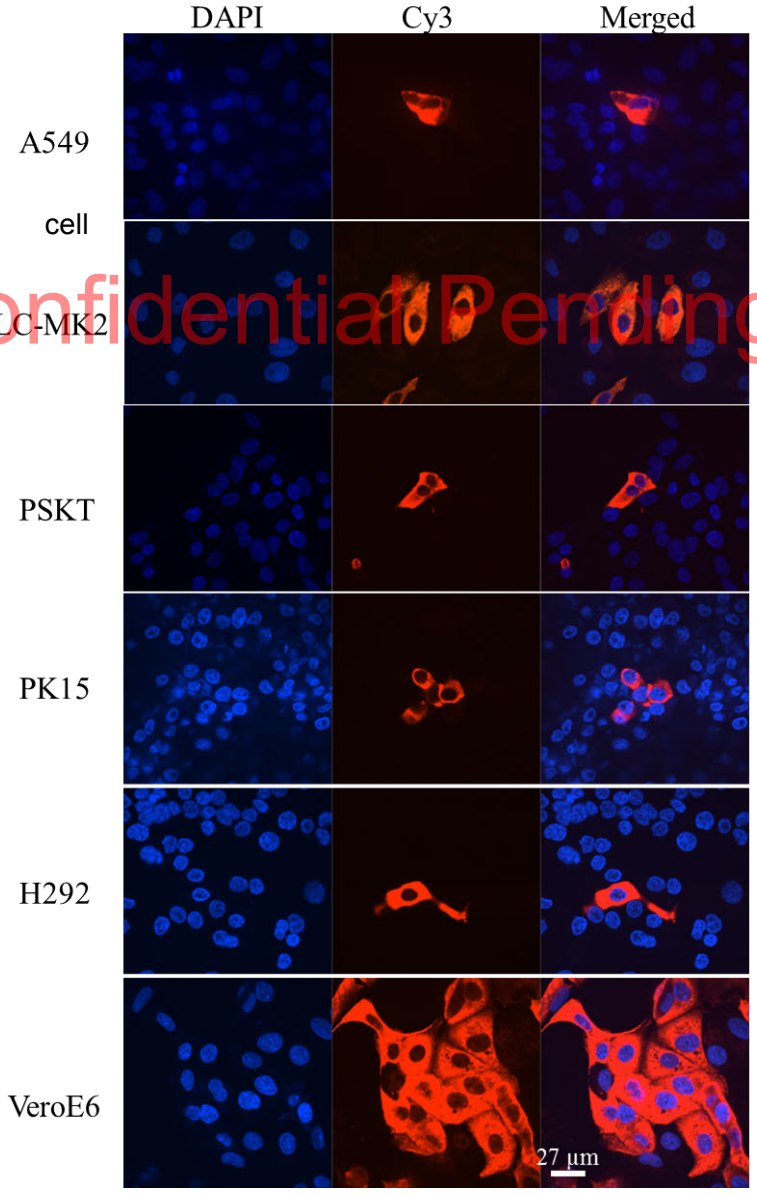





**Figure 6** Cell infection with SL-CoV WIV16 determined by immunofluorescence assay with antibody against SARS-like coronavirus nucleocapsid protein. The columns (from left to right) show staining of nuclei (blue), virus replication (red) and merged double-stained images.

Daszak, Peter, PI

**Accomplishments for Understanding the Risk of Bat Coronavirus Emergence**

**Grant Number 5R01AI110964**

**B4: Opportunities for Training and Professional Development**

In year 1 of this work, we trained undergraduate interns from Columbia University in modeling approaches to understand bat risk of harboring zoonotic CoVs. In the behavioral risk work, we used standardized training materials for all three qualitative behavioral risk data collection methodologies have been created. Materials were used to train six people in New York City and 12 people in Yunnan, China, of which 11 were from three different administrative levels of local government Centers for Disease Control (CDC). The trainees include the Chinese EcoHealth Alliance Field Coordinator and Yunnan Provincial CDC personnel: six researchers from Xiangyun County CDC (4 women, 2 men), two from Yunnan Institute for Endemic Diseases (Yunnan Provincial CDC; 2 men), and three from Lu Feng County CDC (3 men).

## C. PRODUCTS

### C.1 PUBLICATIONS

**Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?**

Yes

**Publications Reported for this Reporting Period**

| Public Access Compliance | Citation |
|---|---|
| N/A: Not Journal | Olival KJ, Weekley CC, Daszak P. Bats and Viruses. Wang L editor. New York: John Wiley & Sons, Inc.; 2015. What we know and need to know |
| Non-Compliant | (b) (4) |
| PMC Journal - In process | (b) (4) |

### C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

### C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

### C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES



**Have inventions, patent applications and/or licenses resulted from the award during the reporting period?**

No

### C.5 OTHER PRODUCTS AND RESOURCE SHARING

**C.5.a Other products**

NOTHING TO REPORT

**C.5.b Resource sharing**

NOTHING TO REPORT

## D. PARTICIPANTS

### D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

| Commons ID | S/K | Name | SSN | DOB | Degree(s) | Role | Cal | Aca | Sum | Foreign Org | Country | SS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (b) (6) | Y | DASZAK, PETER | (b) (6) | (b) (6) | BS,PHD | PD/PI | (b) (6), (b) (4) | | | | | NA |
| | Y | KE, CHANGWEN | | | PHD | Co-Investigator | | | | CDC and Prevention of Guangdong Province | CHINA | NA |
| | Y | ZHANG, YUNZHI | | (b) (6) | PHD | Co-Investigator | | | | Yunnan Institute of Endemic Diseases Control & Prevention | CHINA | NA |
| | Y | ZHU, GUANGJIAN | | (b) (6) | PHD | Co-Investigator | | | | East China Normal University | CHINA | NA |
| (b) (6) | Y | SHI, ZHENGLI | | (b) (6) | PhD | Co-Investigator | | | | Wuhan Institute of Virology | CHINA | NA |
| (b) (6) | N | CHMURA, ALEKSEI A | (b) (6) | (b) (6) | BS | Non-Student Research Assistant | | | | | | NA |
| (b) (6) L | Y | OLIVAL, KEVIN J | (b) (6) | (b) (6) | PHD | Co-Investigator | | | | | | NA |
| (b) (6) | Y | HOSSEINI, PARVIEZ RANA | (b) (6) | (b) (6) | BS,PHD | Co-Investigator | | | | | | NA |
| (b) (6) | Y | ZHANG, SHUYI | | (b) (6) | PHD | Co-Investigator | | | | East China Normal University | CHINA | NA |
| | Y | GE, XINGYI | | | PHD | Co-Investigator | | | | Wuhan Institute of Virology | CHINA | NA |
| (b) (6) | Y | EPSTEIN, JONATHAN H | (b) (6) | (b) (6) | MPH,DVM,BA,PHD | Co-Investigator | | | | | | NA |



**Glossary of acronyms:**
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement

| | |
|---|---|
| Aca - Person Months (Academic) | OT - Other |
| Sum - Person Months (Summer) | NA - Not Applicable |

**D.2 PERSONNEL UPDATES**

**D.2.a Level of Effort**

**Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?**

No

**D.2.b New Senior/Key Personnel**

**Are there, or will there be, new senior/key personnel?**

No

**D.2.c Changes in Other Support**

**Has there been a change in the active other support of senior/key personnel since the last reporting period?**

No

**D.2.d New Other Significant Contributors**

**Are there, or will there be, new other significant contributors?**

No

**D.2.e Multi-PI (MPI) Leadership Plan**



**Will there be a change in the MPI Leadership Plan for the next budget period?**

No

## E. IMPACT

**E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?**

Not Applicable

**E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?**

NOTHING TO REPORT

**E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?**

Not Applicable

**E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?**

| Dollar Amount | Country |
|---|---|
| 50902 | CHINA |

## F. CHANGES

| |
|---|
| **F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE**<br>Not Applicable |
| **F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM**<br>NOTHING TO REPORT |
| **F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS**<br>**F.3.a Human Subjects**<br>No Change |
| **F.3.b Vertebrate Animals**<br>No Change |
| **F.3.c Biohazards**<br>No Change |
| **F.3.d Select Agents**<br>No Change |

## G. SPECIAL REPORTING REQUIREMENTS

### G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

### G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

### G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

### G.4 HUMAN SUBJECTS

**G.4.a Does the project involve human subjects?**

Yes

**Is the research exempt from Federal regulations?**

No

**Does this project involve a clinical trial?**

No

**G.4.b Inclusion Enrollment Data**

Report Attached: Understanding the Risk of Bat Coronavirus Emergence-PROTOCOL-001



**G.4.c ClinicalTrials.gov**

**Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?**

No

### G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

**Are there personnel on this project who are newly involved in the design or conduct of human subjects research?**

Yes

As reported by Dr. Peter Daszak (PI) to NIH in May 2014, all of the following senior/key/other personnel were enrolled in and passed the Human Subjects Research Course provided by the Collaborative Institutional Training Initiative (CITI Program) at the University of Miami (http://citiprogram.org ). The CITI Program is a leading provider of research education content with web based training materials serving millions of learners at academic institutions, government agencies, and commercial organizations in the U.S. and around the world.

Peter Daszak, PI
Zhengli Shi, Co-Investigator
Shuyi Zhang, Co-Investigator
Changwen Ke, Co-Investigator
Jonathan Epstein, Co-Investigator
Kevin Olival, Co-Investigator
Parviez Hosseini, Co-Investigator
Xingyi Ge, Co-Investigator
Guangjian Zhu, Co-Investigator
Yunzhi Zhang, Co-Investigator
Aleksei Chmura, Program Coordinator

### G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

**Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?**

No

**G.7 VERTEBRATE ANIMALS**

**Does this project involve vertebrate animals?**

Yes

**G.8 PROJECT/PERFORMANCE SITES**

| Organization Name: | DUNS | Congressional District | Address |
|---|---|---|---|
| **Primary:** EcoHealth Alliance, Inc. | 077090066 | NY-010 | 460 West 34th Street<br>17th Floor<br>New York NY 100012317 |
| Wuhan Institute of Virology | 529027474 | | Xiao Hong Shan, No. 44<br>Wuchang District<br>Wuhan |
| East China Normal University | 420945495 | | 3663 Zhongshan Beilu<br>Shanghai |

**G.9 FOREIGN COMPONENT**

**Organization Name:** East China Normal University
**Country:** CHINA
**Description of Foreign Component:**
Institu ion of Co Investigators Dr. Shuyi Zhang and Dr. Guangj an Zhu



**Organization Name:** Wuhan Institute of Virology
**Country:** CHINA
**Description of Foreign Component:**
Primary Laboratory and Institute of Co-Investigators Dr. Zhengli Shi and Dr. Xingyi Ge

**Organization Name:** Yunnan Institute of Endemic Diseases Control and Prevention
**Country:** CHINA
**Description of Foreign Component:**
Institution of Co-Investigator Dr. Yunzhi Zhang

**Organization Name:** Center for Disease Control and Prevention of Guangdong
**Country:** CHINA
**Description of Foreign Component:**
Institution of Co-Investigator Dr. Changwen Ke

**G.10 ESTIMATED UNOBLIGATED BALANCE**

**G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?**

No

**G.11 PROGRAM INCOME**

**Is program income anticipated during the next budget period?**

No

G.12 F&A COSTS

Is there a change in performance sites that will affect F&A costs?

No

**Inclusion Enrollment Report**

**Inclusion Data Record (IDR) #:** 166195

**Study Title:** Understanding the Risk of Bat Coronavirus Emergence-PROTOCOL-001

**Foreign/Domestic:** Foreign

## Planned Enrollment Report

**Planned Enrollment Total:** 2,460

**NOTE:** Planned enrollment data exists in the previous format; the PD/PI did not enter the planned enrollment information in the modified format and was not required to do so. Only the total can be provided.

## Cumulative Enrollment Report

**NOTE:** No cumulative inclusion enrollment data exists in the previous inclusion format or modified format. Although prompted to do so, the PD/PI did not enter information in the modified format. No data can be provided.

## A. COVER PAGE

| | |
|---|---|
| **Project Title:** Understanding the Risk of Bat Coronavirus Emergence | |
| **Grant Number:** 5R01AI110964-03 | **Project/Grant Period:** 06/01/2014 - 05/31/2019 |
| **Reporting Period:** 06/01/2015 - 05/31/2016 | **Requested Budget Period:** 06/01/2016 - 05/31/2017 |
| **Report Term Frequency:** Annual | **Date Submitted:** 05/13/2016 |
| **Program Director/Principal Investigator Information:**<br><br>PETER DASZAK , BS PHD<br><br>**Phone number:** (b) (6)<br>**Email:** (b) (6) | **Recipient Organization:**<br><br>ECOHEALTH ALLIANCE, INC.<br>ECOHEALTH ALLIANCE, INC.<br>460 W 34TH ST<br>17TH FLOOR<br>NEW YORK, NY 100012320<br><br>**DUNS:** 077090066<br>**EIN:** 1311726494A1<br><br>**RECIPIENT ID:** |
| **Change of Contact PD/PI:** N/A | |
| **Administrative Official:**<br><br>ALEKSEI CHMURA<br>460 W 34th St., 17th Floor<br>New York, NY 10001<br><br>**Phone number:** (b) (6)<br>**Email:** (b) (6) | **Signing Official:**<br><br>ALEKSEI CHMURA<br>460 W 34th St., 17th Floor<br>New York, NY 10001<br><br>**Phone number:** (b) (6)<br>**Email:** (b) (6) |
| **Human Subjects:** Yes<br>HS Exempt: No<br>Exemption Number:<br>Phase III Clinical Trial: | **Vertebrate Animals:** Yes |
| **hESC:** No | **Inventions/Patents:** No |

## B. ACCOMPLISHMENTS

### B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Zoonotic coronaviruses are a significant threat to global health, as demonstrated with the emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, and the recent emergence Middle East Respiratory Syndrome (MERS-CoV). The wildlife reservoirs of SARS-CoV were identified by our group as bat species, and since then hundreds of novel bat-CoVs have been discovered (including >260 by our group). These, and other wildlife species, are hunted, traded, butchered and consumed across Asia, creating a largescale human-wildlife interface, and high risk of future emergence of novel CoVs.
To understand the risk of zoonotic CoV emergence, we propose to examine 1) the transmission dynamics of bat-CoVs across the human-wildlife interface, and 2) how this process is affected by CoV evolutionary potential, and how it might force CoV evolution. We will assess the nature and frequency of contact among animals and people in two critical human-animal interfaces: live animal markets in China and people who are highly exposed to bats in rural China. In the markets we hypothesize that viral emergence may be accelerated by heightened mixing of host species leading to viral evolution, and high potential for contact with humans. In this study, we propose three specific aims and will screen free ranging and captive bats in China for known and novel coronaviruses; screen people who have high occupational exposure to bats and other wildlife; and examine the genetics and receptor binding properties of novel bat-CoVs we have already identified and those we will discover. We will then use ecological and evolutionary analyses and predictive mathematical models to examine the risk of future bat-CoV spillover to humans. This work will follow 3 specific aims:

Specific Aim 1: Assessment of CoV spillover potential at high risk human-wildlife interfaces. We will examine if: 1) wildlife markets in China provide enhanced capacity for bat-CoVs to infect other hosts, either via evolutionary adaptation or recombination; 2) the import of animals from throughout Southeast Asia introduces a higher genetic diversity of mammalian CoVs in market systems compared to within intact ecosystems of China and Southeast Asia; We will interview people about the nature and frequency of contact with bats and other wildlife; collect blood samples from people highly exposed to wildlife; and collect a full range of clinical samples from bats and other mammals in the wild and in wetmarkets; and screen these for CoVs using serological and molecular assays.

Specific Aim 2: Receptor evolution, host range and predictive modeling of bat-CoV emergence risk. We propose two competing hypotheses: 1) CoV host-range in bats and other mammals is limited by the
phylogenetic relatedness of bats and evolutionary conservation of CoV receptors; 2) CoV host-range is limited by geographic and ecological opportunity for contact between species so that the wildlife trade disrupts the 'natural' co-phylogeny, facilitates spillover and promotes viral evolution. We will develop CoV phylogenies from sequence data collected previously by our group, and in the proposed study, as well as from Genbank. We will examine co-evolutionary congruence of bat-CoVs and their hosts using both functional (receptor) and neutral genes. We will predict host-range in unsampled species using a generalizable model of host and viral ecological and phylogenetic traits to explain patterns of viral sharing between species. We will test for positive selection in market vs. wild-sampled viruses, and use data to parameterize mathematical models that predict CoV evolutionary and transmission dynamics. We will then examine scenarios of how CoVs with different transmissibility would likely emerge in wildlife markets.



Specific Aim 3: Testing p edict ons of CoV inter-species transmission. We will test our models of host range ( e. emergence potent al) experimentally using reverse genetics, pseudovirus and receptor binding assays, and virus infection experiments in cell culture and humanized mice. With bat-CoVs that we've isolated or sequenced, and using live virus or pseudovirus infection in cells of different origin or expressing different receptor molecules, we will assess potential for each isolated virus and those with receptor binding site sequence, to spill over. We will do this by sequencing the spike (or other receptor binding/fusion) protein genes from all our bat-CoVs, creating mutants to identify how significantly each would need to evolve to use ACE2, CD26/DPP4 (MERS-CoV receptor) or other potential CoV receptors. We will then use receptor-mutant pseudovirus binding assays, in vitro studies in bat, primate, human and other species' cell lines, and with humanized mice where particularly interesting viruses are identified phylogenetically, or isolated. These tests will provide public health-relevant data, and also iteratively improve our predictive model to better target bat species and CoVs during our field studies to obtain bat-CoV strains of the greatest interest for understanding the mechanisms of cross-species transmission.

### B.1.a Have the major goals changed since the initial competing award or previous report?

No

### B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: Year 2 NIAID CoV Report Final.pdf

### B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

**For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?**

No

### B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

File uploaded: Year 2 NIAID CoV Report Professional Development.pdf

**B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?**

1) Conference and University lectures: PI Daszak, and Co-investigators Shi, Epstein, Olival, Ge, and Zhang gave >100 invited University and Conference lectures including Forum on Microbial Threats (National Academies of Science), Symposium at École du Val-de-Grâce in Paris, Leadership Roundtable at Concordia University Montreal, 1st annual Global Pandemic Policy Summit at Texas A&M Univ., Intl. Conf. of the Wildlife Disease Association in Australia, Intl. Conf. of Conservation Biol in Montpellier France, Michigan State University, Duke University, WDA, ISID conference, Zoological Society of London Symposium, Future Earth meeting, North American Bat Research Symposium, and others that included specific discussion of the current project and results.

2) Agency and other briefings: PI Daszak and Research Technician Dr. Guangjian Zhu introduced this project to potential collaborators within the following agencies: Forestry Dept of Peoples' Republic of China, FAO, TNC, TRAFFIC, China CDC, and TA Foundation in Beijing China in meetings (2015) and also at presentations at the first Wildlife and Public Health Workshop in China (2016) co-hosted by EcoHealth Alliance, the State Forestry Administration of China, and China CDC.

3) Public outreach: PI Daszak presented this work to members of the NIH, NSF, DoD, IUCN, EPA, and the general public, at an EcoHealth Alliance meeting hosted by the Cosmos Club, Washington D.C. (2015); PI Daszak and Co-investigator Zhu reported on this project at a Wildlife Trade and Public Health Seminar, Beijing (2016); PI Daszak introduced this project in a lecture on Pandemics at a New York Academy of Science Panel (2016); Co-PI Y-Z Zhang presented project and results-to-date to department heads and senior researchers at Infectious Disease Departments of four Yunnan Hospitals (2015)

**B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?**

Specific Aim 1: Assessment of CoV spillover potential at high risk human-wildlife interfaces.

- Given the reduced amount of wildlife in the local markets within Southern China, and the continued expansion of the Chinese wildlife trade within SE Asia, we would like to conduct short field trips to assess markets, identify wildlife in them, and sample species of bats and other high-risk hosts in countries that neighbor China (Myanmar, Vietnam, Cambodia, Lao PDR) and others that supply wildlife to the international trade to China (Thailand, Malaysia, Indonesia. EcoHealth Alliance has other activities in these countries which would provide leverage to reduce costs of fieldwork, and samples would be tested in Wuhan, China.

- Following the successful collection of ethnographic interviews and focus groups in Year 2, we will be analyzing the qualitative data collection from Years 1 and 2.

- Finalize and conduct survey collection tool for a network study of wildlife farmers using a questionnaire to characterize and map the wildlife value chain.



- After the success of our pilot studies in Year 2, we will continue targe ed (at ndividuals with high risk of exposure to bats), integrated behavioral and biological survey work in Yunnan and expand to Guangxi and Guangdong provinces.

- We will commence our anonymized, surveillance data collection from acutely ill hospital in-patients who satisfy syndromic eligibility criteria; have complete medical records; non-normative laboratory confirmed diagnostic results; and suspected acute viral infection. Eligibility criteria are: (a) suspected acute viral infection; (b) fever > 38˚C, and (c) presenting symptoms of at least one of the following:
•Encephalitis of unknown origin
•Hemorrhagic fever of unknown origin
•Respiratory disease
oInfluenza-like illness (ILI)
oSevere Acute Respiratory like Illness (SARI)
•Rash
•Diarrhea
Some patients with particular infections such as with HIV, HCV, and HBV, may be excluded from the study on that basis. Hospital surveillance has the advantage of monitoring an acutely ill population. Anonymized, passive hospital surveillance allows for data collection and viral testing from all eligible hospital patients thereby limiting population sample bias and increasing the likelihood of identifying positive cases. The strengths of this approach are enormous: an unbiased patient population; prospectively collected, anonymized patient data; a low resource effort with a high efficiency design; and impactful research potential for both case series and case control studies. We have already secured approval from the Institutional Review Boards of the Wuhan School of Public Health and Hummingbird IRB.

Specific Aim 2: Receptor evolution, host range and predictive modeling of bat-CoV emergence risk.
Future steps to optimize the model of role of species diversity in CoV emergence risk will include:

- Test and implement our respondent-driven survey to collect specific data on the diversity, abundance, and turnover of species along the wildlife trade network in south China.

- Model viral mixing across the full range parameters found along the wildlife trade network to identify the trade nodes with highest mixing potential. This will include a network analysis of market facility/site connectivity including wild harvest sites, wildlife farming operations, transit holding facilities, and small and large wildlife markets.

- Phylogeographic study of bat-CoV to better understand the geographic distribution and evolution of bat-CoV genetic diversity in south

China.

- Phylogeographic study of bat host (Rhinolophus) species to assess the connectivity of bat populations and infer their historical movements and demographic history to improve our understanding of CoV transmission among bat populations in southern China. Preliminary sequences data has been generated and will be completed and analyzed.

- Cophylogenetic analyses of bat host and CoV phylogenies to assess frequency of cross-species transmission. Comparison of Alpha- and Beta-CoV cophylogenetic patterns building on Year 2 analyses using published sequences and also including Spike gene and additional sequences obtained in Year 2.

- Test and implement our respondent-driven survey to assess diversity, abundance, and turnover of species along the wildlife trade network.

- Examine co-evolutionary congruence of bat-CoVs and their hosts using both functional (receptor) and neutral genes;

- Parameterize mathematical models that predict CoV evolutionary and transmission dynamics
- Continued surveillances of SARS-like CoVs and lineage C betacoronaviruses (MERS-related CoVs) in Southern China;

- Full-length genome sequencing and evolution analysis of SARS-like coronaviruses identified from different bat species and different geographical locations across China;

- Full-length genome sequencing and evolution analysis of Lineage C betacoronaviruses identified from different bat species and different geographical locations across China;

- Full-length genome sequencing and evolution analysis of HKU9-related and HKU10-related bat coronaviruses in China;

Specific Aim 3: Testing predictions of CoV inter-species transmission. The following experiments will be undertaken in Year 2:

- Humanized mice with human ACE2 receptors will be infected with WIV1 and the two rescued chimeric SARS-like coronaviruses to determine the tissue tropism and pathogenicity of bat SL-CoV

- Isolation of novel bat coronaviruses. Live virus or pseudovirus will be used to infect cells of different origin or expressing different receptor molecules. Spillover potential for each isolated virus will be assessed.

- An infectious clone of full-length MERS-CoV will be constructed using reverse genetic method. Using the S sequence of different MERS-related viruses identified from Chinese bats, he chimeric viruses with S gene of bat MERS-related coronaviruses and backbone of the nfectious c one of MERS-CoV wil be const ucted o study the receptor usage and infectivity of bat MERS-related co onavirus.



- Surveillance of infection in human populations by SARS-like CoVs. This work will be performed at locations in Yunnan, Guangxi, and Guangdong provinces, in previously identified areas with human populations of high risk of exposure to bats. PCR and ELISA will be used, respectively, for detection of viral replicase gene and antibodies against the viral nucleocapsid protein.

**Year 1 Report:** Understanding the Risk of Bat Coronavirus Emergence

**Award Number:** 1R01AI110964-02

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**Section B: Accomplishments**

**B.1 What are the Major Goals of the Project**

Zoonotic coronaviruses are a significant threat to global health, as demonstrated with the emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, and the recent emergence Middle East Respiratory Syndrome (MERS-CoV). The wildlife reservoirs of SARS-CoV were identified by our group as bat species, and since then hundreds of novel bat-CoVs have been discovered (including >260 by our group). These, and other wildlife species, are hunted, traded, butchered and consumed across Asia, creating a largescale human-wildlife interface, and high risk of future emergence of novel CoVs. To understand the risk of zoonotic CoV emergence, we propose to examine 1) the transmission dynamics of bat-CoVs across the human-wildlife interface, and 2) how this process is affected by CoV evolutionary potential, and how it might force CoV evolution. We will assess the nature and frequency of contact among animals and people in two critical human-animal interfaces: live animal markets in China and people who are highly exposed to bats in rural China. In the markets we hypothesize that viral emergence may be accelerated by heightened mixing of host species leading to viral evolution, and high potential for contact with humans. In this study, we propose three specific aims and will screen free ranging and captive bats in China for known and nove coronaviruses; screen people who have high occupational exposure to bats and other wildlife; and examine the genetics and receptor binding properties of novel bat-CoVs we have already identified and those we will discover. We will then use ecological and evolutionary analyses and predictive mathematical models to examine the risk of future bat-CoV spillover to humans. This work will follow 3 specific aims:



Specific Aim 1: Assessment of CoV spillover potential at high risk human-wildlife interfaces. We will examine if: 1) wildlife markets in China provide enhanced capacity for bat-CoVs to infect other hosts, either via evolutionary adaptation or recombination; 2) the import of animals from throughout Southeast Asia introduces a higher genetic diversity of mammalian CoVs in market systems compared to within intact ecosystems of China and Southeast Asia; We will interview people about the nature and frequency of contact with bats and other wildlife; collect blood samples from people highly exposed to wildlife; and collect a full range of clinical samples from bats and other mammals in the wild and in wetmarkets; and screen these for CoVs using serological and molecular assays.

Specific Aim 2: Receptor evolution, host range and predictive modeling of bat-CoV emergence risk. We propose two competing hypotheses: 1) CoV host-range in bats and other mammals is limited by the phylogenetic relatedness of bats and evolutionary conservation of CoV receptors; 2) CoV host-range is limited by geographic and ecological opportunity for contact between species so that the wildlife trade disrupts the 'natural' co-phylogeny, facilitates spillover and promotes viral evolution. We will develop CoV phylogenies from sequence data collected previously by our group, and in the proposed study, as well as from Genbank. We will examine co-evolutionary congruence of bat-CoVs and their hosts using both functional (receptor) and neutral genes. We will predict host-range in unsampled species using a generalizable model of host and viral ecological and phylogenetic traits to explain patterns of viral sharing between species. We will test for positive selection in market vs. wild-sampled viruses, and use

data to parameterize mathematical models that predict CoV evolutionary and transmission dynamics. We will then examine scenarios of how CoVs with different transmissibility would likely emerge in wildlife markets.

Specific Aim 3: Testing predictions of CoV inter-species transmission. We will test our models of host range (i.e. emergence potential) experimentally using reverse genetics, pseudovirus and receptor binding assays, and virus infection experiments in cell culture and humanized mice. With bat-CoVs that we've isolated or sequenced, and using live virus or pseudovirus infection in cells of different origin or expressing different receptor molecules, we will assess potential for each isolated virus and those with receptor binding site sequence, to spill over. We will do this by sequencing the spike (or other receptor binding/fusion) protein genes from all our bat-CoVs, creating mutants to identify how significantly each would need to evolve to use ACE2, CD26/DPP4 (MERS-CoV receptor) or other potential CoV receptors. We will then use receptor-mutant pseudovirus binding assays, in vitro studies in bat, primate, human and other species' cell lines, and with humanized mice where particularly interesting viruses are identified phylogenetically, or isolated. These tests will provide public health-relevant data, and also iteratively improve our predictive model to better target bat species and CoVs during our field studies to obtain bat-CoV strains of the greatest interest for understanding the mechanisms of cross-species transmission.

**B.1a Have the major goals changed since the initial competing award or previous report?** No.

**B.2 What was accomplished under these goals?**

***Specific Aim 1: Assessment of CoV sp llover potential at high risk human-wildlife interfaces***



In year 2, we continued and expanded the qualitative research begun at the end of Year 1. In addition, a community based integrated biological behavioral surveillance system was developed and pilot tested to identify specific animal exposure risk factors associated with biological evidence of exposure to SARS-like CoV (i.e., seropositive status).

**QUALITATIVE RESEARCH**

Targeted, in-depth ethnographic interviews were conducted with 47 individuals (18 women; 29 men) in rural Southern China where wildlife trade routes have been documented. Yunnan, Guangxi and Guangdong provinces were specifically selected for study because they have large wildlife populations, a diversity of wildlife species and numerous live animal markets. Individuals who were 18 years of age or older and who were able to provide informed consent were eligible to participate. Twenty-three (49%) in-depth interviews were conducted in Yunnan province at nine different sites, 24 (51%) in Guangxi province at six different sites. In addition, one focus group was conducted in Guangxi. The study was approved by the Institutional Review Boards of the Wuhan School of Public Health and Hummingbird IRB.

Recruitment sites in each province included forested areas or preserves, wildlife farms, hunting areas, wildlife restaurants, live animal markets, caves where people dwell or collect guano and residential areas/farms near known bat caves or roosts. Participants were recruited primarily through local contacts developed as part of wildlife conservation and health research conducted by team members over the past decade. Contacts including wildlife conservationists and researchers, local government health outreach workers and wildlife farmers facilitated introductions and provided referrals. To achieve a sample with sufficient representation of categories of interest, participants were recruited using

purposive sampling, which provides minimum quotas in terms of sex, age and wildlife exposure setting (e.g., live animal market, forest preserve).

The five core themes that guided the in-depth discussions are: 1) human-animal contact, 2) unusual illness experience and response, 3) socioeconomics and daily living, 4) biosafety and 5) human environments and movement/travel. An ethnographic interview guide was developed with examples of questions that could be asked for each theme. In addition, field based participant-observation was ongoing throughout the study and involved observing and talking informally with people in their own natural setting. Field notes were maintained of these ongoing observations and discussions.

Table 1: Species Observed in Wetmarkets in Guangdong Province from 2015 - 2016

| Genus species | Common Name |
|---|---|
| *Prionailurus bengalensis* | Leopard Cat |
| *Nyctereutes procyonoides* | Raccoon Dog |
| *Sus scrofa* | Wild Boar |
| *Lepus sinensis* | Chinese Hare |
| *Arctonyx collaris* | Hog Badger |
| *Hystrix brachyura* | Porcupine |
| *Marmota sp.* | Marmot |
| *Rhizomes sinensis* | Bamboo Rat |
| *Erinaceus sp.* | Hedgehog |
| *Mustela pu o ius* | Ferrets |
| *Muridae* | Rat (species unknown) |
| *Myocastor coypus* | Nutria |
| *Vulpes sp.* | Fox |
| *Mustela sibirica* | Siberian weasel |
| *Paguma larvata* | Masked Palm Civet |
| *Felis catus* | Domestic Cat |
| *Canis lupus familiaris* | Domestic Dog |
| *Cervinae* | Sambar Deer |
| *Ovis aries* | Sheep |
| *Capra sp.* | Domestic Goat |
| *Ratus norvegicus* | Common Rat |

Interviews were conducted between March and June 2105 by 10 trained interviewers, none of whom had social science training. Interviewers conducted between one and 22 interviews; three interviewers conducted two thirds of all interviewers. Interviews lasted between 20 and 60 minutes, and were tape-recorded and transcribed verbatim before they were translated into English. All participants received cooking oil valued at US$10 in appreciation of their time.

The data are currently being coded and an analytic database is being constructed. Initial insights include observations by a number of participants, especially those who are older, that there has been a decrease in wildlife in the surrounding environment. This decrease is attributed to many factors including infrastructure development. The government has invested resources to build new roads and renovate local infrastructure with the intention of increasing tourism. This has reduced forested area.



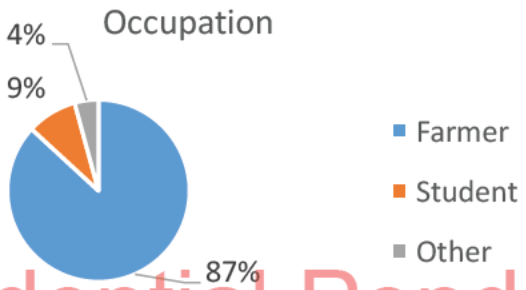
Observations by research staff in live animal markets in Guangzhou found wildlife to be plentiful (see Table 1), although no bats were seen for sale during the observation period. In contrast, wildlife was not found in live animal markets at the sites we visited in either Yunnan or Guangxi. This is a change from previous research visits to the same or similar communities, when bats, rodents and wild boar could be found. Locals in Yunnan and Guangxi attribute the change to conservation law enforcement. The success of conservation enforcement may have moved hunting and trapping underground and made the capture of local wildlife less economically feasible than other income generating activities.

Preliminary analyses are underway. Three specific studies in support of Specific Aim 1 are being developed: the changing wildlife trade in Southern China, the economics of wildlife farming, and zoonotic disease risks resulting from a rapidly changing wildlife trade.

**INTEGRATED BIOLOGICAL BEHAVIORAL SURVEILLANCE PILOT STUDY**

Currently, mechanisms of zoonotic viral spillover are unknown. In order to evaluate potential risk factors, it is necessary to measure both exposure and outcome data. Therefore, a behavioral risk survey was developed that assessed both animal exposure and experiences of unusual illness both during lifetime and in the past 12 months. In addition, participants were requested to provide serum to test for previous exposure to SARS-like CoV. The integrated surveillance was pilot tested in October 2015 among residents living near bat caves or roosts where SARS-like-CoV has been previously detected in the bat population in Jinning County, Yunnan. Please view the full survey here:

https://www.dropbox.com/s/sv62neywuvl027r/Questionnaire%20Complete.docx?dl=0




Of 218 participants, 139 (64%) were women and 79 (36%) were men, with a mean age of 48 (range: 12-80). Most reported being farmers (87%, and see chart to left); a majority were long term residents (97%). Animal exposures in the past year were extensive, including general (e.g., buying live animals at markets [61%]) and intimate (e.g., being scratched or bitten [9%], s aughter [38%]). In fact, two-thirds of participants reported handling recently killed animal parts and 2 out of 5 reported slaughtering animals. Only 20 (9%) participants reported known exposure to bats.



Standardized syndromic case definitions informed questions concerning unusual illness experience (e.g. severe acute respiratory infections [SARI], influenza-like illness [ILI]). Lifetime, 12 month and unusual illness experience in family for the past 12 months were assessed for all participants. In the past year, SARI was reported by 4 (2%) respondents and for 4 additional family members. Table 2 provides data for all unusual illness experience assessed. None of the participants were found to be seropositive for SARS-like CoV.

Table 2. Unusual Illness Experience

| Symptoms | Ever | Past 12 months | Family (12m) |
|---|---|---|---|
| Severe Acute Respiratory Infections (SARI) | 15 (6.9%) | 4 (1.8%) | 4 (1.8%) |
| Influenza Like Illness (ILI) | 54 (24.8%) | 16 (7.3%) | 26 (11.9%) |
| Encephalitis | 19 (8.7% | 4 (1.8%) | 3 (1.4%) |
| Hemorrhagic Fever | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Fever with Diarrhea /Vomiting | 12 (5.5.%) | 2 (0.9%) | 3 (1.4%) |
| Fever with Rash | 2 (0.9%) | 2 (0.9%) | 3 (1.4%) |

Although the sample size was small, animal exposures among those who reported unusual illness experiences in the past 12 months were evaluated. Of the four respondents who reported SARI symptoms, 75% reported: raising animals, animals in the home, preparing recently killed animals and buying live animals; 50% reported slaughter. Among the 16 respondents who reported ILI symptoms, 12 (75%) reported handling/preparing recently killed animals, 11 (69%) Handling live animals or having animals in the home, 10 (63%) reported slaughtering/killing animals or buying live animals at wet market, 9 (56%) raised live animals, 7 (44%) reported a pet, and 1 (6%) reported animal feces near food or eating animal touched or damaged food, hunting, or eating raw/undercooked animal products. Finally, among the four respondents who reported encephalitis symptoms, 3 (75%) reported hunting, handling or raising animals, 2 (50%) reported animals in the home, 1 (25%) reported having animals as pets, slaughtering/killing animals, or having bought live animals at wet market.

Respondents were asked about the source of their unusual illnesses. None reported any kind of animal exposure as a potential source of infection and most stated they had no idea how they had become infected. However, when asked about potential behavior changes made at live animal markets in the last 12 months, participants reported a great deal of change. In particular, respondents reported buying live animals less often (38%), only buying farmed wildlife (54%) or buying meat at the supermarket (23%). (See Table 3).

**Table 3: Behavior Change at Wet Market in the last 12 months**

| Behavior | N | (%) |
|---|---|---|
| Wear a mask | 4 | (3.0) |
| Wear gloves | 5 | (3.8) |
| Wash hands | 80 | (60.6) |
| Sometimes shop for meat at supermarket | 30 | (22.7) |
| Buy live animals less often | 50 | (37.9) |
| Buy only farmed wildlife | 71 | (53.8) |
| No longer buy wildlife at wet market | 39 | (29.5) |



The results of this pilot study conducted with a largely female farmer population found high levels of unusual illness, as well as high levels of exposure to animals. There was a notable lack of know edge of animals' ability to transmit infection Despite this lack of knowledge, there may be a sense of unease about animal exposures, given the fairly dramatic behavior changes reported at live animal markets. The finding of a reduction in wildlife purchase may be due to sensitivity to the legality of wildlife trade, biasing respondents towards not admitting purchasing wildlife. Although, there were no participants seropositive for SARS-like CoV, serological data may add support to the findings from self-reported syndromic surveillance, once serological assays are optimized.

In preparation for full implementation of the integrated biological behavioral surveillance, the survey has been programmed as an application for use on either a mobile device or computer. Electronic data collection will facilitate survey implementation in the field and quality control of the data being collected. Four field team leads were trained on behavioral survey data collection, data collection technologies (the tablet application) and analysis.

Nucleic acid test results of human biological samples

*Testing High-Risk Human Populations for Coronavirus Infection*

Surveillance of CoV infections in human populations by SARS-like CoVs was significantly expanded in Year 2, including both custom-built ELISA serology (an assay developed by the Wuhan Institute of Virology to test antibodies against the N protein of SL-CoV) and PCR detection of viral RNA.

*Serological test for SL-CoV antibodies in human samples from Jinning, Yunnan Province*
In order to assess past exposure to bat CoVs, 223 human sera samples were collected in villages in proximity to the bat habitat from which two SL-CoVs with potential for interspecies infection, WIV1 and WIV16, were discovered in our previous research. An ELISA developed by the Wuhan Institute of Virology was used to test antibodies against the N protein of SL-CoV. A number of human specimens generated high OD values and neutralization test to WIV1 and WIV16 was then performed. These findings are encouraging; however, no neutralization antibodies were detected. In Year 3, we will continue to validate and optimize these ELISA assays and other serological tests to obtain data on past CoV exposure.

*PCR test for CoV Nucleic Acid in human samples from several Provinces*
We tested 405 individual human samples for CoV RNA to identify evidence of active infection in human populations and to obtain sequence data on strain variation. Individual samples (4 each) were pooled prior to nucleic acid extraction then tested using PCR. When a group tested positive, we then conducted the confirmation test in the individual samples. One single sample (14XN611) from someone who had identified as having had a fever and suffered both a cough and headache in the past 7-days was then identified to be positive for HCoV-HKU1. The low number of PCR detections in human specimens is not unexpected, and will be improved in Year 3-5 by better targeting syndromic individuals for specimen collection and continuing to optimize PCR assays. Refined serological assays (above) will provide sufficient data to assess past exposure to specific CoV lineages, and optimizing of PCR detections will allow for more CoV positive human sequences moving forward.



***Specific Aim 2: Receptor evolution, host range and predictive modeling of bat-CoV emergence risk***

*Bat CoV PCR detection and sequencing from live-sampled bat populations*
We collected 1,714 anal swab samples, 677 fecal samples, 53 blood samples, and 38 serum samples from 15 bat genera in Guangdong, Yunnan, Sichuan, Hubei, Hunan, Guizhou, Guangxi provinces (Table 4).

**Table 4 Bat Samples collected for CoV surveillance in 2015**

| Sample date | Sample location | Anal | Fecal | Blood | Serum |
|---|---|---|---|---|---|
| Mar. 2015 | Huidong, Guangdong | 69 | -- | -- | -- |
| Jun. 2015 | Guangdong | 495 | -- | 12 | -- |
| Apr. 2015 | Menglun, Yunnan | 51 | -- | -- | -- |
| May 2015 | Jinning, Yunnan | -- | 193 | -- | -- |
| May. 2015 | Mojiang, Yunnan | 93 | -- | -- | -- |
| Oct. 2015 | Jinning, Yunnan | 30 | -- | -- | -- |

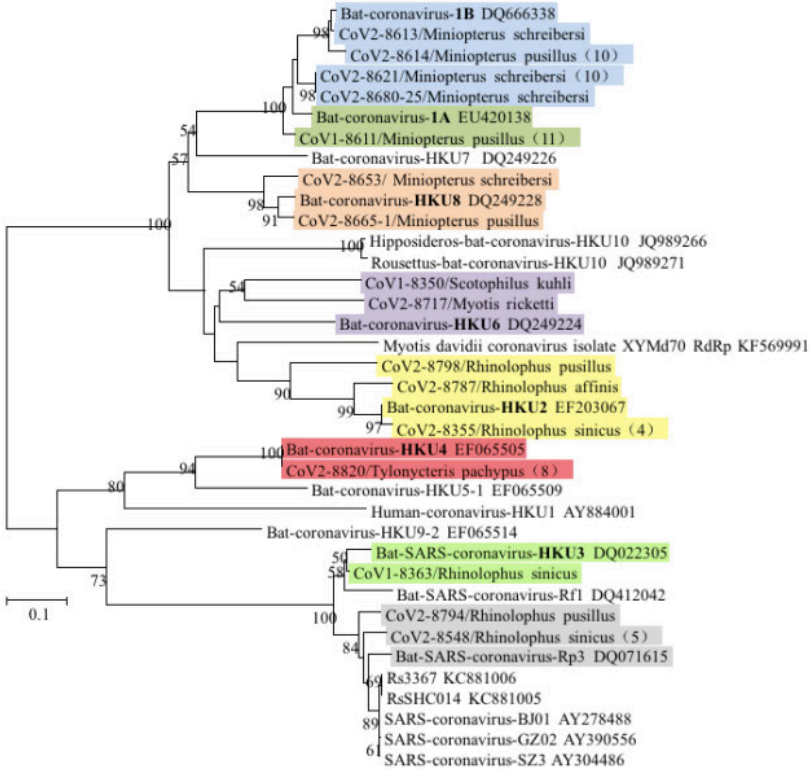
| | | | | | |
|---|---|---|---|---|---|
| Dec, 2015 | Jingna, Yunnan | 15 | 15 | 13 | 13 |
| | Miaoxin, Yunnan | | 42 | 28 | 25 |
| Jul, 2015 | Zigong, Sichuan | 128 | -- | -- | -- |
| Aug, 2015 | Hubei | | 332 | | |
| Sep, 2015 | Xianning, Hubei | | 95 | | |
| Aug, 2015 | Jishou, Hunnan | 204 | | | |
| Aug-Sep, 2015 | Tongren, Guizhou | 438 | | | |
| Dec, 2015 | Longzhou, Guangxi | 191 | | | |
| | Total | 1714 | 677 | 53 | 38 |

We tested 2,256 samples for CoV RNA and 280 tested positive. The total positive rate is 12.4% (Table 5). Diverse alphacoronaviruses related to Bat CoV 1A, 1B, HKU2, HKU6, HKU7, HKU8 and HKU10 were identified; SARS-like coronaviruses were detected in *Rhinolophus* bats in both Yunnan and Guangdong (Fig 1). Novel lineage B betacoronaviruses more distantly related to SARS-CoV than other SL-CoVs were detected in *Vespertilo superans* in Sichuan. HKU4-related coronaviruses were found in *Tynolycteris pachypus* in Guangdong and Guangxi while HKU5-related coronaviruses were found to be highly prevalent in *Vespertilio superans* in Zigong, Sichuan (41 bats out of 128 tested positive).

**Table 5 Test result of bat CoV surveillance in 2015 – 12% positive (280/2,256)**

| | Yunnan | Guangdong | Hubei | Sichuan | Guangxi | Guizhou | Hunan | Total |
|---|---|---|---|---|---|---|---|---|
| **Bat species** | **No.positive/No.tested** | | | | | | | |
| *Rhinolophus spp.* | 47/98 | 12/103 | | | | 16/225 | 8/63 | 83/489 |
| *Hipposideros spp.* | 0/35 | 0/51 | 26/152 | | | 0/131 | 0/91 | 26/460 |
| *Ia io* | | | | | | 0/3 | | 0/3 |
| *Pipistrellus spp.* | 1/1 | 0/19 | | | | 0/2 | 0/4 | 1/26 |
| *Miniopterus spp.* | 6/7 | 34/83 | | | | 2/6 | | 42/96 |
| *Eonycteris spp.* | 0/3 | | | | | | | 0/3 |
| *Vespertilio superans* | | | | 41/128 | | | | 41/128 |
| *Myotis spp.* | | 1/38 | | | | 0/70 | 0/35 | 1/143 |
| *Taphozous spp.* | 0/25 | | | | | 0/1 | | 0/26 |
| *Tynolycteris pachypus* | | 8/25 | | | 27/191 | | | 35/216 |
| *Scotophilus kuhlii* | | 1/1 | | | | | | 1/1 |
| *Eptesicus fuscus* | | 0/1 | | | | | | 0/1 |
| *Tadrida spp.* | | 0/5 | | | | | | 0/5 |
| *Barbastella* | | | | | | | 0/1 | 0/1 |
| *Nyclatus velutiaus* | | | | | | | 0/10 | 0/10 |
| Fecal samples | 28/468 | | 22/180 | | | | | 50/648 |
| **Sub-total** | 82/637 | 56/326 | 48/332 | 41/128 | 27/191 | 18/438 | 8/204 | **280/2256** |

**A**






**B**

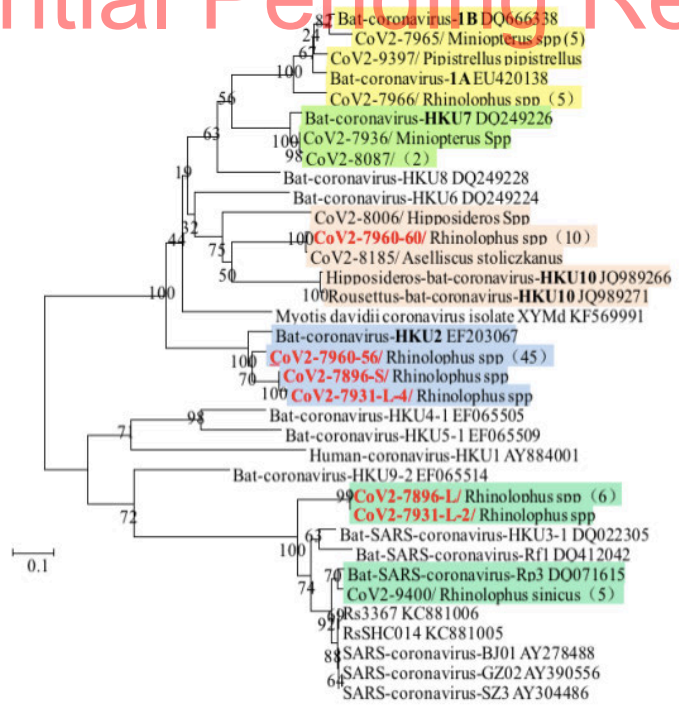



**Fig 1** Phylogenetic analysis of partial RdRp gene of CoV (440-nt partial sequence). CoVs identified in 2015 are named by the sample numbers. Sequence amplified from samples co-infected with two CoV strains are indicated in red. (A) CoVs detected in Guangdong. (B) CoVs detected in Yunnan.

*Cophylogenetic analysis of CoV host switching*

We completed preliminary cophylogenetic analysis of bat host – CoV sequences using data published in the literature and available on Genbank. Two figures from these analyses are highlighted below (Figs 2 and 3) and these methods are currently being extended using partial RdRp CoV and bat mitochondrial DNA sequences from a large number of bat specimens found CoV positive in Year 2 (Table 5, above).

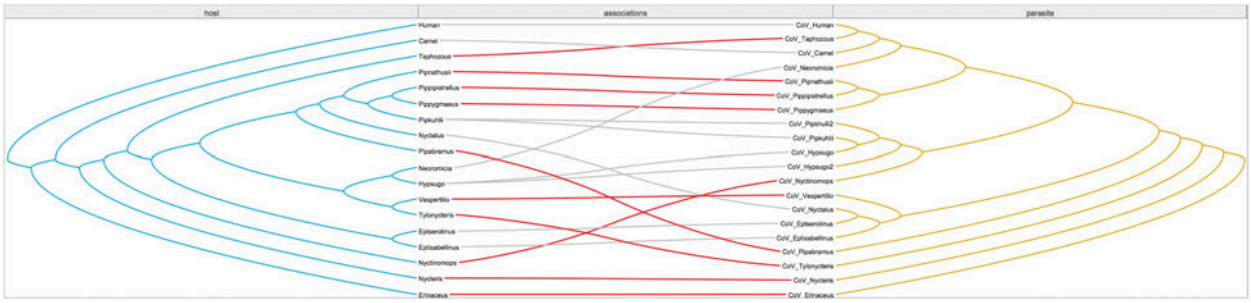



Figure 2: Tanglegram depicting the pattern of infection of bats (and outlier mammalian hosts) by CoVs. The CoV tree was reconstructed from DNA sequences available in GenBank (partial RdRp gene) using Bayesian inference (MrBayes). The topology of host tree was reconstructed using the mammal and bat phylogenies available in Asher & Helgen (2010) and Agnarsson et al. (2011), using methods our group has previously applied to bat parasite cophylogenetic analyses (Lei and Olival 2014). Both ParaFit (ParaFitGlobal = 64957.61, p-value = 0.001) and PACo (m2 = 366.44, p-value = 0.013) provided evidence for significant global congruence between the two topologies, and evidence for coevolution. Lines connecting taxa indicate host-CoV associations. Red lines indicate significant host-CoV associations as indicated by ParaFit ($p \leq 0.05$, 999 permutations).



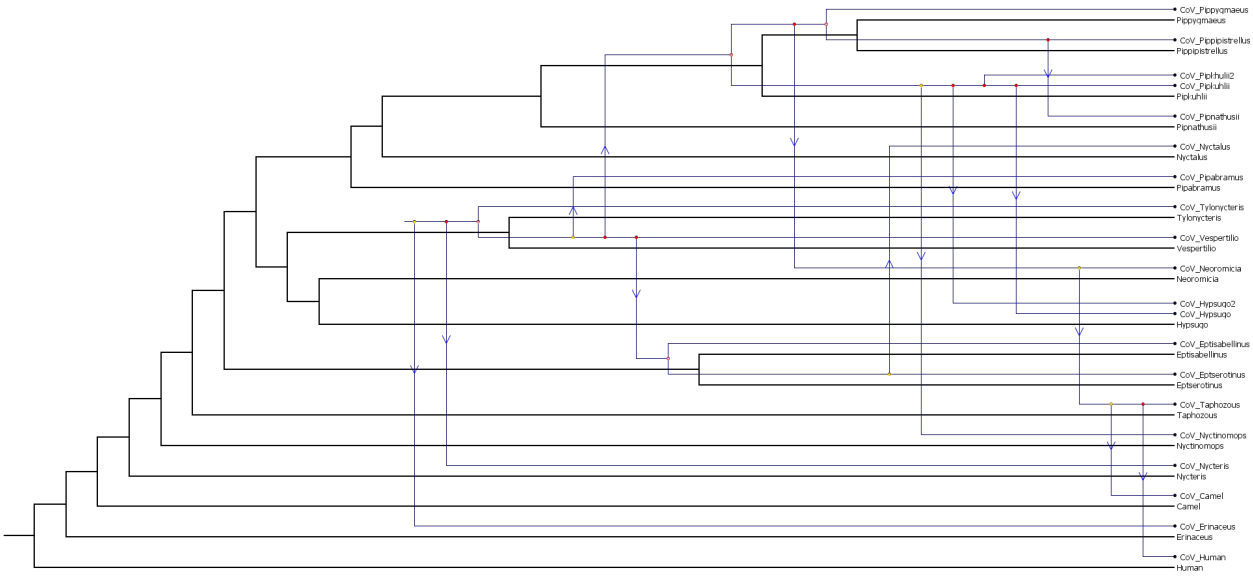



Figure 3: Reconstruction of one of 3 potentially optimal solutions of reconciled host-CoV trees recovered from a Jane analysis. Black and blue lines represent the host and CoV trees, respectively. For each solution, the number of co-speciation events inferred by Jane was always significantly greater than expected by chance. Jane inferred 4 co-speciation events (hollow colored circles), 1 duplication (solid

colored circle), 14 host switches (solid colored circle with arrow), 0 loss and 0 failure to diverge.

Our findings demonstrate co-speciation alone is not sufficient to explain the observed co-phylogenetic pattern and several host switches can be specifically identified. This is the case even if a significant global signal of co-speciation has been detected. This work highlights, the need for these types of detailed cophylgoenetic analyses to best explain the evolutionary history and host-switching of bat-CoVs.

*References cited for the above analysis*: Agnarsson, I., Zambrana-Torrelio, C.M., Flores-Saldana, N.P. & May-Collado, L.J. (2011) A time-calibrated species-level phylogeny of bats (Chiroptera, Mammalia). *PLOS Currents*, 3:RRN1212. Asher, R.J. & Helgen, K.M. (2010) Nomenclature and placental mammal phylogeny. *BMC Evolutionary Biology*, 10, 1-9. Lei BR, Olival KJ (2014) Contrasting Patterns in Mammal–Bacteria Coevolution: *Bartonella* and *Leptospira* in Bats and Rodents. *PLoS Negl Trop Dis* 8(3): e2738.

*Market Characterization Model Parameterization*

Our ongoing observational research and mapping of farms and markets suggests that rapid changes in the market and regulatory environment are changing the nature and location of the wildlife market trade. The nexus of the wildlife trade and the potential hotspots of interspecies viral mixing is now in many cases in animal storage facilities and transport between high-volume customers. To define realistic parameters for intermixing wildlife species in areas of high potential mixing, we have developed a preliminary survey and sampling protocol to assess these values as animals move along the value chain – through these storage facilities - using respondent-driven questionnaires to follow and sample along the wildlife trade network and reveal hidden nodes and sites of intermixing of species.



We have expanded our intermixing modeling framework to incorporate the variations along this value chain, where the diversity, abundance, residence time, and contact rates between species change as animals move through the trade network.

*Specific Aim 3: Testing predictions of CoV inter-species transmission.*

In Year 2, we continued surveillance for novel SARS-like CoVs from bats in Yunnan and Guangdong provinces and obtained full genome sequence for 11 CoV isolates. Full genome analysis of these CoV isolates was completed, including phylogenetic and recombination analyses. Importantly, recombination analysis of the full-length SL-CoV genome sequences from a single bat population revealed that frequent recombination events among different SL-CoV strains occur. Several SL-CoVs that are more genetically similar to SARS-CoV (2003) than any previously discovered were also identified from bat populations in Yunnan province. Full genome analysis suggests that an epicenter of SL-CoV occurs in rhinolophid bats and provides more insight into the evolutionary origin of SARS-CoV.

*Full-length genome sequencing of SL-CoVs identified from a single bat colony*

To date, including preliminary data submitted for this R01 that we are now analyzing under the current funding, we have conducted 5-years of surveillance of SL-CoV in a single bat colony in Yunnan Province (from 2011 to 2015), leading to the discovery of diverse novel SL-CoVs. Based on genotyping of these SL-CoVs by the region corresponding to the receptor-binding domain (RBD) of SARS-CoVs, 11 isolates were selected and full-length genome sequencing was performed in Year 2.

These SL-CoVs, including four others isolated previously from this colony, Rs3367, RsSHC014, WIV1 and WIV16, are highly diversified in the S gene, but share similar sequence identity to SARS-CoV in ORF1ab (Fig 4). Genomic phylogenetic analysis showed that the SL-CoVs detected in this colony are more closely

related to SARS-CoVs from other geographic regions, especially three isolates, WIV16, Rs4874 and Rs4231 (Fig 5). Notably, among the 15 SL-CoVs, two isolates, Rs4084 from *Rhinolophus sinicus* and Rf4092 from *Rhinolophus ferrumequinum*, are highly similar to SARS-CoV in the ORF8 region (Fig 5). Rf4092 possessed a single ORF8 of the same length (369bp) as that in civet SARS-CoV SZ3, and the sequence showed only 10 nucleotide substitution (Fig 6). The ORF8 sequence of Rs4084 is highly similar to that of Rf4092, however in the region corresponding to the 29-bp deletion acquired in human SARS CoVs (e.g Tor2), a shorter deletion of only 5-bp is present, resulting in two overlapping ORF8s, ORF8a and ORF8b. The position of start codon and stop codon of the two ORFs were consistent with those in human strains (Fig 6).

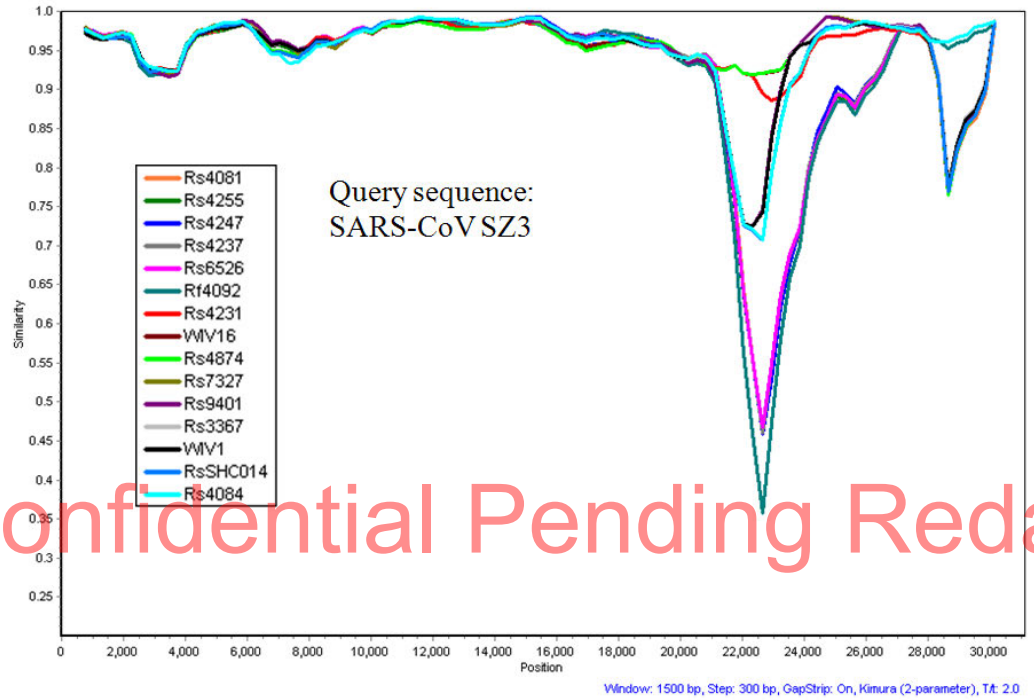





Fig 4. Simplot analysis of the 15 SL-CoVs identified from a single bat colony in Yunnan. SARS-CoV SZ3 is used as query sequence.

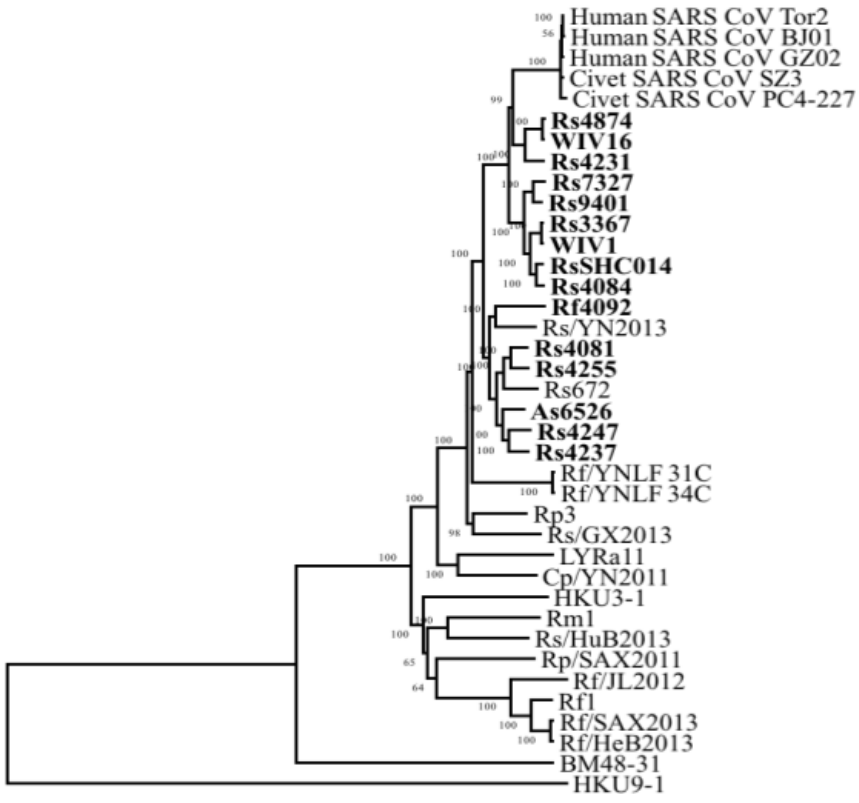


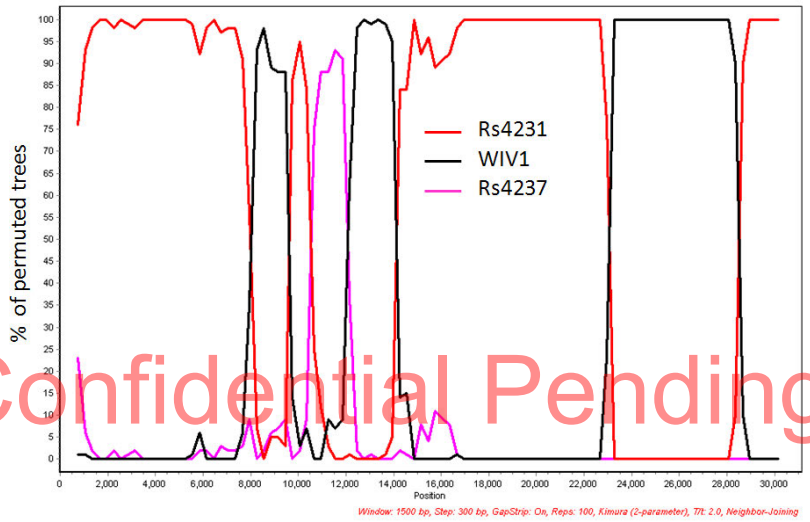



Fig 5 Phylogenetic analysis of full-length genome sequences of SL-CoVs and SARS-CoVs. Isolates identified in the single investigated bat colony in Yunnan in bold.


Fig 6. Alignment of ORF8 nucleotide sequences of SARS-CoV and bat SL-CoVs. The red box indicates the 29-nt deletion present in SARS-CoV of middle and late phase.

Recombination analysis of the full-length genome sequences reveals frequent recombination events among different SL-CoV strains circulating in this bat population. For example, WIV16 appears to be a recombination product of WIV1 and Rs4231. An important breakpoint is identified between the N-terminal domain (NTD) and RBD region in the S gene (Fig 7A). Consequently, WIV16 is identical to Rs4231 and WIV1 in NTD and RBD of the spike protein, respectively, and is highly homologous to SARS-CoV in both NTD and RBD. This makes it the SL-CoV most closely related to the direct progenitor of SARS-CoV discovered to date. Moreover, evidence is found to support the hypothesis that the direct progenitor of SARS-CoV was generated from recombination of WIV16 with Rf4092 at the site near ORF8. This work, which identifies diverse SL-CoVs highly homologous to SARS-CoV in different regions of the genome, suggests that rhinolophid bats are an evolutionary epicenter of SL-CoV and offers more insights into the evolutionary origin of SARS-CoV.

A.






B.

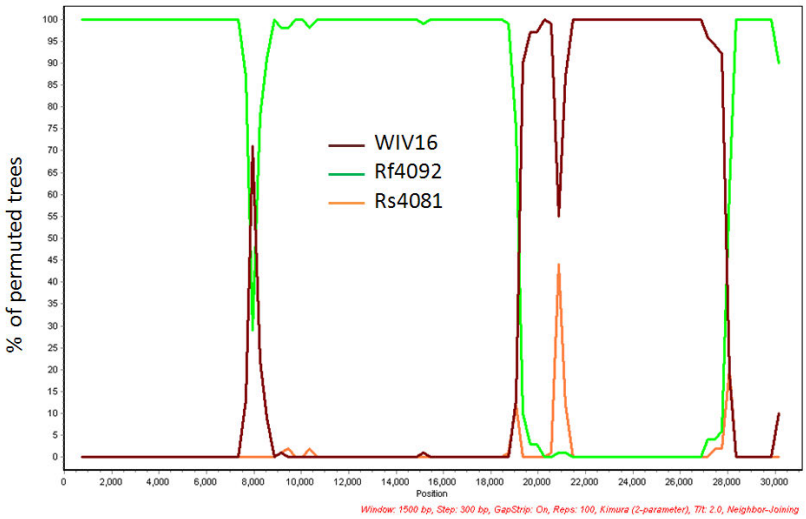



Fig 7 Bootscan analysis of full-length genome sequences of SL-CoVs. (A) WIV16 is used as query sequence. (B) SARS-CoV SZ3 is used as the query sequence. (Kimura model, window size, 1500bp, step size, 300bp)

*Additional Year 2 items for Specific Aim 3:*

- The infectious clone of WIV1 was successfully constructed using reverse genetic methods;
- Two chimeric bat SARS-like coronavirus strains were constructed by replacing the S gene in the backbone of WIV1;
- Permission to import mice with human ACE2 to China was obtained, so as to conduct the experimental infections proposed in our R01 specific aims.

*Specific Goals Not Met.*

- Comparative cophylogenetic analyses of bat host and CoV RdRp and Spike gene phylogenies, to assess patterns of evolutionary congruence and frequency of cross-species transmission (This will be conducted in year 3);
- Animal infection experiments of SARS-like coronaviruses were not done, because of the unavailability of mice with human ACE2 in Year 2. We now have secured these mice and will begin this work in year 3.
- Sampling of bat and other mammalian species in markets to screen for CoVs. We will begin this work in year 3.

**Section C: Accomplishments: Publications**

PUBLISHED



Xing-Yi Ge, Ning Wang, Wei Zhang, Ben Hu, Bei Li, Yun-Zhi Zhang, Ji-Hua Zhou, Chu-Ming Luo, Xing-Lou Yang, Li-Jun Wu, Bo Wang, Yun Zhang, Zong-Xiao Li, and Zheng-Li Shi. Coexistence of multiple coronaviruses in several bat colonies in an abandoned mineshaft. *Virologica Sinica* 31, 31–40 (2016).

Mei-Niang Wang, Wei Zhang, Yu-Tao Gao, Ben Hu, Xing-Yi Ge, Xing-Lou Yang, Yun-Zhi Zhang, Zheng-Li Shi. Longitudinal surveillance of SARS-like coronaviruses in bats by quantitative real-time PCR, *Virologica Sinica* 31(1): 78-80 (2016).

Cristin C. W. Young and Kevin J. Olival. Optimizing Viral Discovery in Bats. *PLoS ONE* 11(2) (2016).

Kevin J. Olival. To Cull, or Not To Cull, Bat is the Question. *Ecohealth* 13, 6–8 (2015).

Xing-Lou Yang, Ben Hu, Bo Wang, Mei-Niang Wang, Qian Zhang, Wei Zhang, Li-Jun Wu, Xing-Yi Ge, Yun-Zhi Zhang, Peter Daszak, Lin-Fa Wang, Zheng-Li Shi. Isolation and characterization of a novel bat coronavirus closely related to the direct progenitor of Severe Acute Respiratory Syndrome Coronavirus, *Journal of Virology* 90(6): 3253-6 (2015).

Ben Hu, Xingyi Ge, Lin-Fa Wang, Zhengli Shi. Bat origin of human coronaviruses. *Virology Journal* 12 (1): 221 (2015)

ACCEPTED, IN PRESS

Lei-Ping Zeng, Yu-Tao Gao, Xying-Yi Ge, Qian Zhang, Cheng Peng, Xinglou Yang, Bin Tan, Jing Chen, Aleksei Chmura, Peter Daszak, and Zheng-Li Shi. Bat SARS-like coronavirus WIV1 encodes an extra accessory protein ORFX involving in modulation of host immune response. *Journal of Virology* (in press, 2016)

**B.4 What opportunities for training and professional development has the project provided?**

We presented our project to graduate students, laboratory personnel, directors, and doctors from three Hospitals in Yunnan Province: Yunnan Provincial Institute of Endemic Diseases Control & Prevention (YNCDC); Dali Provincial Hospital; and The Third People's Hospital of Kunming. Select doctors at YNCDC (1) and Dali Provincial Hospital (3) were trained in the passive Hospital surveillance project protocols.

We trained graduate students from Dali School of Public Health (1) and the Wuhan University School of Public Health (3) in qualitative behavioral risk data collection methodologies and data collection technologies, survey data collection and analysis. These were also enrolled in and passed the Human Subjects Research Course provided by the Collaborative Institutional Training Initiative (CITI Program) at the University of Miami (http://citiprogram.org). The CITI Program is a leading provider of research education content with web based training materials serving millions of learners at academic institutions, government agencies, and commercial organizations in the U.S. and around the world.

## C. PRODUCTS

### C.1 PUBLICATIONS

**Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?**

Yes

**Publications Reported for this Reporting Period**

| Public Access Compliance | Citation |
|---|---|
| Complete | Yang XL, Hu B, Wang B, Wang MN, Zhang Q, Zhang W, Wu LJ, Ge XY, Zhang YZ, Daszak P, Wang LF, Shi ZL. Isolation and Characterization of a Novel Bat Coronavirus Closely Related to the Direct Progenitor of Severe Acute Respiratory Syndrome Coronavirus. J Virol. 2015 Dec 30;90(6):3253-6. PubMed PMID: 26719272; PubMed Central PMCID: PMC4810638. |
| Complete | Olival KJ. To Cull, or Not To Cull, Bat is the Question. Ecohealth. 2016 Mar;13(1):6-8. PubMed PMID: 26631385; PubMed Central PMCID: PMC4833651. |

**Non-compliant Publications Previously Reported for this Project**

| Public Access Compliance | Citation |
|---|---|
| Non-Compliant | (b) (4) |



### C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

### C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

### C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

**Have inventions, patent applications and/or licenses resulted from the award during the reporting period?**

No

### C.5 OTHER PRODUCTS AND RESOURCE SHARING

**C.5.a Other products**

NOTHING TO REPORT

**C.5.b Resource sharing**

NOTHING TO REPORT

## D. PARTICIPANTS

### D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

| Commons ID | S/K | Name | SSN | DOB | Degree(s) | Role | Cal | Aca | Sum | Foreign Org | Country | SS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (b) (6) | Y | DASZAK, PETER | (b) (6) | (b) (6) | BS,PHD | PD/PI | (b) (6), (b) (4) | | | | | NA |
| | N | HOSSEINI, PARVIEZ RANA | (b) (6) | (b) (6) | BS,PHD | Co-Investigator | | | | | | NA |
| (b) (6) | Y | Ross, Noam Martin | | (b) (6) | PhD | Co-Investigator | | | | | | NA |
| | N | OLIVAL, KEVIN J | (b) (6) | (b) (6) | PHD | Co-Investigator | | | | | | NA |
| | N | KE, CHANGWEN | | | PHD | Co-Investigator | | | | Center for Disease Control and Prevention of Guangdong Province | CHINA | NA |
| | N | ZHANG, SHUYI | | (b) (6) | PHD | Co-Investigator | | | | East China Normal University | CHINA | NA |
| | N | ZHANG, YUNZHI | | (b) (6) | PHD | Co-Investigator | | | | Yunnan Provincial Institute of Endemic Diseases Control & Prevention | CHINA | NA |
| | N | ZHU, GUANGJIAN | | (b) (6) | PHD | Co-Investigator | | | | East China Normal University | CHINA | NA |
| | N | GE, XINGYI | | | PHD | Co-Investigator | | | | Wuhan Institute of Virology | CHINA | NA |
| | N | EPSTEIN, JONATHAN H | (b) (6) | (b) (6) | MPH,DVM,BA,PHD | Co-Investigator | | | | | | NA |
| | N | CHMURA, ALEKSEI A | (b) (6) | (b) (6) | BS | Non-Student Research Assistant | | | | | | NA |
| | N | SHI, | | (b) (6) | PhD | Co- | | | | Wuhan | CHINA | NA |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ZHENGLI | | | | Investigator | | | | Institute of Virology | | |

**Glossary of acronyms:**

S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

**D.2 PERSONNEL UPDATES**

**D.2.a Level of Effort**

**Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?**

No

**D.2.b New Senior/Key Personnel**

**Are there, or will there be, new senior/key personnel?**

Yes

File uploaded: Noam Ross CV 2016.pdf

**D.2.c Changes in Other Support**

**Has there been a change in the active other support of senior/key personnel since the last reporting period?**

No



**D.2.d New Other Significant Contributors**

**Are there, or will there be, new other significant contributors?**

No

**D.2.e Multi-PI (MPI) Leadership Plan**

**Will there be a change in the MPI Leadership Plan for the next budget period?**

NA

# Noam Ross

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@noamross

## EDUCATION

**University of California** Davis, CA
*Doctoral Candidate in Ecology* Expected Completion Summer 2015

- Dissertation Committee: Alan Hastings (major professor, Ecology), David Rizzo (Plant Pathology), Jim Sanchirico (Natural Resource Economics)
- Dissertation Research: "Managing Emerging Forest Disease Under Uncertainty"

**Brown University** Providence, RI
*Bachelor of Science in Environmental Science, Magna Cum Laude* May 2006

- Honors Thesis: "Soil Organic Matter in Northern Mongolia: Permafrost and Land-Use interactions"
- Phi Beta Kappa, Sigma Xi, Environmental Science Honors, Rosenberger Prize for Outstanding Service

## SCIENTIFIC PUBLICATIONS

- Carl Boettiger*, **Noam Ross***, Alan Hastings (2013) *Early Warning Signals: The Charted And Uncharted Territories*. Theoretical Ecology http://dx.doi.org/10.1007/s12080-013-0192-6
- Fuller, Kate, David Kling, Kaelin Kroetz, **Noam Ross**, and James N. Sanchirico (2013) *Economics and Ecology of Open-Access Fisheries*. In: Shogren, J.F., (ed.) Encyclopedia of Energy, Natural Resource, and Environmental Economics, Vol. 2 Encyclopedia of Energy, Natural Resource, and Environmental Economics p.39-49. Amsterdam: Elsevier. http://dx.doi.org/10.1016/B978-0-12-375067-9.00114-5



***In preparation***

- **Ross, Noam**. *Comparative dynamics of SI and multi-infection disease models.* To be submitted to Ecology Letters.

(b) (4)

### POSTERS

- **Ross, Noam**. "Optimal Control of Disease in Space: An Approach Using Individual-based Models," June 1-4, 2014. 12th Annual Conference of Ecology and Evolution of Infectious Disease, Fort Collins, Colorado.
- **Ross, Noam**. "Designing Protective Treatments for Forest Disease Using a Spatial Point Process Model," November 20-21, 2014. California Forest Pest Council Annual Meeting, McClellan, CA.
- **Ross, Noam**. "Optimal Control of Forest Disease Under Changing Community and Spatial Structure," November 4-18, 2013. Sustainable Management of Natural Resources Workshop, Mathematical Biosciences Institute, Columbus, OH.

### PRESENTATIONS

- **Ross, Noam**, "Fungal Disease Mortality: Modeling for Management of Sudden Oak Death." Dec 1, 2014 Invited talk at EcoHealth Alliance, New York, NY.
- **Ross, Noam**, "Modeling forest disease using a macroparasite framework ," Agust 13, 2014. 99th Annual Ecological Society of America Meeting, Sacramento, CA.
- Ashander, Jamie, Kelly Gravuer, Megan Kelso, Mary E. Mendoza and **Noam Ross** "Managing River-Floodplains Systems: A Historical and Ecological Perspective" September 14, 2002. Presentation at NSF REACH IGERT Floodplains Workshop

## AWARDS + FELLOWSHIPS (*Total received $225,429*)

- Don Dahlsten Memorial Grant ($325) — California Forest Pest Council, 2012
  *Designing Protective Treatments for Forest Disease Using Spatial Point Process Models*
- NSF IGERT Bridge Fellowship ($57,500) — UC Davis, CA, 2012
  *Managing Emerging Forest Disease Under Uncertainty*
- NSF IGERT Traineeship in Rapid Environmental Change ($115,00) — UC Davis, CA, 2010
  *Modifying River-Floodplain Systems: A Historical and Ecological Approach*
- UC Davis Graduate Group in Ecology Fellowship ($40,604) — UC Davis, CA, 2010
- NSF Research Experience for Undergraduates Fellowship ($8,000) — Acad. of Natural Sciences, PA, 2005
- Undergraduate Research Fellowship ($4,000) — Brown University, RI, 2003

## SERVICE + PROJECTS

- **Workshop Instructor,** Software Capentry and Data Carpentry Foundations — Jan 2015–Present
- **Student Rep,** UC Davis Graduate Group in Ecology Executive Committee — Sep 2013–Present
- **Reviewer:** *Theoretical Ecology* (4 reviews) — Feb 2013–Present
- **Web Developer and Technology Chair,** Ecology Graduate Student Association — June 2013–Present
  *Creator + Maintainer of graduate student blog, resources, and news site* (egsa.ucdavis.edu)
- **Founder + Organizer,** Davis R Users' Group — Sep 2012–Present
  *Created users group that provides tutoring and seminars to graduate students in 10+ departments*
- **Contributor,** R packages `knitr, knitcitations, rcrossref, rethinking` — 2012-Present
- **Organizer:** NSF REACH IGERT Workshop on Multiple Goals in Floodplain Restoration — Sep 2012
- **Organizer,** UC Davis Conference on Ecology and the Business Sector — Apr 2011
- **Organizer** UC Davis Graduate Group in Ecology Symposium — May 2010-2011
- **External Reviewer,** World Resources Institute Corporate Ecosystem Services Review — Jan 2008
- **External Reviewer,** McKinsey-Clinton Global Initiative Forestry Project — Mar 2008
- **Business Stewardship Volunteer,** NY Coastal Marine Resources Center — Feb-Apr 2007



## OTHER WORK EXPERIENCE

**GreenOrder** — New York, NY
*Analyst, Senior Analyst: Corporate Environmental Strategy + Governance* — Sep 2006–Oct 2009

- Conducted environmental performance analysis for products in energy, transportation, and water sectors
- Created green product metrics system R&D stage-gating system for construction products manufacturer
- Managed engagement with equipment rental company to identify growth opportunities in green building
- Performed market and competitive analyses for a wide array of clients in retail, real estate financial and cleantech sectors; prepared and delivered client presentations; managed projects
- Managed analysts performing environmental product certifications and market research
- Developed firm seminar series and analyst training materials; conducted trainings on topics including auditing, statistical analysis, and environmental performance benchmarking
- Audited certifications for environmental products and facility performance

**Wal-Mart** — Providence, RI
*Contract Researcher/Consultant: Energy Efficient Products Initiative* — May-Sep 2006

- Developed forecasting model for sales of energy-efficient lamps at Wal-Mart stores
- Created guidelines for design of lamp recycling program

**Brown University Facilities Management** Providence, RI
*Administrative, Research, + Teaching Assistant: Energy and Design* Jan 2003–May 2006

- Developed energy-use and financial projections for university energy usage scenarios
- Performed background research and feasibility analysis for university energy efficiency projects
- Provided tutoring, logistical support and web design for two courses in sustainable design
- Responsible for maintenance of energy efficient, low-impact building

**Hovsgol Lake Global Environmental Facility and Brown University** Mongolia + Providence, RI
*National Science Foundation REU Fellow, Thesis Research* June 2005-May 2006
Advisor: Clyde Goulden

- Independent research on climate-land use interactions on permafrost soil carbon storage
  Plant surveys, soil pit excavation, soil physical and chemical analysis, soil microbial process incubations

**Marine Biological Laboratory Ecosystems Center** Woods Hole, MA
*Semester in Environmental Science Student* Aug-Dec 2004
Advisor: Charles Hopkinson

- Examined effects of nitrogen pollution on structure of microplankton food webs
- Microcosm experiments, fluorescence microscopy, dissolved nutrient analysis, planktonic growth incubations

**Brown Center for Environmental Studies** Providence, RI
*Undergraduate Research Fellow* Jun-Aug 2003
Advisor: Steven Hamburg

- Conducted research in biogeochemistry at Hubbard Brook Experimental Forest and surrounding region; oversaw soil pit excavation by undergraduate and graduate field crew
- Plant surveys, forest floor measurements, litter collection, soil pit excavation, soil physical and chemical analysis, GIS analysis in ESRI ArcMap



## PUBLICATIONS IN POPULAR PRESS

- "Extinction Debt,"(Initial author) Wikipedia. Wikimedia Foundation, Inc., February 23, 2011 http://en.wikipedia.org/wiki/Extinction_debt
- “If Everyone Moves to the City, What Gets Left Behind?" *Good.is,* January 17, 2011. http://www.good.is/post/if-everyone-moves-to-the-city-what-is-left-behind/
- “Why the Ethanol Debate Isn’t Helping Anyone,” *GreenBiz.com*, Jun 3, 2009. http://www.greenbiz.com/blog/2009/06/03/why-ethanol-debate-isnt-helping-anyone
- “Four Lean, Green Strategies for an Uncertain Economy,” (with Andrew Shapiro) *Harvard Business Review’s Leading Green*, Oct 29, 2008. http://blogs.hbr.org/2008/10/4-lean-green-strategies-for-an/
- “What a Silent Spring Means for Business Risk,” *GreenBiz.com*, Mar 6, 2007. http://www.greenbiz.com/blog/2007/03/05/what-silent-spring-means-business-risk

## E. IMPACT

**E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?**

Not Applicable

**E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?**

NOTHING TO REPORT

**E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?**

Not Applicable

**E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?**

| Dollar Amount | Country |
|---|---|
| 211699 | CHINA |

## F. CHANGES

| |
|---|
| **F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE**<br>Not Applicable |
| **F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM**<br>NOTHING TO REPORT |
| **F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS**<br>**F.3.a Human Subjects**<br>No Change |
| **F.3.b Vertebrate Animals**<br>No Change |
| **F.3.c Biohazards**<br>No Change |
| **F.3.d Select Agents**<br>No Change |

## G. SPECIAL REPORTING REQUIREMENTS

### G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

### G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

### G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

### G.4 HUMAN SUBJECTS

**G.4.a Does the project involve human subjects?**

Yes

**Is the research exempt from Federal regulations?**

No

**Does this project involve a clinical trial?**

No

**G.4.b Inclusion Enrollment Data**

Report Attached: Understanding the Risk of Bat Coronavirus Emergence-PROTOCOL-001



**G.4.c ClinicalTrials.gov**

**Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?**

No

### G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

**Are there personnel on this project who are newly involved in the design or conduct of human subjects research?**

No

### G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

**Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?**

No

### G.7 VERTEBRATE ANIMALS

**Does this project involve vertebrate animals?**

Yes

### G.8 PROJECT/PERFORMANCE SITES

| Organization Name: | DUNS | Congressional | Address |
|---|---|---|---|

| | | District | |
|---|---|---|---|
| **Primary:** EcoHealth Alliance, Inc. | 077090066 | NY-010 | 460 West 34th Street<br>17th Floor<br>New York NY 100012317 |
| Wuhan Institute of Virology | 529027474 | | Xiao Hong Shan, No. 44<br>Wuchang District<br>Wuhan |
| East China Normal University | 420945495 | | 3663 Zhongshan Beilu<br>Shanghai |
| ECOHEALTH ALLIANCE | 077090066 | | ECOHEALTH ALLIANCE, INC.<br>460 W 34TH ST<br>NEW YORK NY 100012320 |
| EcoHealth Alliance, Inc. | 077090066 | NY-010 | 460 West 34th Street<br>17th Floor<br>New York NY 100012317 |
| Wuhan Institute of Virology | 529027474 | | Xiao Hong Shan, No. 44<br>Wuchang District<br>Wuhan |
| East China Normal University | 420945495 | | 3663 Zhongshan Beilu<br>Shanghai |

**G.9 FOREIGN COMPONENT**

**Organization Name:** Wuhan Institute of Virology
**Country:** CHINA
**Description of Foreign Component:**
Principal Laboratory for all Research in China as per section G8 (above) and detailed in our Specific Aims

**Organization Name:** East China Normal University
**Country:** CH NA
**Description of Foreign Component:**
Principal Coordinating Team for all project field work as per section G8 (above) and detailed in our Specific Aims



**G.10 ESTIMATED UNOBLIGATED BALANCE**

**G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?**

No

**G.11 PROGRAM INCOME**

**Is program income anticipated during the next budget period?**

No

**G.12 F&A COSTS**

**Is there a change in performance sites that will affect F&A costs?**

No

Inclusion Enrollment Report

**Inclusion Data Record (IDR) #:** 166195

**Using an Existing Dataset or Resource:** No

**Delayed Onset Study ?:** No

**Clinical Trial:** No

**Enrollment Location:** Foreign

**NIH Defined Phase III Clinical Trial:** No

**Study Title:** Understanding the Risk of Bat Coronavirus Emergence-PROTOCOL-001

## Planned Enrollment

**Planned Enrollment Total:** 2,460

**NOTE:** Planned enrollment data exists in the previous format; the PD/PI did not enter the planned enrollment information in the modified format and was not required to do so. Only the total can be provided.

## Cumulative Enrollment

| Racial Categories | Ethnic Categories | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | Not Hispanic or Latino | | | Hispanic or Latino | | | Unknown/Not Reported Ethnicity | | | |
| | Female | Male | Unknown/ Not Reported | Female | Male | Unknown/ Not Reported | Female | Male | Unknown/ Not Reported | |
| American Indian/Alaska Native | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| Asian | 157 | 108 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **265** |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| Black or African American | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| White | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| More than One Race | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| Unknown or Not Reported | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| **Total** | **157** | **108** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **265** |

## A. COVER PAGE

| | |
|---|---|
| **Project Title:** Understanding the Risk of Bat Coronavirus Emergence | |
| **Grant Number:** 5R01AI110964-05 | **Project/Grant Period:** 06/01/2014 - 05/31/2019 |
| **Reporting Period:** 06/01/2017 - 05/31/2018 | **Requested Budget Period:** 06/01/2018 - 05/31/2019 |
| **Report Term Frequency:** Annual | **Date Submitted:** 09/16/2020 |
| **Program Director/Principal Investigator Information:**<br><br>PETER DASZAK , PHD BS<br><br>**Phone number:** (b) (6)<br>**Email:** (b) (6) | **Recipient Organization:**<br><br>ECOHEALTH ALLIANCE, INC.<br>ECOHEALTH ALLIANCE, INC.<br>460 W 34TH ST<br>17TH FLOOR<br>NEW YORK, NY 100012320<br><br>**DUNS:** 077090066<br>**EIN:** 1311726494A1<br><br>**RECIPIENT ID:** NIAID Coronavirus |
| **Change of Contact PD/PI:** N/A | |
| **Administrative Official:**<br><br>ALEKSEI CHMURA<br>460 W 34th St., 17th Floor<br>New York, NY 10001<br><br>**Phone number:** 1 (b) (6)<br>**Email:** (b) (6) | **Signing Official:**<br><br>ALEKSEI CHMURA<br>460 W 34th St., 17th Floor<br>New York, NY 10001<br><br>**Phone number:** (b) (6) 3<br>**Email:** (b) (6) |
| **Human Subjects:** Yes<br>HS Exempt: No<br>Exemption Number:<br>Phase III Clinical Trial: | **Vertebrate Animals:** Yes |
| **hESC:** No | **Inventions/Patents:** No |

## B. ACCOMPLISHMENTS

### B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Zoonotic coronaviruses are a significant threat to global health, as demonstrated with the emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, and the recent emergence Middle East Respiratory Syndrome (MERS-CoV). The wildlife reservoirs of SARS-CoV were identified by our group as bat species, and since then hundreds of novel bat-CoVs have been discovered (including >260 by our group). These, and other wildlife species, are hunted, traded, butchered and consumed across Asia, creating a largescale human-wildlife interface, and high risk of future emergence of novel CoVs.
To understand the risk of zoonotic CoV emergence, we propose to examine 1) the transmission dynamics of bat-CoVs across the human-wildlife interface, and 2) how this process is affected by CoV evolutionary potential, and how it might force CoV evolution. We will assess the nature and frequency of contact among animals and people in two critical human-animal interfaces: live animal markets in China and people who are highly exposed to bats in rural China. In the markets we hypothesize that viral emergence may be accelerated by heightened mixing of host species leading to viral evolution, and high potential for contact with humans. In this study, we propose three specific aims and will screen free ranging and captive bats in China for known and novel coronaviruses; screen people who have high occupational exposure to bats and other wildlife; and examine the genetics and receptor binding properties of novel bat-CoVs we have already identified and those we will discover. We will then use ecological and evolutionary analyses and predictive mathematical models to examine the risk of future bat-CoV spillover to humans. This work will follow 3 specific aims:

Specific Aim 1: Assessment of CoV spillover potential at high risk human-wildlife interfaces. We will examine if: 1) wildlife markets in China provide enhanced capacity for bat-CoVs to infect other hosts, either via evolutionary adaptation or recombination; 2) the import of animals from throughout Southeast Asia introduces a higher genetic diversity of mammalian CoVs in market systems compared to within intact ecosystems of China and Southeast Asia; We will interview people about the nature and frequency of contact with bats and other wildlife; collect blood samples from people highly exposed to wildlife; and collect a full range of clinical samples from bats and other mammals in the wild and in wetmarkets; and screen these for CoVs using serological and molecular assays.

Specific Aim 2: Receptor evolution, host range and predictive modeling of bat-CoV emergence risk. We propose two competing hypotheses: 1) CoV host-range in bats and other mammals is limited by the
phylogenetic relatedness of bats and evolutionary conservation of CoV receptors; 2) CoV host-range is limited by geographic and ecological opportunity for contact between species so that the wildlife trade disrupts the 'natural' co-phylogeny, facilitates spillover and promotes viral evolution. We will develop CoV phylogenies from sequence data collected previously by our group, and in the proposed study, as well as from Genbank. We will examine co-evolutionary congruence of bat-CoVs and their hosts using both functional (receptor) and neutral genes. We will predict host-range in unsampled species using a generalizable model of host and viral ecological and phylogenetic traits to explain patterns of viral sharing between species. We will test for positive selection in market vs. wild-sampled viruses, and use data to parameterize mathematical models that predict CoV evolutionary and transmission dynamics. We will then examine scenarios of how CoVs with different transmissibility would likely emerge in wildlife markets.



Specific Aim 3: Testing p edict ons of CoV inter-species transmission. We will test our models of host range ( e. emergence potent al) experimentally using reverse genetics, pseudovirus and receptor binding assays, and virus infection experiments in cell culture and humanized mice. With bat-CoVs that we've isolated or sequenced, and using live virus or pseudovirus infection in cells of different origin or expressing different receptor molecules, we will assess potential for each isolated virus and those with receptor binding site sequence, to spill over. We will do this by sequencing the spike (or other receptor binding/fusion) protein genes from all our bat-CoVs, creating mutants to identify how significantly each would need to evolve to use ACE2, CD26/DPP4 (MERS-CoV receptor) or other potential CoV receptors. We will then use receptor-mutant pseudovirus binding assays, in vitro studies in bat, primate, human and other species' cell lines, and with humanized mice where particularly interesting viruses are identified phylogenetically, or isolated. These tests will provide public health-relevant data, and also iteratively improve our predictive model to better target bat species and CoVs during our field studies to obtain bat-CoV strains of the greatest interest for understanding the mechanisms of cross-species transmission.

### B.1.a Have the major goals changed since the initial competing award or previous report?

No

### B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: Year 4 NIAID CoV Report_Final for eRA Commons.pdf

### B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

**For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?**

No

### B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

File uploaded: Year 4 NIAID CoV Training and Prof Devlp.pdf

**B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?**

1.Conference and University Lectures: PI Daszak, and Co-investigators Shi, Epstein, Olival, and Zhang gave invited University and Conference lectures including Harvard Univ. Columbia Univ., Tufts Univ., Mt. Sinai, the 2nd International Symposium on Emerging Viral Disease in China, the 2nd International Symposium on the Infectious Diseases of Bats in Colorado, Cell Symposia: Emerging and Re-emerging Viruses 2017 in Virginia, The International Union of Microbiological Societies 2017 National Academy of Sciences in Singapore, 2018 Borneo Quality of Life Conference in Malaysia, 2017 Chemical and Biological Defense Science and Technology (CBD S&T) in California, Prince Mahidol Award Conference in Bangkok, Collaboration for Environmental Evidence Meeting in Paris, US-China NSF Ecology and Evolution of Infectious Disease (EEID) Meeting, and others that included specific discussion of the current project and results.

2.Agency and other briefings: PI Daszak and Co-investigator Shi introduced this project and discussed new opportunities about predicting and preventing zoonoses within National Institute of Allergy and Infectious Disease Office, Defense Advanced Research Projects Agency, National Natural Science Foundation of China, Chinese Center for Disease Control and Prevention, US NASEM Forum on Microbial Threats, Chinese Academy of Sciences, and the Health Working Group at the US Embassy in Beijing.

3.Public outreach: PI Daszak and Co-investigator Shi, Epstein, Olival, have presented this work to the general public in a series of meetings over Year 4 including at Cosmos Club briefings that EcoHealth Alliances hosts in Washington DC, over 10 meetings on the China National Virome Project and the Global Virome Project in China, Europe, Australia, Southeast Asia and Latin America. Co-investigator Olival presented this work at a public event on Disease Transmission and Technologies in New York, co-investigator Ross presented this work at EcoHealth Webinar on wildlife trade network research. Zhu broadly introduced this work to the conservation and ecological research community in China through field training workshops.

**B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?**

Specific Aim 1: Assessment of CoV spillover potential at high risk human-wildlife interfaces.

•To commence an in-depth analysis of data collected from the integrated biological behavioral surveillance from Yunnan, Guangxi, and Guangdong provinces, incorporating questionnaires and serological testing results.
•To initiate lab analysis of human samples collected from the passive hospital surveillance from four hospitals in Yunnan province: 1) Dali College Affiliated Hospital; 2) Dali Prefecture Hospital; 3) Kunming No. 3 People's Hospital, and 4) Chuxiong Prefecture Hospital. The goal will be to identify examples of CoV spillover events in China that may lead to illness.

Specific Aim 2: Receptor evolution, host range and predictive modeling of bat-CoV emergence risk



•To repeat and continue in vivo exper men s of SARSr-CoVs with spike variants on hACE-expressing transgenic mice (survival rate histopathological analysis, etc) to eva uate the risk of cross-species infection of different SARSr-CoVs to humans;
•Continue searching for the receptor of SARSr-CoVs with deletions in the homologous region of SARS-CoV RBD (i.e. Rp3, Rs672), and SARSr-CoVs that are unable to utilize bat ACE2 (e.g. Rs4231).
•Continue the phylogeographic study of bat-CoV with newly collected samples to better understand the geographic distribution and evolution of bat-CoV genetic diversity in south China and SE Asia.

Specific Aim 3: Testing predictions of CoV inter-species transmission.

•Using the full-length infectious cDNA clone of MERS-CoV, chimeric viruses with the spikes of newly identified MERSr-CoVs will be constructed. The pathogenesis of these MERSr-CoVs will be tested on the human DPP4-expressing mouse model that has already been developed and validated in Y4.
•To conduct a population genetics study of Rhinolophus sinicus ACE2s, including the amplification of ACE2 genes from R. sinicus samples of different origin, test of the usage efficiency of R. sinicus ACE2s of different origins by SL-CoVs and kinetics study on the binding of SL-CoV RBD to different R. sinicus ACE2s.
•In collaboration with South China Agrricultural University, gather data on the spatial structure and barn-level mortality records to parameterize our mathematical model of virus spread that incorporates a meta-population structure in individual and use this to fit the model on a training set of farms and validate it on a hold-out set.
•Using the intra-farm transmission model, we will (a) determine the characteristics of a farm that determine the likelihood and size of an outbreak given a spillover event, and (b) determine whether SADS and PEDV outbreaks on farms can be distinguished by differing dynamics, as measured by transmission parameters in our intra-farm transmission model.

**Year 4 Report:** Understanding the Risk of Bat Coronavirus Emergence

**Award Number:** R01AI110964-03

**Reporting Period**: 06/01/2017 – 05/31/2018

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**B.2 What was accomplished under these goals?**

**Summary**

The results of the 4th year of our R01 work are detailed below. They include:

- Completed behavioral risk survey questionnaires and biological sample data collection for 1,585 people in Yunnan, Guangxi, and Guangdong provinces.
- Preliminary analysis of behavioral survey responses exploring key risk factors relating to potential viral zoonotic disease spillover in China, indicating notable differences among the respondents in Guangdong, Guangxi, and Yunnan.
- Completed serologic testing of collected human samples for MERS-CoV, SARSr-CoV, HKU9 CoV and HKU10 CoV, showing the serologic evidence of spillover of bat SARS-related CoVs (7 people in Yunnan province) and HKU9 CoV (2 people in Guangxi province).
- Testing of samples from 671 individual bats to identify diverse alpha- and beta-coronaviruses.
- Genetic diversity and genomic characterization of beta-coronaviruses in fruit bats and characterization of the full-length genome sequence of a novel HKU9-related CoV.
- Analysis of host-virus phylogeography for all bat CoV RdRp sequences collected by our group in China from 2008-2015 (Alpha-CoVs: n = 491; Beta-CoVs: n = 326) to identify the geographic areas that are likely sources of origin/diversity for this important group of viruses.
- Identification of two novel MERS-related CoVs that use DPP4 receptor.
- *In vivo* infection of SARSr-CoVs with variants of S protein in human ACE2 (hACE2) expressing mice.
- Identification of a novel bat-origin CoV (swine acute diarrhea syndrome coronavirus, SADS-CoV) causing a multi-farm outbreak of fatal acute diarrhea in piglets in Guangdong (published in *Nature* in April 2018).
- Development of an intra-farm transmission model to understand SADS-CoV spread and help predict and prevent future outbreaks.



**Specific Aim 1: Assessment of CoV spillover potential at high-risk human-wildlife interfaces**

During Year 4 we completed behavioral risk surveys and biological sample collection from people at selected sites in three provinces in southern China (Guangdong, Guangxi, and Yunnan) and began analyzing the results.

**Behavioral Survey**

We administered 1,585 surveys in Guangdong, Guangxi, and Yunnan provinces. Questions explored respondent health-seeking behavior, experiences with unusual illnesses, contact with wildlife and livestock, and general background information. Blood samples were collected from respondents and tested for SAS-related CoVs (SARSr-CoVs) and HKU10-CoV using serological assays. Survey data was analyzed by province to examine patterns among respondent characteristics and behavioral risk factors across provinces.

## Respondent General Background Information

Of the 1,585 respondents who completed the survey, 420 were from Guangdong, 412 were from Guangxi, and 753 were from Yunnan. More females than males completed the survey in all provinces. The mean age of the overall survey sample was 52 years **(Figs. 1, 2)**.

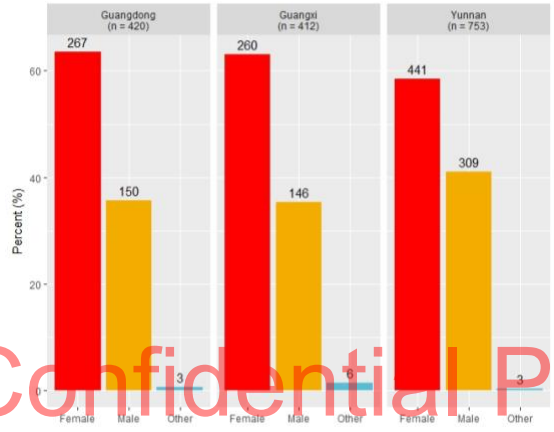



***Figure 1:*** *Gender of respondents*

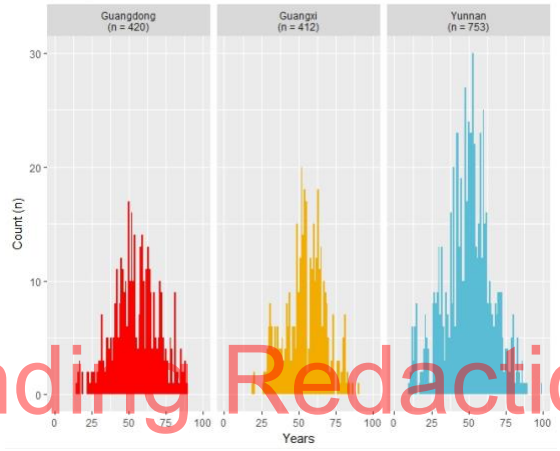



***Figure 2:*** *Age distribution of respondents.*



Across all provinces, most respondents had lived in their respective locales for more than 5 years (96.3%) **(Fig. 3)** and earned less than 10,000 renminbi (RMB) annually (84.6%) **(Fig. 4)**. In 2016, the updated poverty standard in China was 3,000 RMB as defined by Poverty Alleviation Office of State Council. More families in Guangxi (61.8%) lived at or below the poverty level as compared to those in Guangdong (36.9%) and Yunnan (43.3%).

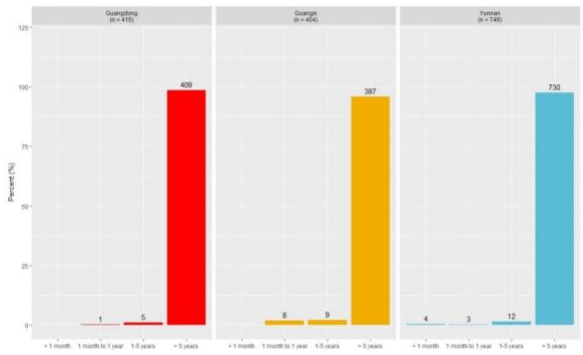


***Figure 3:*** *Duration of residency.*

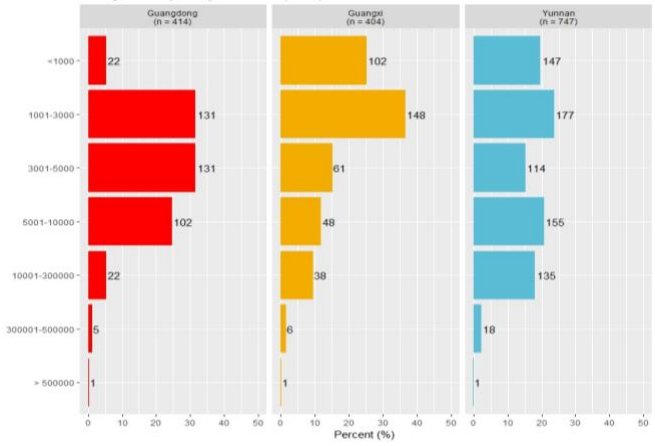



***Figure 4:*** *Family annual per capita income (RMB).*

In Guangdong, Guangxi, and Yunnan, 73.9%, 57.0% and 69.6% of respondents, respectively, had a primary school-level education or less **(Fig. 5)**. Across all provinces the most common livelihood was crop production. In Yunnan, 699 out of 753 (92.8%) individuals from the province identified crop production as a livelihood activity. In comparison, 237 out of 420 (56.4%) individuals from Guangdong, and 260 out of 412 (63.1%) individuals from Guangxi **(Fig. 6)** named crop production as a livelihood in the last year. Respondents, however, where not restricted to defining a single livelihood, many indicated engaging in multiple types of livelihoods.

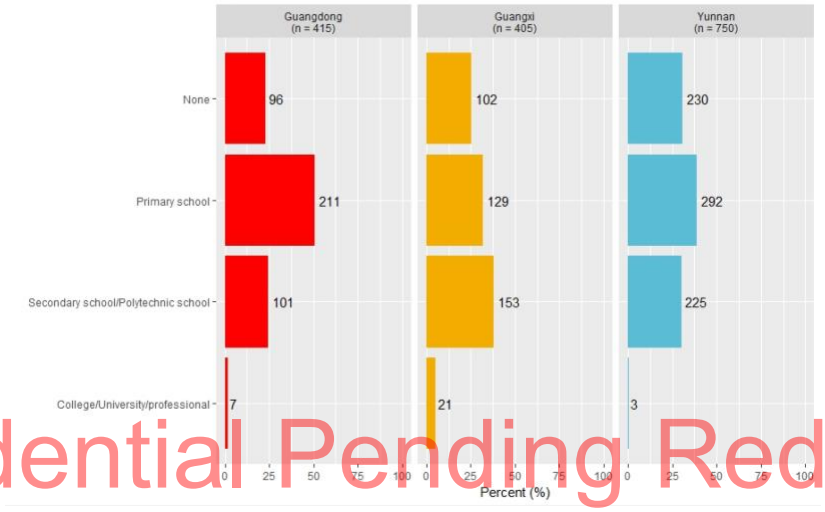





***Figure 5:*** *Highest level of education completed*

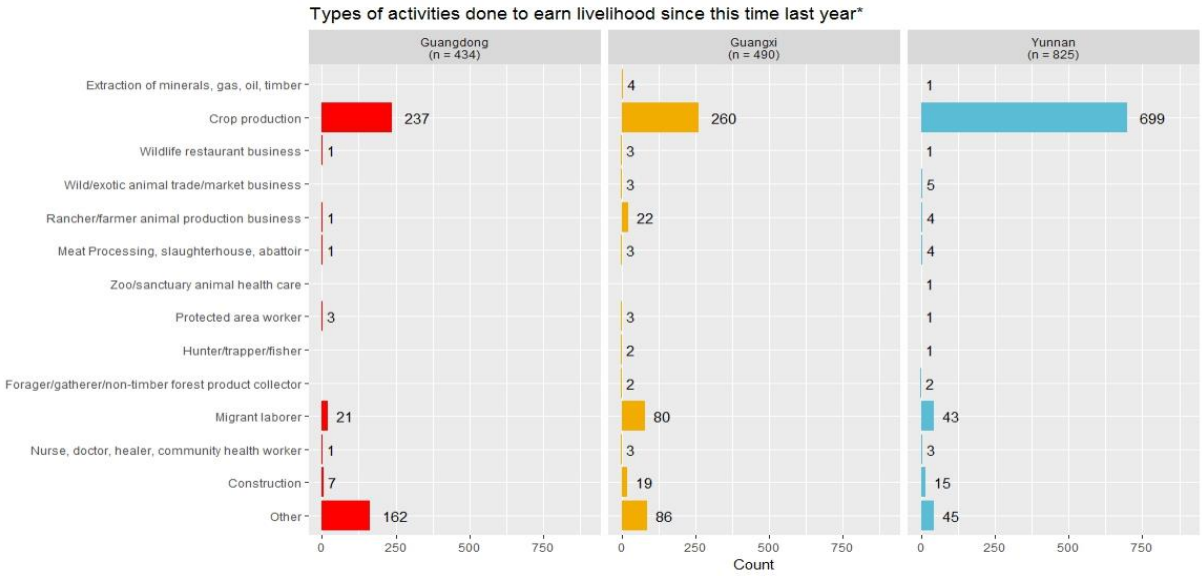



***Figure 6:*** *Types of activities conducted to earn a livelihood since this time last year (above)*

In Guangdong, Guangxi, and Yunnan, 41.7%, 50.7% and 59.6% of respondents, respectively, indicated that they traveled outside of their village town or city in the past year. Among those who traveled, the average number of trips was 5 in Guangdong and Guangxi, and 6 in Yunnan. The average distance traveled by respondents in Guangdong and Yunnan were 113 Km and 118 Km, respectively, compared to 66 Km by respondents in Guangxi.

***Health-Seeking Behavior and Experiences with Unusual Illnesses***

When asked where they usually get treatment for illness or infection, the top 3 responses across all provinces in aggregate were hospitals, clinics, and pharmacies/dispensaries in descending order **(Fig. 7)**. However, within Yunnan, most respondents went to hospitals, followed by pharmacies, then clinics.

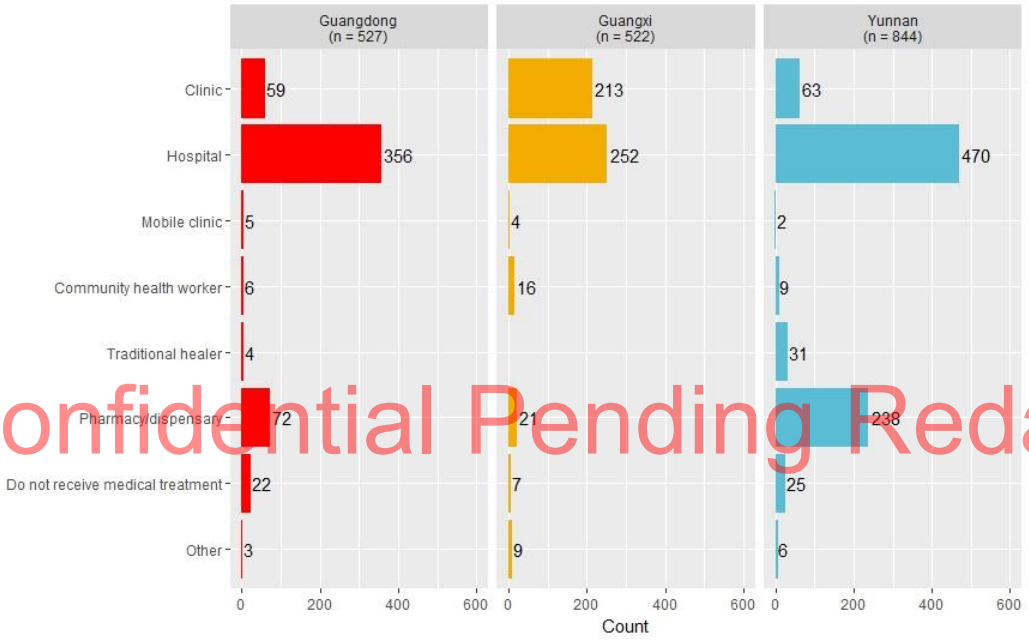


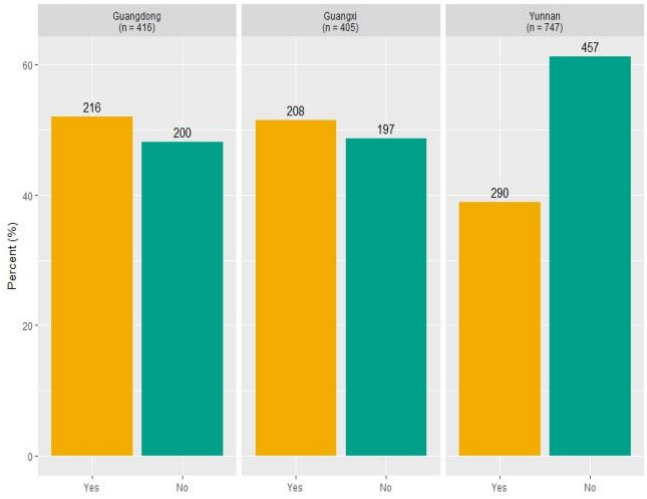



***Figure 7:*** *Location where care was usually received for illness or infection.*

All survey respondents were asked whether they had experienced an unusual illness in their lifetime and in the past year, defined by a series of the most common symptoms associated with encephalitis, hemorrhagic fever (HF), severe acute respiratory infection (SARI), and influenza-like illness (ILI). Additional symptoms that were asked about included: fever with diarrhea or vomiting; fever with rash; and, persistent rash or sores on skin. Respondents were not restricted to selecting one illness and could provide multiple responses.

The proportion of respondents who had an unusual illness with any of the above-mentioned symptoms in their lifetime varied slightly by province. Between the three provinces, Yunnan had the fewest number of respondents who reported experiencing the symptoms provided (38.8%), compared to Guangdong and Guangxi (51.9% and 51.3%, respectively). Yunnan was also the only province where less than half of the respondents reported experiencing the symptoms provided **(Fig. 8)**.

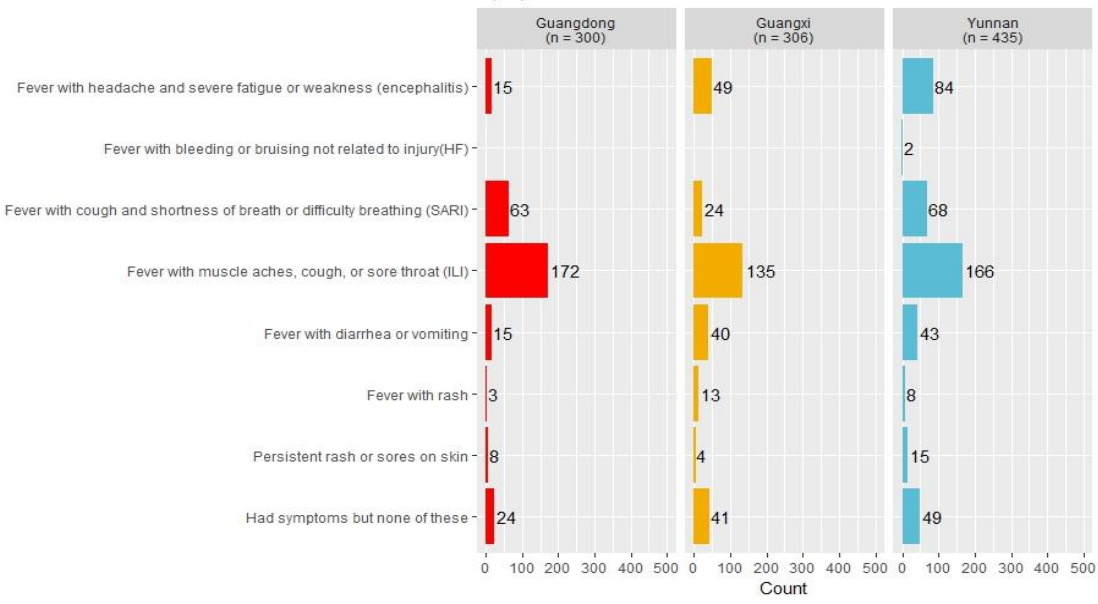
***Figure 8:*** *Respondent's experience of unusual illnesses.*




Across all three provinces, among those who had experienced any symptoms of unusual illness in their lifetimes, those associated with ILI were the most commonly reported. In Guangdong province, this was followed by symptoms associated with SARI, then by other symptoms not mentioned in the survey. In Guangxi province, the second most reported symptoms were ones associated with encephalitis, followed by other symptoms not mentioned in the survey. Similarly, in Yunnan, symptoms associated with encephalitis were the second most commonly reported, but this was followed by symptoms associated with SARI **(Fig. 9)**.

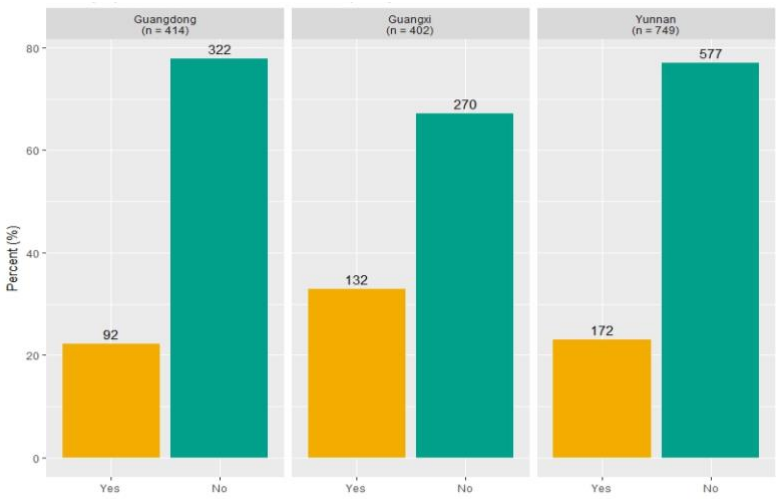


***Figure 9:*** *Symptoms reported by people who had experienced unusual illness in their lifetime.*




In each province, just under one-third of respondents who experienced the symptoms associated with an unusual illness in their lifetime indicated experiencing any of the symptoms in the past year – 22.2% in Guangdong, 32.8% in Guangxi and 23.0% in Yunnan **(Fig. 10)**.

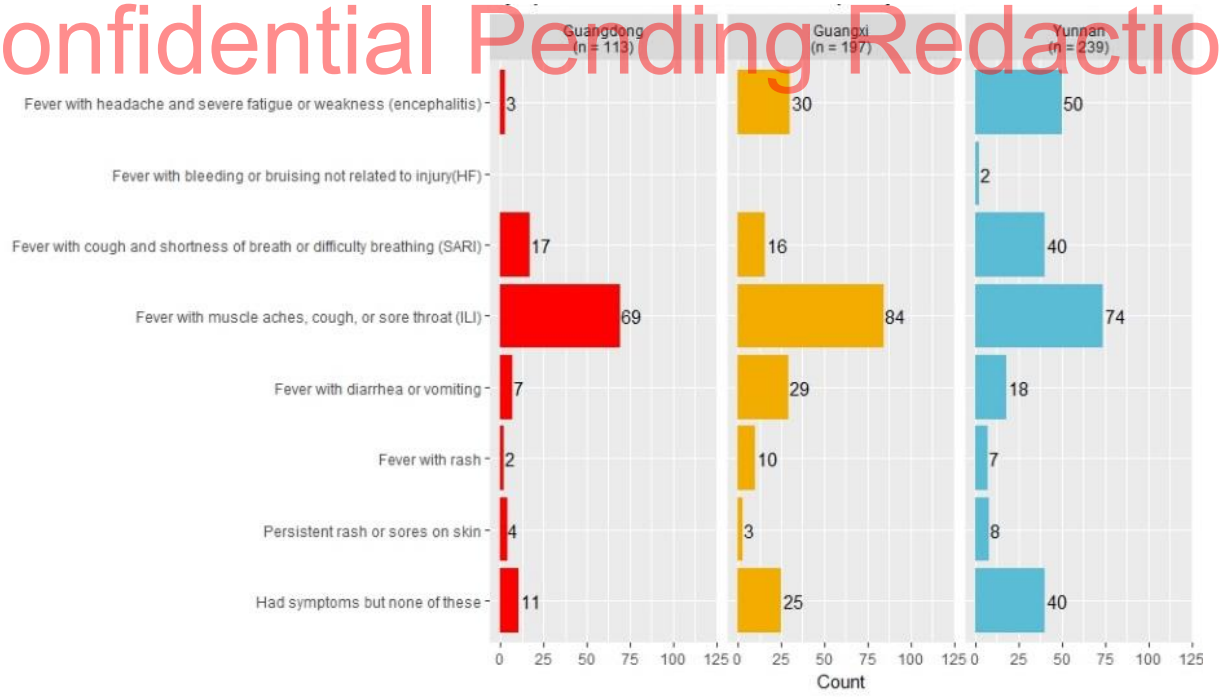
***Figure 10:*** *Whether respondents had experienced symptoms associated with an unusual illness, in the past year.*




Of the respondents who reported having symptoms of unusual illness in the past year, across all three provinces, symptoms associated ILI were the most commonly reported. In Guangdong province, this was followed by symptoms associated with SARI then by other symptoms not provided in the survey. In Guangxi, symptoms associated with ILI were followed by symptoms associated with encephalitis, then by fever with diarrhea or vomiting. In Yunnan, symptoms associated with ILI were followed by symptoms associated with encephalitis, then by both SARI and other symptoms not provided in survey **(Fig. 11)**.

***Figure 11:*** *Symptoms experienced by those reporting unusual illness in the past year.*






When respondents were asked what caused the symptoms associated with unusual illness experienced in the past year, 64.4% in Guangxi (85 of 132 respondents), and 50.0% in both Guangdong and Yunnan (46 of 92 respondents and 86 of 172, respectively), said they did not know the cause **(Fig. 12)**. Only one respondent in Guangxi said their symptoms were due to

contact with animals (wild animals, specifically). Two respondents in Guangdong and one respondent in Guangxi said their symptoms were due to contact with animals (non-wild animals, specifically), whereas none of the respondents in Yunnan attributed their cause to contact with animals.

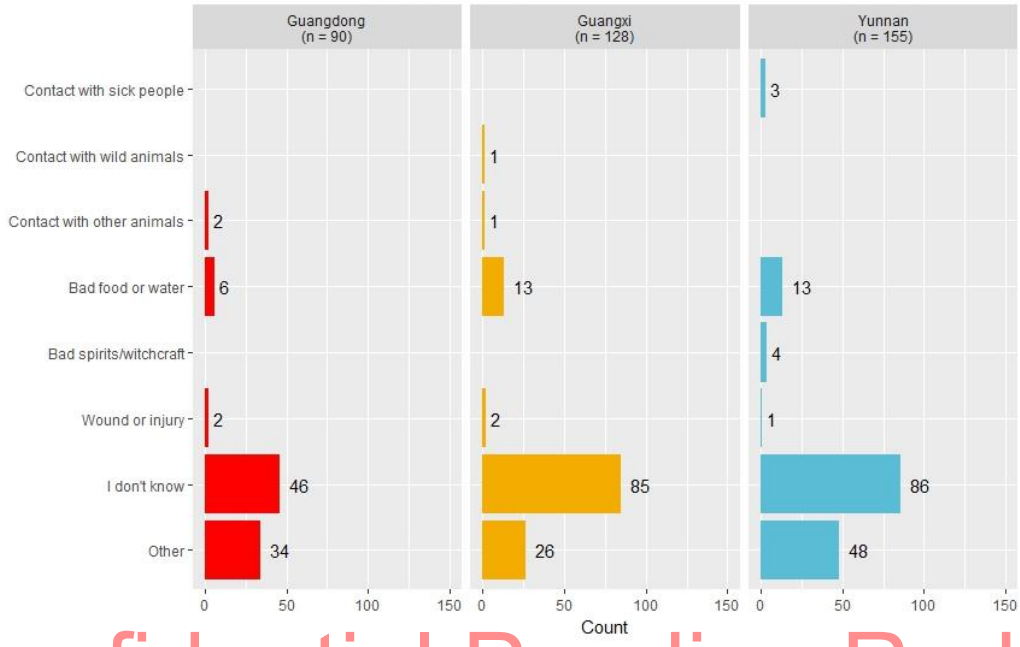
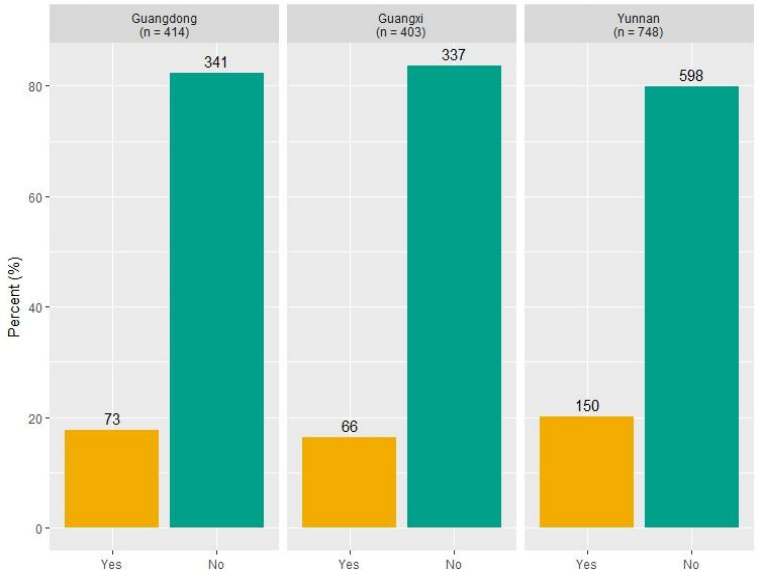





***Figure 12:*** *Reported cause of sickness in the past year.*

Respondents reporting an unusual illness in the past year were asked if any of the people they lived with in the past year had symptoms similar to theirs, to assess possibilities of transmission among household members. Most respondents did not, across all three provinces: 82.4% in Guangdong, 83.6% in Guangxi and 79.9% in Yunnan **(Fig. 13)**.

***Figure 13:*** *Whether household members had similar symptoms of unusual illness, in the past year*



Of the household members who experienced symptoms of unusual illness in the past year, the most commonly reported symptoms were those associated with ILI **(Fig. 14)**.

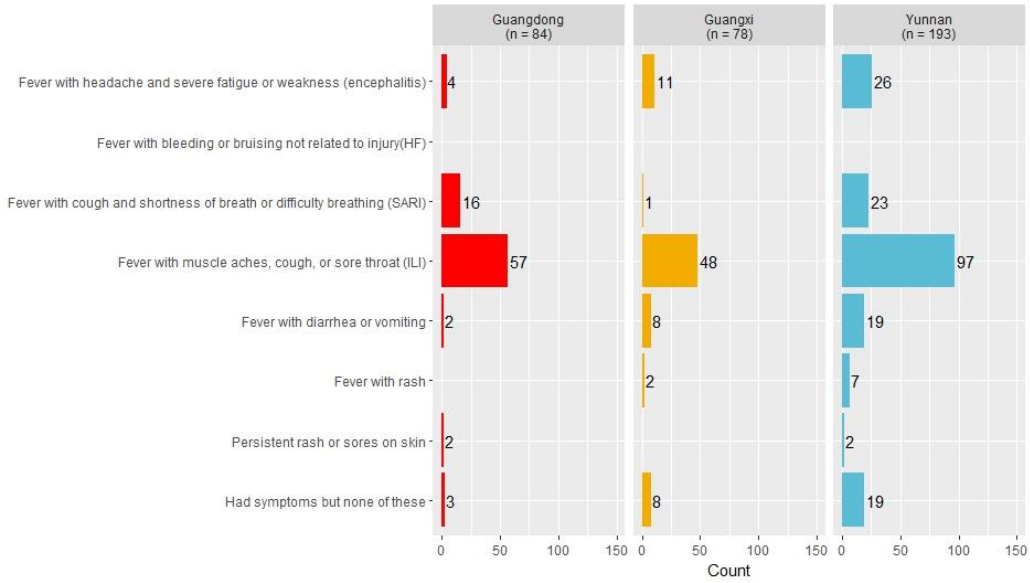



***Figure 14:*** *Symptoms of household members who were ill, in past year.*

Respondents were also asked if any members of their household who experienced symptoms of unusual illness died as a result of their illness in the past year. Across all the three provinces, almost none had died from these illnesses **(Fig. 15)**.



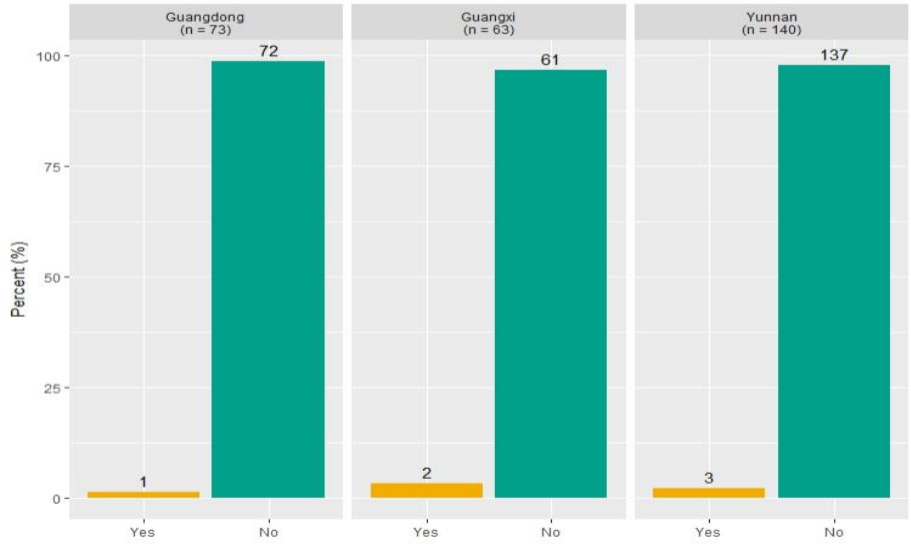



***Figure 15:*** *Whether household members died from illness, in the past year.*

***Contact with Animals***

All respondents were asked about various types of animal contacts in their lifetime and in the past year. More than two-thirds of the respondents across all provinces, as well as in each of the provinces, reported raising an animal within their lifetime (71.2% in Guangdong, 77.7% in Guangxi, and 97.7% in Yunnan). More than half of the respondents in each province reported having animals come inside their dwellings (83.1 % in Guangdong, 60.2% in Guangxi, and 92.5% in Yunnan). More than half of respondents in each province reported handling live animals (51.5 % in Guangdong, 56.9% in Guangxi, and 62.9% in Yunnan) **(Table 1)**. Respondents from Yunnan had more types of contact with animals in their lifetime than those from Guangdong and Guangxi. With the exception of cooking or handling meat, organs, or blood from a recently killed animal and being scratched or bitten by an animal, the proportion of respondents from Yunnan who engaged in all types of animal activities was higher than the other provinces.

| Type of animal contact (past year) | Guangdong | | Guangxi | | Yunnan | |
|---|---|---|---|---|---|---|
| | (n) | (%) | (n) | (%) | (n) | (%) |
| Lived with an animal as a pet | 43 | 100 % | 72 | 98.6 % | 335 | 100 % |
| Handled live animals | 212 | 100 % | 226 | 98.3 % | 332 | 99.7 % |
| Raised a live animal | 296 | 100 % | 312 | 99.4 % | 518 | 99.8 % |
| Shared water source with animals for washing | 47 | 100 % | 19 | 95.0 % | 97 | 100 % |
| Seen animal feces in or near food before you have eaten it | 18 | 100 % | 15 | 93.8 % | 43 | 100 % |
| Eaten food after an animal has touched or damaged it | 6 | 100 % | 6 | 100 % | 29 | 100 % |
| Animals come inside the dwelling where you live | 345 | 100 % | 239 | 98.0 % | 493 | 100 % |
| Cooked or handled meat, organs, or blood from a recently killed animal | 333 | 100 % | 144 | 97.3 % | 412 | 100 % |
| Eaten raw or undercooked meat or organs or blood | 2 | 100 % | 25 | 89.3 % | 65 | 98.5 % |
| Eaten an animal that was not well/sick | -- | -- | 1 | 100 % | 6 | 100 % |
| Found a dead animal and collected it to eat, share, or sell | -- | -- | 3 | 100 % | 10 | 100 % |
| Been scratched or bitten by an animal | 1 | 100 % | 31 | 100 % | 28 | 96.6 % |
| Slaughtered an animal | 145 | 100 % | 69 | 98.6 % | 303 | 100 % |
| Hunted or trapped an animal | 9 | 100 % | 4 | 100 % | 22 | 95.7% |



***Table 1:*** *Types of animal contact, within a respondent's lifetime.*

Respondents who reported having animal contact in their lifetime were also asked to indicate if they had the same type of animal contact in the past year **(Table 2)**. In the past year, across all three provinces and in each province, almost all respondents engaged in all contact types with the exception of eating an animal that was not well/sick, and finding a dead animal and collecting it to eat, share, or sell (0% for both in Guangdong).

| Type of animal contact (lifetime) | Guangdong | | Guangxi | | Yunnan | |
|---|---|---|---|---|---|---|
| | (n) | (%) | (n) | (%) | (n) | (%) |
| Lived with an animal as a pet | 43 | 10.4 % | 73 | 18.1 % | 335 | 62.9 % |
| Handled live animals | 212 | 51.5 % | 230 | 56.9 % | 334 | 62.8 % |
| Raised a live animal | 296 | 71.2 % | 314 | 77.7 % | 521 | 97.7 % |
| Shared water source with animals for washing | 47 | 11.5 % | 21 | 5.2 % | 97 | 18.2 % |
| Seen animal feces in or near food before you have eaten it | 18 | 4.4 % | 16 | 3.9 % | 43 | 8.1 % |
| Eaten food after an animal has touched or damaged it | 6 | 1.5 % | 6 | 1.5 % | 29.0 | 5.4 % |
| Animals come inside the dwelling where you live | 345 | 83.1 % | 244 | 60.2 % | 493 | 92.5 % |
| Cooked or handled meat, organs, or blood from a recently killed animal | 333 | 80.4 % | 148 | 36.7 % | 413 | 77.5 % |
| Eaten raw or undercooked meat or organs or blood | 2 | 0.5 % | 28 | 6.9 % | 68 | 12.8 % |
| Eaten an animal that was not well/sick | -- | -- | 1 | 0.3 % | 6 | 1.1 % |
| Found a dead animal and collected it to eat, share, or sell | -- | -- | 3 | 0.7 % | 10 | 1.9 % |

***Table 2:*** *Types of animal contact, in past year.*

Respondents who had animal contact in the past year were asked to identify the animals involved in the interaction. *(Figs. 16-26, below: the first two figures are enlarged to show row labels, which are identical for all)*. Cats and dogs were the most common pets reported across all provinces and in each province **(Fig. 16b)**.



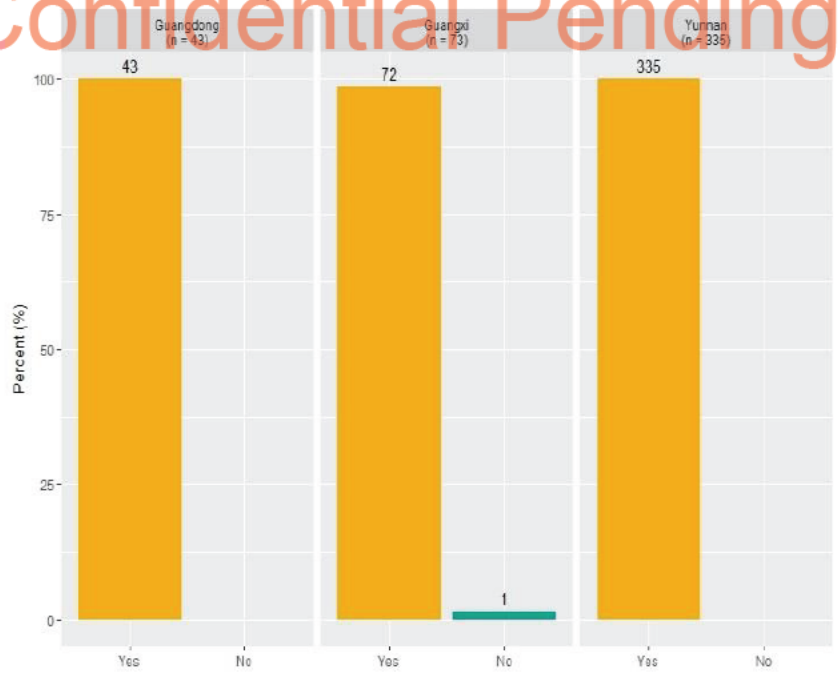
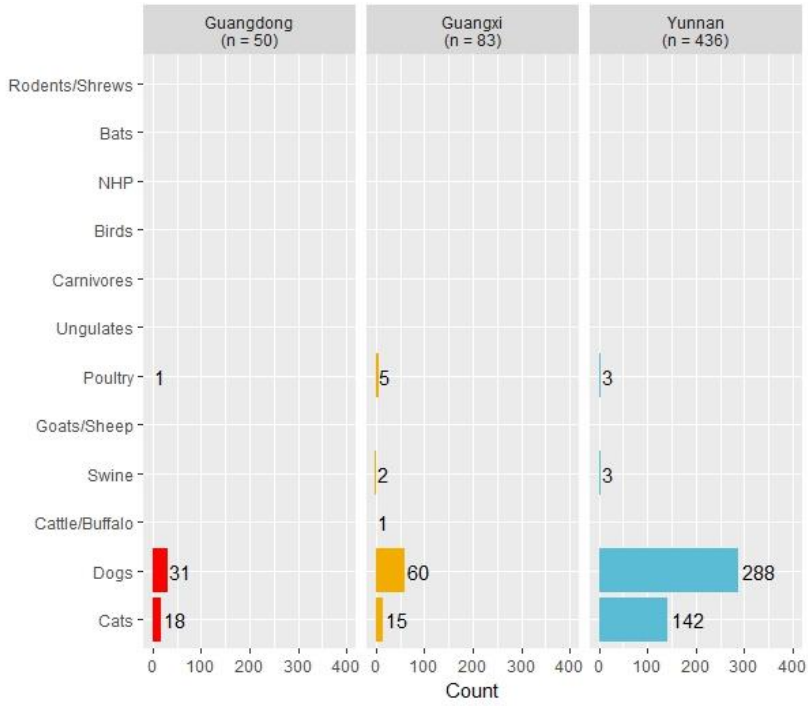



***Figure 16a (top) & b (below):*** *(a) Whether respondents had lived with an animal as a pet, in the past year, and (b) among those who had, types of animal kept as pets.*




Poultry was the most common type of animal handled across all provinces as well as in each province, with 96.2%, 90.3%, and 92.8% of respondents handling animals in Guangdong, Guangxi and Yunnan, respectively **(Fig. 17b)**.



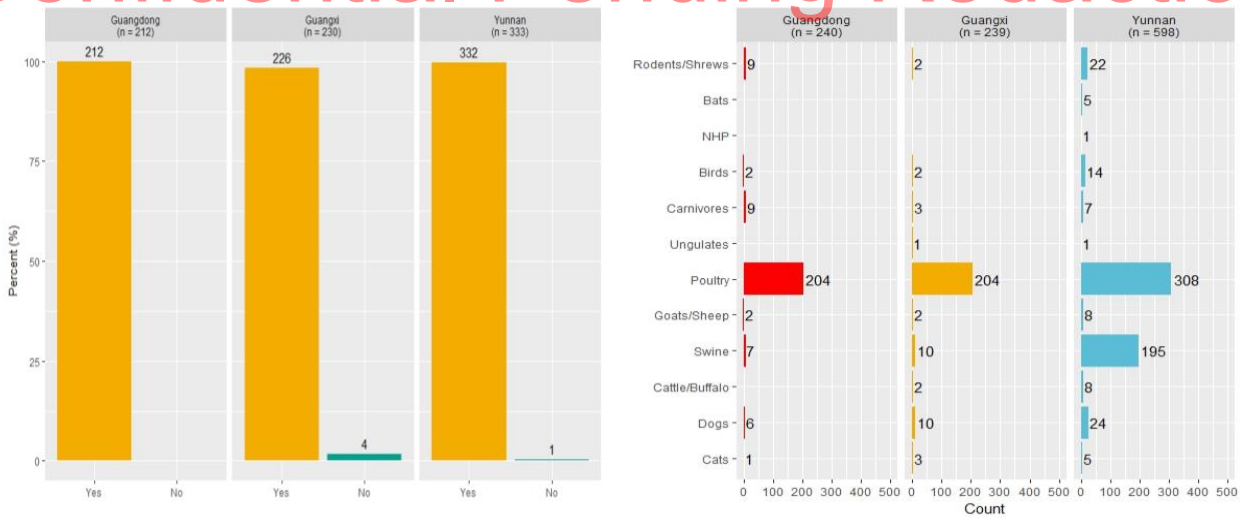
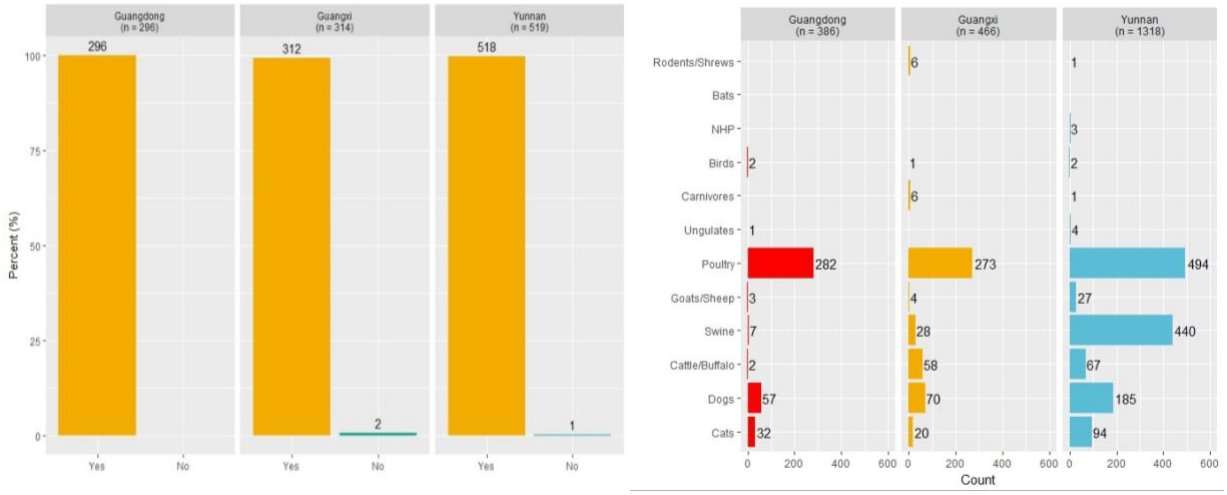



***Figure 17a & b:*** *(a) Whether respondents had handled live animals, in the past year, and (b) among those who had, types of live animals handled.*

Poultry was also the most commonly raised animal in each of the three provinces; 95.3%, 87.5%, 95.4% in Guangdong, Guangxi, and Yunnan, respectively **(Fig. 18b)**.




***Figures 18a & b:*** *(a) Whether respondents had raised live animals in the past year, and (b) among those who had, types of animals raised.*

In all three of the provinces, the most common type of animals found in respondent dwellings were rodents or shrews. In Guangdong and Yunnan, birds were the second most common animal type found in dwellings. In Guangxi province, birds along with poultry were the second most common animal type. Respondents in Guangdong and Yunnan reported that all 12 animal taxa had come inside their dwellings in the past year. Taxa seen in the dwellings of respondents from Guangdong and Yunnan and not Guangxi were non-human primates, ungulates, goats or sheep, swine, and cattle or buffalo **(Fig. 20b)**.



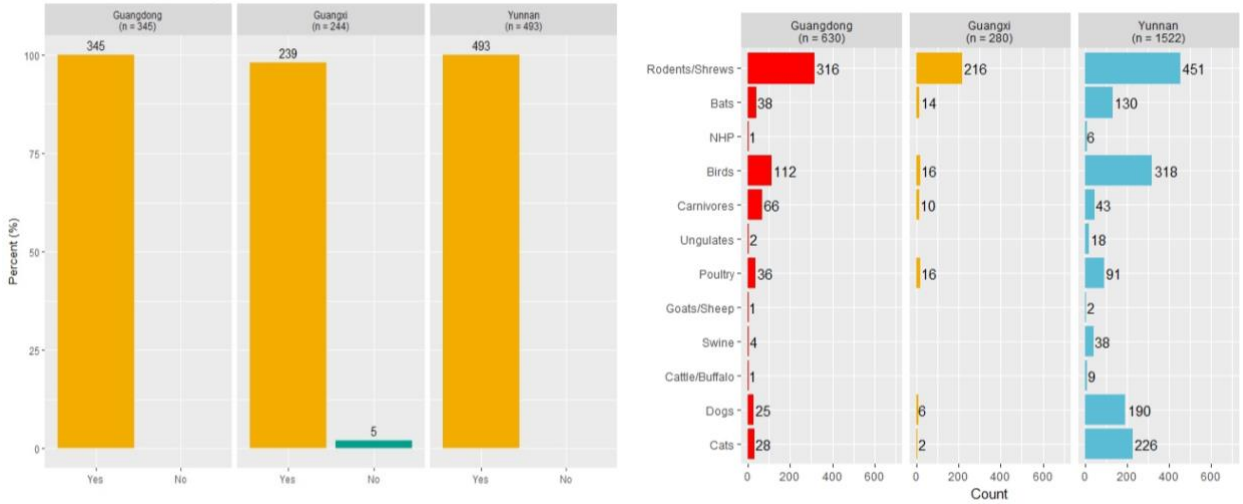



***Figure 19a & b:*** *(a) Whether respondents had animals come inside dwelling, in the past year, and (b) among those who had, types of animals in dwelling.*

Almost all of the respondents who said they have cooked or handled meat, organs, or blood in their lifetime reported doing so in the past year. Common animal types that were cooked handled included poultry and swine in all three provinces **(Fig. 20)**.

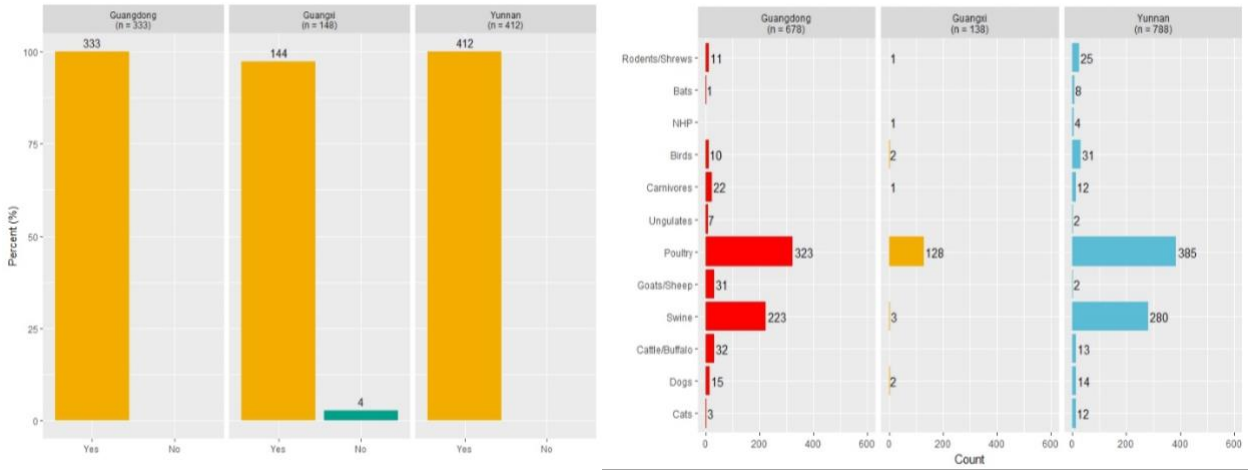



***Figure 20a & b:*** *(a) Whether respondents had cooked or handled meat, organs or blood from a recently killed animal, in the past year, and (b) among those who had, types of animals whose meat, organs or blood was cooked or handled.*

More respondents in Yunnan reported eating raw or undercooked meat compared to respondents in Guangdong and Guangxi **(Fig. 21)**. In Yunnan, 96% of respondents who ate raw or undercooked meat in their lifetime did so in the past year. The types of animal products that were eaten raw or undercooked by respondents in Yunnan were mostly from swine. In Guangxi, the most commonly reported type of animal meat that had been eaten raw or undercooked was that of carnivores.



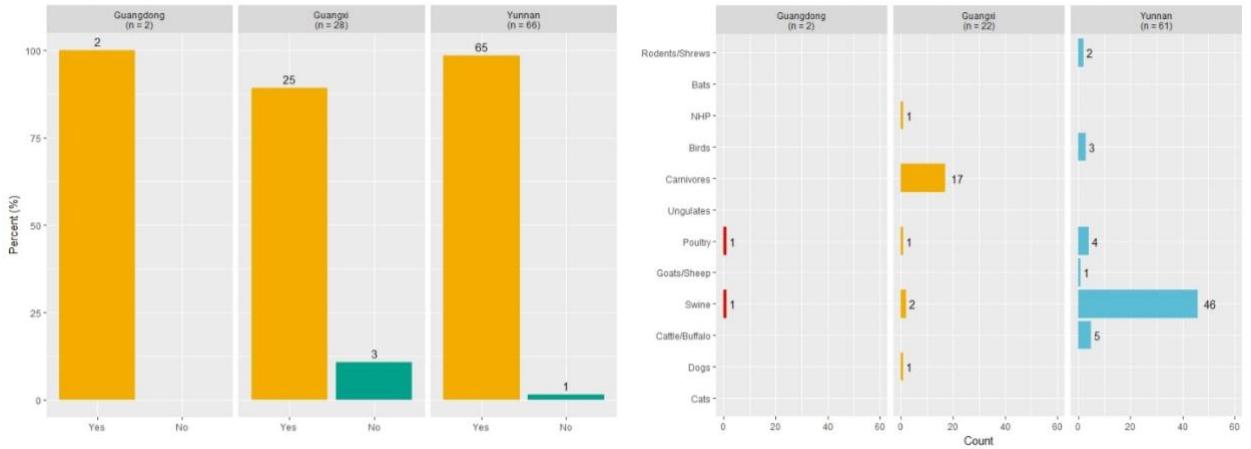



***Figure 21 a & b:*** *(a) Whether respondents had eaten raw or undercooked meat or organs or blood, in the past year, and (b) among those who had, types of animals whose meat, organs or blood were eaten raw or undercooked.*

Across all provinces, a total of 13 respondents in Guangxi and Yunnan indicated that they collected an animal that was found dead to eat, share or sell. In Guandong, no respondents reported finding a dead animal and collecting it to eat, share, or sell. The most common type of animal collected across all provinces in aggregate was poultry. In Yunnan, poultry was the most common type of animal found dead and collected to eat, share or sell (80.0%), whereas dogs were the most common type in Guangxi (66.7%) **(Fig. 22)**.

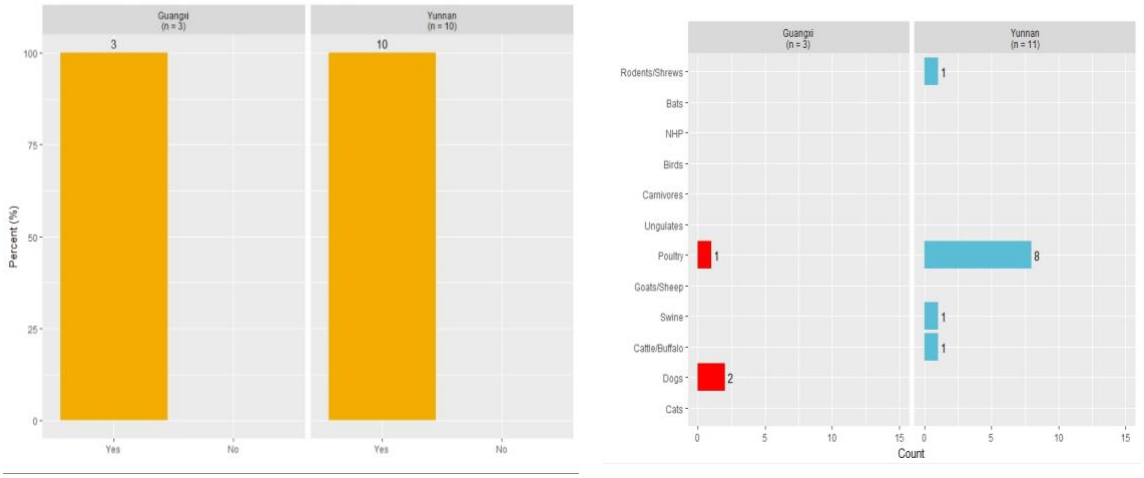



***Figure 22 a & b:*** *(a) Whether respondents had found a dead animal and collected it to eat, share, or sell, in the past year, and (b) among those who had, types of animals that were found dead and collected to eat, share, or sell.*



In each province, almost all of the respondents who indicated being scratched or bitten by an animal in their lifetime said it occurred in the past year (100% in Guangdong, 98.6% in Guangxi, and 100% in Yunnan). In both Guangxi and Yunnan, dogs were the common type of animal that respondents said they were scratched or bitten by (64.5% in Guangxi and 50.0% in Yunnan). Cats were the second most common in Guangxi and Yunnan (9.6% in Guangxi, and 28.5% in Yunnan). Across all three provinces, only one respondent from Yunnan said that they were scratched or bitten by a bat **(Fig. 23)**.

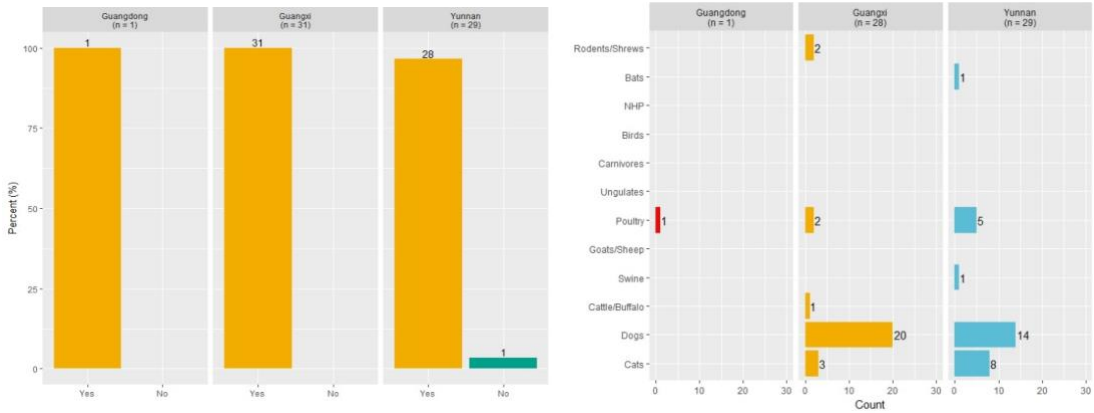



***Figure 23 a & b:*** *(a) Whether respondents had been scratched or bitten by an animal, in the past year, and (b) among those who had, types of animals that scratched or bit respondents.*

Poultry was the most common type of animal slaughtered during the past year across all provinces as well as in each province (95.8% in Guangdong, 79.7% in Guangxi, and 94.1% in Yunnan). In addition to poultry, respondents in Yunnan also commonly only slaughtered swine (43.9%), compared to 1.4% in Guangdong and 7.3% in Guangxi **(Fig. 24)**.

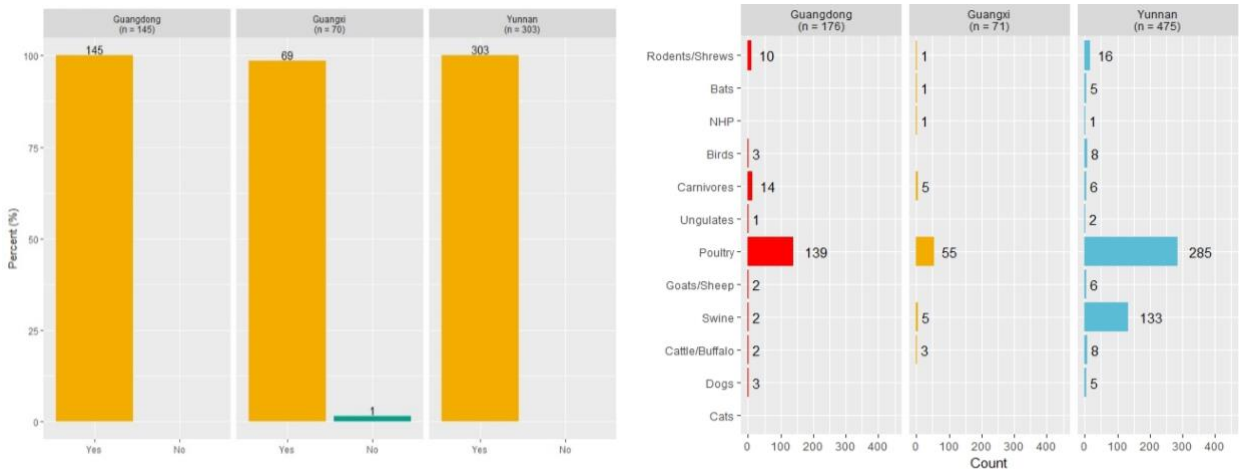



***Figure 24 a & b:*** *(a) Whether respondents had slaughtered an animal, in the past year, and (b) among those who had, types of animals slaughtered.*



Carnivores were the most common taxa of animals hunted or trapped in the past year, in Guangdong and Guangxi. In Yunnan, rodents or shrews and birds were reported as the most common. Bats, non-human primates and dogs were animal types hunted by respondents in Yunnan but not by respondents in Guangdong and Guangxi **(Fig. 25)**.

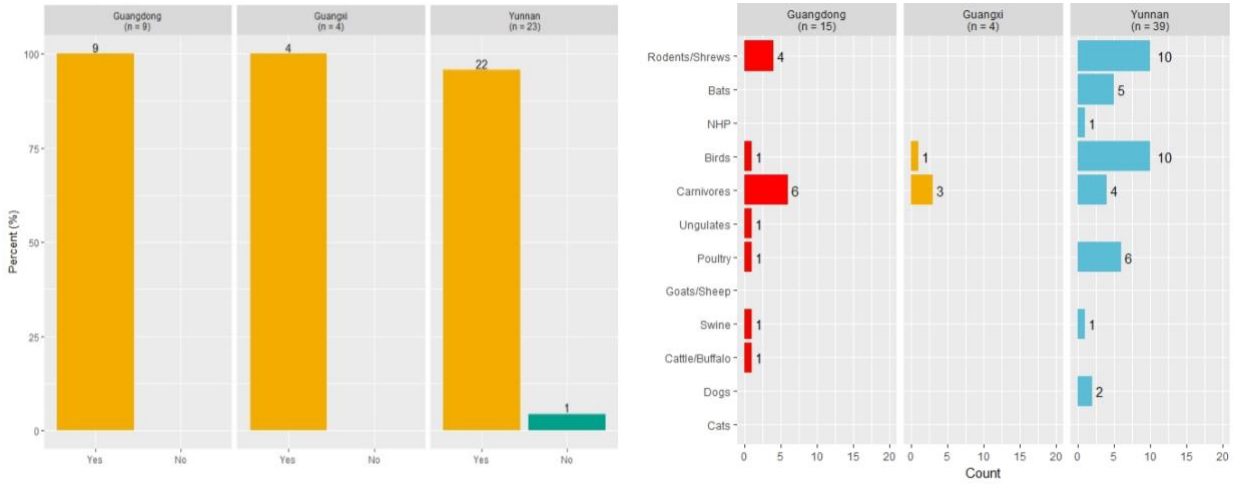



***Figure 25 a & b:*** *(a) Whether respondents had hunted or trapped an animal, in the past year, and (b) among those who had, types of animals hunted or trapped.*

In examining bat-specific contact, across all provinces and within each province, the most common interaction with bats was finding them inside their houses. Respondents in Yunnan also hunted/trapped and handled bats, and were scratched/bitten by bats, whereas these did not occur in Guangdong or Guangxi **(Fig. 26)**.

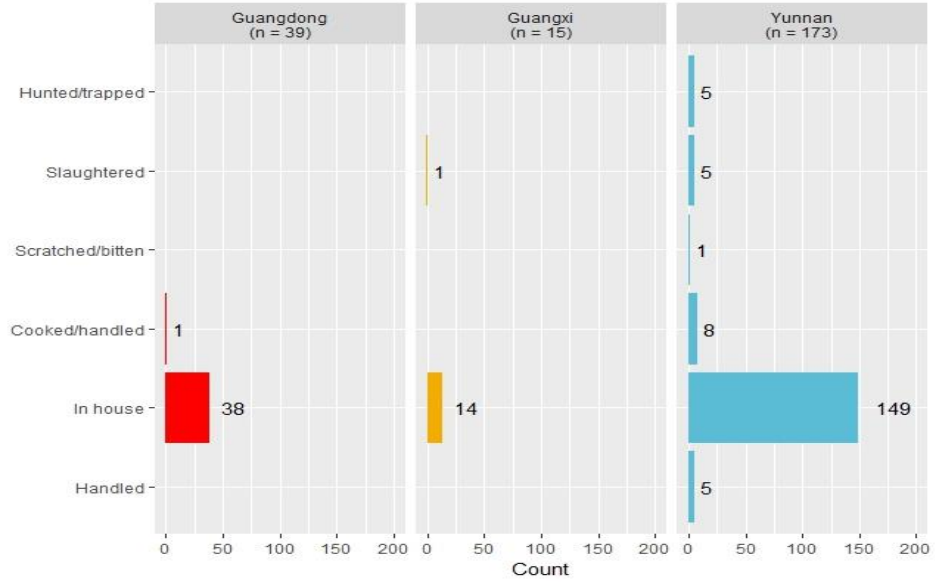



***Figure 26:*** *Types of bat contact.*



After respondents were asked about their contact with wildlife and livestock, they were asked about their knowledge of whether animals can spread diseases and whether they were worried about diseases and disease outbreaks at wet markets. The proportion of respondents who thought that animals can spread disease was highest in Guangdong province (72.3%). In Guangxi and Yunnan, the proportion of those who thought animals could spread disease compared to those who thought that they did not were roughly equivalent – 47.5% versus 50.7% in Guangxi and 49.2% versus 49.3% in Yunnan **(Fig. 27)**.

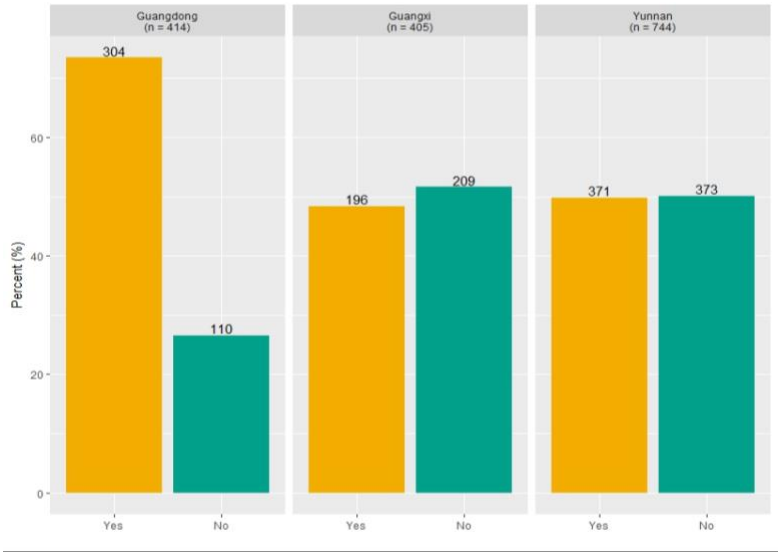



***Figure 27:*** *Whether respondents thought that animals can spread disease.*

Similarly, when respondents were asked about whether they were worried about diseases or disease outbreaks in animals at wet markets, Guangdong had the highest proportion of respondents who said they were worried (67.3%). In both Guangxi and Yunnan, the proportion of respondents that was not worried (57.5% and 51.5%, respectively) was higher than the proportion that was worried **(Fig. 28)**

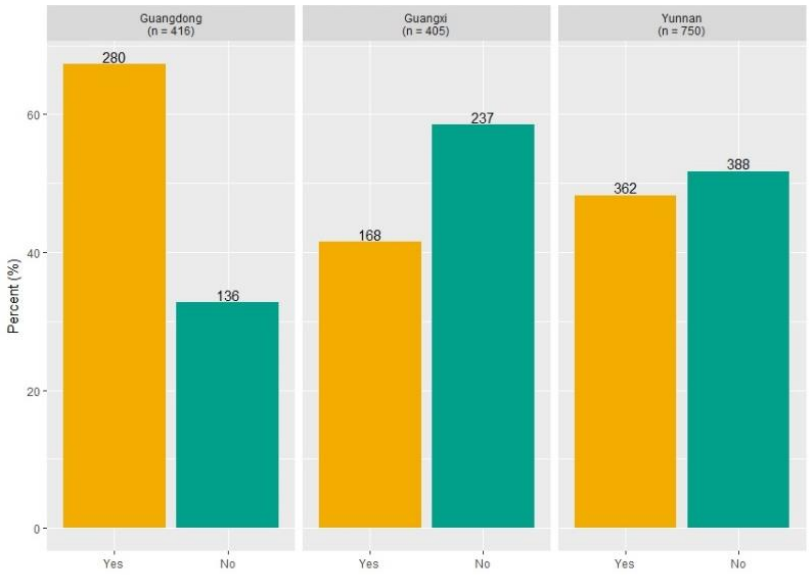



***Figure 28:*** *Whether respondents were worried about diseases or disease outbreaks in animals at wet markets.*



**Serological Evidence of Bat SARS-related CoV Infection in Humans**

Respondents were asked to provide a biological sample to assess whether SARS-CoV spillover had occurred at the high-risk location where the survey has been implemented. A total of 1,530 serum samples were collected from 2016 to 2017 from individual residents in villages close to bat caves where coronaviruses were previously detected.

We developed an ELISA serology test using the purified NP protein of MERS-CoV, SARSr-CoV, HKU9 CoV and HKU10 CoV as coating antigen respectively and using Anti-Human IgG Monoclonal antibody as secondary antibody. All sera were screened for antibodies against these 4 bat-origin coronaviruses. Anti-SARSr-CoV NP IgG was detected in 10 samples, and 6 samples were positive for IgG against HKU10 NP. The 16 ELISA positive samples were further tested by confirmatory western blot, 7 samples from Yunnan province were confirmed positive for anti-SARSr-CoV, two samples (one from Guangdong province and one Guangxi province) were confirmed positive for anti-HKU10 **(Table 3)**.

| Locations | | Sample No. | NP Antibody Positive No. | | | |
|---|---|---|---|---|---|---|
| | | | HKU9 CoV | MERS CoV | SARSr-CoV | HKU10 CoV |
| Yunnan (2016) | Jinning | 209 | | | *6 | |
| | Mengla | 168 | | | 2 (*1) | |
| | Jinghong | 212 | | | | 2 |
| | Lufeng | 144 | | | | |
| Guangdong (2016) | Zengcheng | 234 | | | 1 | 2 |
| | Ruyuan | 179 | | | | |
| Guangxi (2017) | Mashan | 160 | | | 1 | |
| | Guilin | 224 | | | | *2 |
| Total | | 1,530 | 0 | 0 | *7 | *2 |

***Table 3*** *Results of ELISA testing of human sera for antibodies to 4 different bat CoV species (*confirmed with western blot).*

*Links Between ELISA Results and Behavior*

Only one out of the seven SARS-related CoV seropositive respondents said that they had an unusual illness in their lifetime with reported symptoms similar to encephalitis or neural involvement. Two of the respondents said they had experienced symptoms in the past year with only one respondent specifying that they experienced epigastric pain and dizziness. The seven seropositive SARSr-CoV respondents reported various types of animal contacts in the past year. Three had lived with an animal as a pet, four handled a live animal, four raised a live animal, five saw animals inside their dwellings, five had cooked or handled meat, organs, or blood from a recently killed animals, one ate an animal that they knew was not well or sick, one was scratched or bitten by an animal, and four had slaughtered an animal. The only bat contact reported was by one respondent who saw a bat in their dwelling.



Both of the respondents who tested positive for HKU10-CoV antibodies said they had experienced an unusual illness in their lifetime, with symptoms associated with encephalitis and SARI. Neither respondent had experienced any symptoms of unusual illness in the past year. Both had reported handling and raising animals, with one indicating they saw animals come inside their dwelling, and one indicating cooking or handling meat, organs, or blood from a recently killed animal. No bat contact was reported by either of the respondents. Overall, five of the total nine SARS-related CoV and HKU10-CoV seropositive respondents reported being worried about disease or disease outbreaks at wet markets. Seven of the nine reported purchasing live animals from a wet market.

**Specific Aim 1: Summary of Key Findings**

Our analysis of the key risk factors relating to potential viral zoonotic disease spillover in China indicated some notable differences among the respondents in Guangdong, Guangxi, and Yunnan. With respect to demographic factors, Guangxi fared the lowest on key socio-economic

status indicators when compared to Guangdong and Yunnan provinces as reflected by the higher proportion of respondents in Guangxi living under the poverty level.

When assessing the type of animal contact and the associated animal taxa over the course of a respondent's lifetime, the results show that respondents in Yunnan engaged in greater contact with animals then those from Guangdong and Guangxi. For example, for 12 of the 14 animal contact types, a higher proportion of Yunnan respondents engaged in these respective activities than in Guangdong and Guangxi. Respondents in Yunnan also reported hunting bats, dogs, and non-human primates which were not reported to being hunted in Guangdong and Guangxi. Swine contact was higher in Yunnan for handling, raising, and slaughtering activities. When examining the various types of animal contact associated with bats only, our results also show that Yunnan respondents reported more varied types of contact with bats. Respondents in Yunnan indicated handling, being scratched by, slaughtering, and hunting bats, but these interactions did not occur in Guangdong or Guangxi. Additional analyses that examine predictors of animal contact in each province will be the focus of human behavioral analyses in Year 5 of the study.

Even though our sample population lives in areas that have dense and diverse bat populations, our results show an overall low proportion of respondents reporting hunting and trapping bats in all three provinces. The low proportion of hunting practice could be attributed to the success of conservation enforcement efforts undertaken by the government. These efforts may have effectively reduced the illegal practice of hunting wildlife or, as a consequence, moved the activity underground which made respondents less forthcoming about revealing their engagement in such practices. Further investigation into the potential causes is also warranted.



Our analyses also reveal differences in perceptions associated with zoonotic disease spillover between Guangdong, and Guangxi and Yunnan. For example, the proportion of respondents who thought that animals can spread disease was highest in Guangdong province at 72.3%, as compared to Guangxi (48.3%) and Yunnan (49.9%). Moreover, about two-thirds of respondents in Guangdong were worried about diseases and disease outbreaks in wet markets. These differences in perception observed in Guangdong compared to Guangxi and Yunnan could potentially be attributable to a heightened awareness of zoonotic disease emergence due to the 2001 SARS outbreak.

Finally, our serological testing results provide the first evidence ever of a bat SARSr-CoV spilling over into people in the wild. All of the SARSr-CoV positive individuals were from Yunnan province, which is the site of a cave in which we have identified a large diversity of SARSr-CoVs within the virome of which every genetic element of SARS-CoV can be identified. These findings warrant further investigations into the type of exposures that may have contributed to bat SARS-related CoVs to infect humans in this particular region. **They also highlight this region as a hotspot for SARSr-CoV future spillover risk.**

## Specific Aim 2: Receptor evolution, host range and predictive modeling of bat-CoV emergence risk

### Bat CoV PCR Detection and Sequencing from Live-Sampled Bat Populations

We collected rectal swab and oral swab samples from 671 individual bats from 20 species in Guangdong and Guangxi provinces in southern China in Year 4 **(Table 4)**. 671 rectal swab samples were tested for CoV RNA and 154 (23.0%) were positive **(Table 5)**.

| Date of Sampling | Sampling Locations | Rectal swabs | Oral swabs |
|---|---|---|---|
| May 10th 2017 | Hezhou, Guangxi | 6 | 6 |
| May 11-12th 2017 | Chongzuo, Guangxi | 67 | 67 |
| May 13th 2017 | Nanning, Guangxi | 66 | 66 |
| May 17th, 2017 | Beihai, Guangxi | 23 | 23 |
| May 19th 2017 | Chongzuo, Guangxi | 36 | 36 |
| May 21st 2017 | Yangshan, Qingyuan, Guangdong | 46 | 46 |
| May 22nd, June 7th 2017 | Huidong, Huizhou, Guangdong | 103 | 103 |
| June 9th 2017 | Nanning, Guangxi | 71 | 71 |
| June 9th 2017 | Ningming, Chongzuo, Guangxi | 63 | 63 |
| September 10th 2017 | Huidong, Huizhou, Guangdong | 100 | 100 |
| September 11th 2017 | Yingde, Guangdong | 90 | 90 |
| **Total** | | **671** | **671** |

***Table 4.*** *Bat samples collected for CoV surveillance in Year 4*



| Species | Guangdong | Guangxi | Tota |
|---|---|---|---|
| *Rhinolophus sinicus* | **9**/27 | 6 | **9**/33 |
| *Rhinolphus rex* | | 4 | 4 |
| *Rhinolophus pusilus* | 1 | 2 | 3 |
| *Rhinolophus pearsoni* | 5 | | 5 |
| *Hipposideros armiger* | 24 | 8 | 32 |
| *Hipposideros larvatus* | 9 | 9 | 18 |
| *Hipposideros pomona* | | 20 | 20 |
| *Hipposideros pratti* | 26 | | 26 |
| *Aselliscus stoliczkanus* | | 1 | 1 |
| *Miniopterus fuliginosus* | 1 | | 1 |
| *Miniopterus pusillus* | **29**/39 | | **29**/39 |
| *Myotis chinensis* | **2**/27 | | **2**/27 |
| *Myotis daubentonii* | 2 | | 2 |
| *Myotis ricketti* | **86**/178 | | **86**/178 |
| *Pipistrellus abramus* | | 2 | 2 |
| *Pipistrellus pipistrellus* | | 2 | 2 |
| *Scotophilus kuhli* | | **24**/137 | 24/137 |
| *Tylonycteris pachypus* | | **4**/115 | **4**/115 |
| *Tylonycteris robustula* | | 3 | 3 |
| *Cynopterus sphinx* | | 23 | 23 |
| **Total** | **126/339** | **28/332** | **154/671** |

***Table 5****. Number of bat specimens tested and positive (bold) in Year 4*

A high prevalence of HKU6-related coronaviruses (48.3%), Scotophilus coronavirus 512 (17.5%), and coronavirus 1B (71.8%) was detected in *Myotis ricketii*, *Schotophilus khulii* and *Miniopterus pusillus*, respectively. SARS-related coronaviruses and HKU2-related coronaviruses were discovered in 4 and 5 *Rhinolophus sinicus* samples respectively from Guangdong. HKU4 coronaviruses were identified in 4 *Tylonycteris pachypus* from Guangxi **(Fig. 29)**.

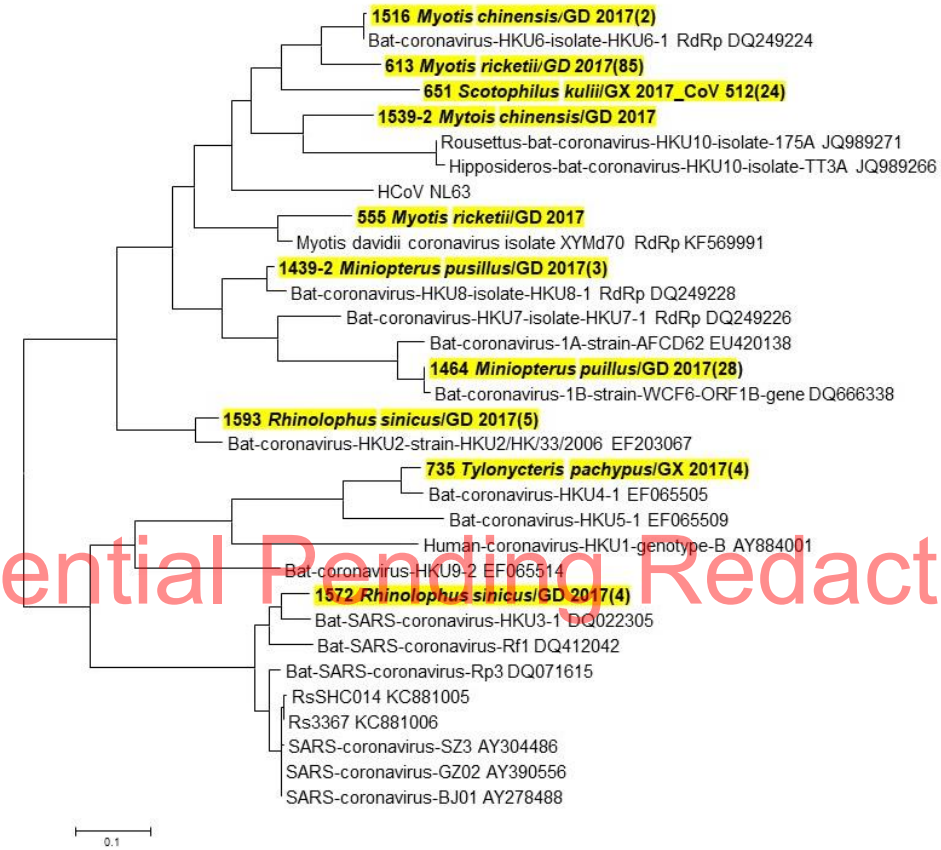





***Figure 29:*** *Phylogenetic analysis of partial RdRp gene of CoV (440-nt partial sequence)*

**Genetic Diversity and Genomic Characterization of Betacoronaviruses in Fruit Bats**

In Year 4, we analyzed the genetic diversity of betacoronaviruses we have detected since 2009 in different species of fruit bats in Yunnan province, including *Eonycteris spelaea*, *Rousettus leschenaultia* and an unclassified *Rousettus* species. These viruses are classified into two betacoronavirus species, HKU9-CoV and GCCDC1-CoV. All HKU9-related viruses (n=46) were found in *Rousettus* spp. bats while GCCDC1-related viruses (n=13) from *E. spelaea*. Phylogenetic analysis of the full-length N gene suggests that HKU9-related CoVs are highly diverse and divided into 5 lineages with previously reported strains, and the GCCDC1-related CoVs were more similar between each other **(Fig. 30)**.

The full-length genome sequence of a novel HKU9-related CoV termed 2202 was determined. It shares 83% nt identity with other HKU9 strains, with the most divergent regions located in the S

protein, but shares only 68% aa identity with those of other HKU9 strains. Virus quantification revealed that intestine was the primary infected organ for HKU9-related CoVs while kidney and lungs could also be target tissues, suggesting potential for spillover through oral-fecal, respiratory, or uro-genitary routes.

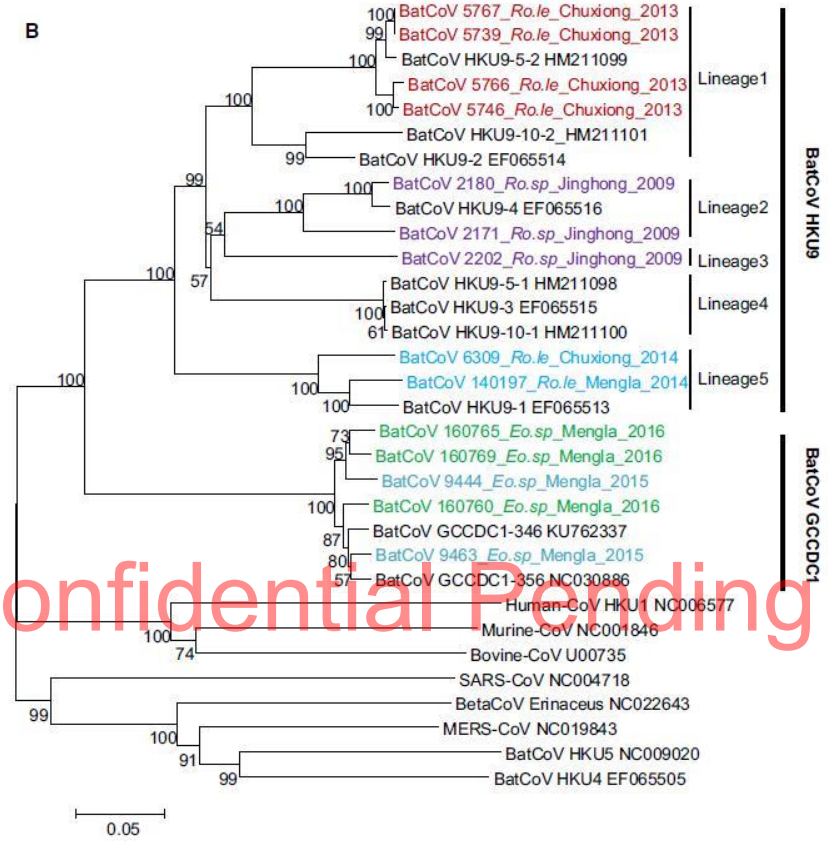



***Figure 30***. *Phylogenetic analysis of full-length N gene of HKU9 and GCCDC1 CoVs*



**Bat Coronavirus Host-Virus Phylogeography in China**

We used discrete ancestral character state reconstruction to estimate viral history and reconstructed the inferred bat host genus for each node within the phylogenetic tree **(Figs. 31, 32)**. The color of tree branches indicates the inferred ancestral host bat genus for the reconstructed phylogeny. *Rhinolophus* is the inferred ancestral host of lineages B and C (SARS-like CoVs and MERS-like CoVs, respectively). This genus played an important role in the diversification of Beta-CoVs. A larger host diversity is observed for Alpha-CoVs. Our dataset for this analysis includes all CoV RdRp sequences isolated from bat specimens collected by our team from 2008-2015 (Alpha-CoVs: n = 491 – Beta-CoVs: n = 326), including those collected under prior NIAID funding (1 R01 AI079231), funding from Chinese Federal Agencies, and a large majority from our current NIAID project. All Chinese bat CoV RdRp sequences available in GenBank were also added to our dataset (Alpha-CoVs: n = 226 – Beta-CoVs: n = 206).

Phylogenetic trees were reconstructed for Alpha- and Beta-CoVs separately using Bayesian inference (BEAST 1.8).

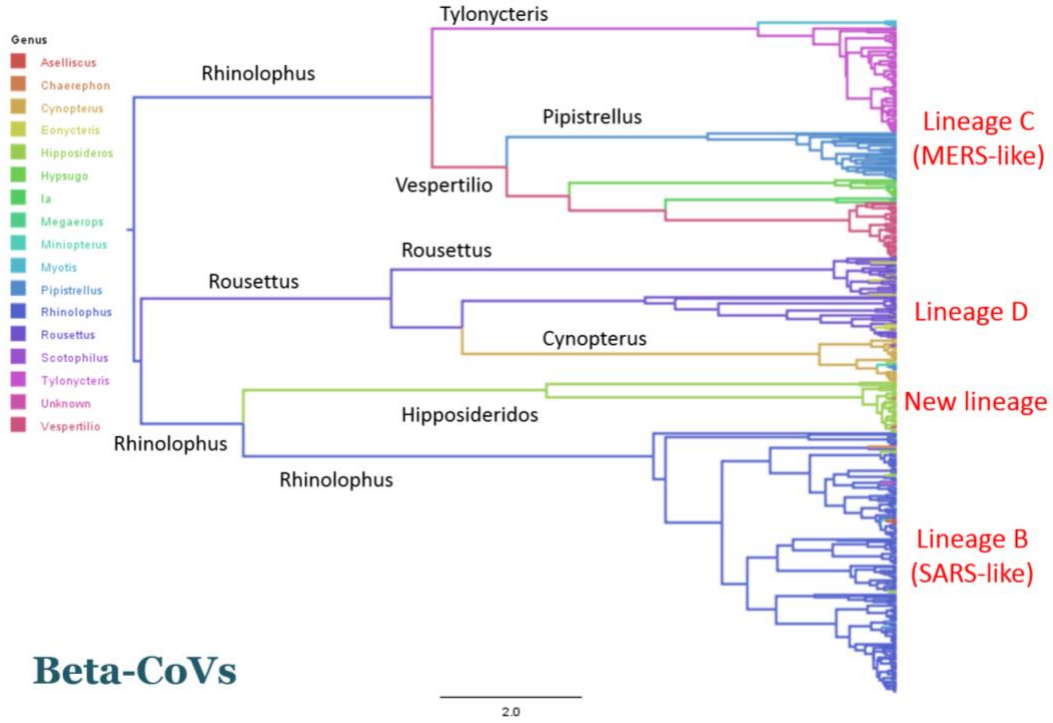



***Figure 31.*** *Ancestral host reconstruction for Beta-CoVs, at a host genus level.*



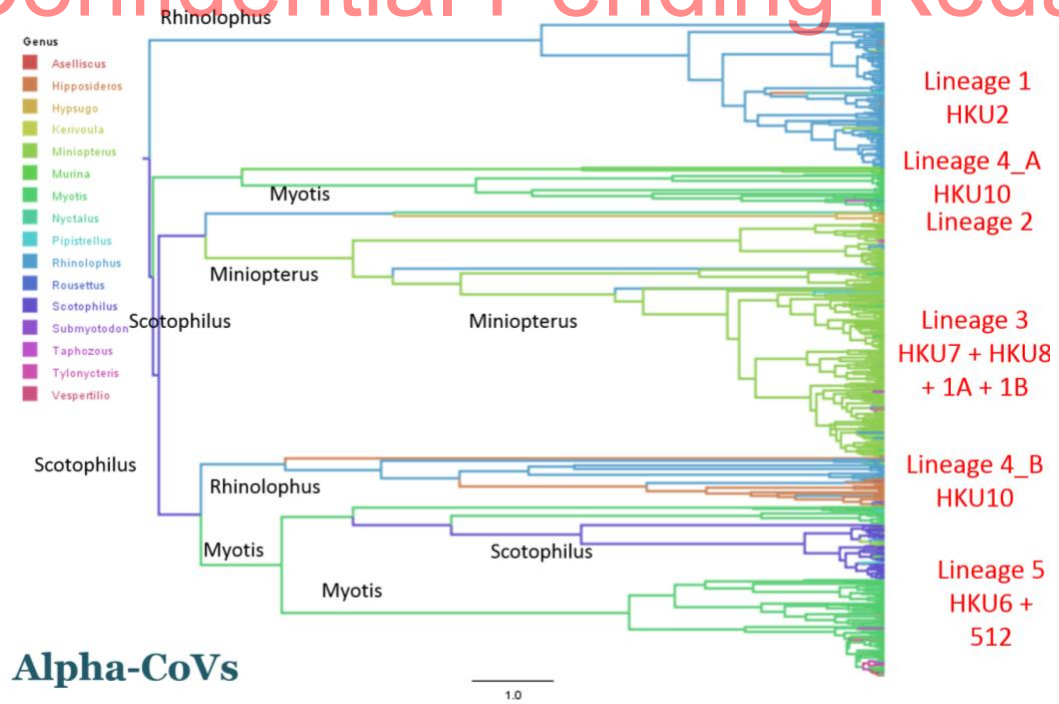



***Figure 32.*** *Ancestral host reconstruction for Alpha-CoVs, at a host genus level.*

To better understand the geographic origins and extent of specific CoV clades, we also used discrete ancestral character state reconstruction in BEAST to reconstruct the ancestral location of each branch of the tree. We used SPREAD to visualize the tree in its geographic context and infer CoV spatial spread in China **(Fig. 33)**. These analyses allow us to identify the geographic areas that are likely sources of origin/diversity for this important group of viruses. The common ancestor of most Beta-CoVs lineages is located in Hong Kong and Guangdong. The common ancestor of most Alpha-CoV lineages was located in Yunnan province, and our results suggest they spread to other provinces from Yunnan.

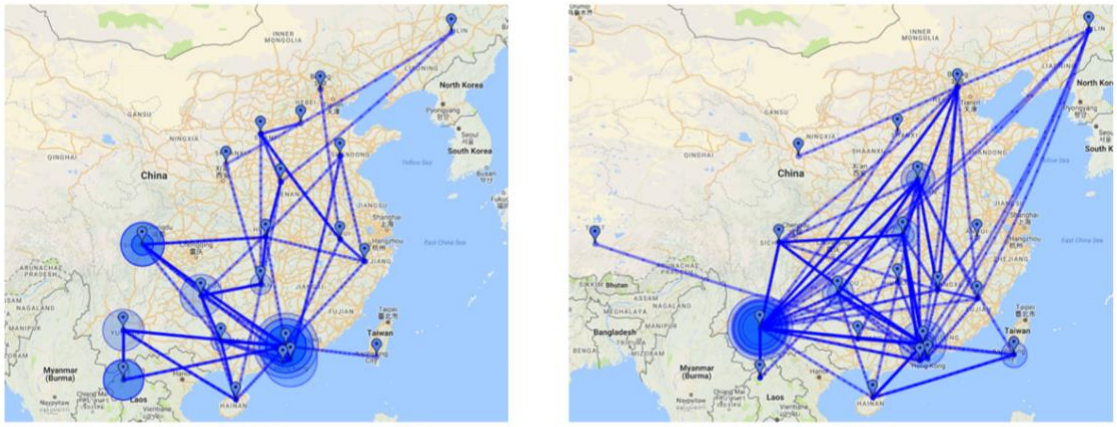





***Figure 33.*** *Ancestral location reconstruction for Beta- and Alpha-CoVs. The bigger the circle is, the more ancestral the corresponding node is.*

**Specific Aim 3: Testing Predictions of CoV Inter-Species Transmission**

**Identification of two novel MERS-related CoVs that use DPP4 receptor**

Two novel MERSr-CoVs, BtCoV/li/GD/2013-845 and BtCoV/li/GD/2014-422, were identified from great evening bats (*Ia io*) in Guangdong province. Phylogenetic analysis of polyprotein 1 and the E, M, and N proteins suggests that the two novel strains are more closely related to MERS-CoV than to other lineage C Beta-CoVs. Their RdRp sequences are closely related to those of MERS-CoV and other MERSr-CoVs, with 94.4–97.0% aa identities. In contrast, they are divergent from MERS-CoV and other MERSr-CoVs in the spike protein, with only 58.9–64.7% aa identities. However, in the receptor-binding domain (RBD) of the spike protein, the two novel MERSr-CoVs are identical to MERS-CoV at six out of the 13 residues that directly interact with human DPP4 receptor, making them more similar to MERS-CoV than any other known lineage C BetaCoVs **(Fig. 34a)**. Protein–protein interaction assays demonstrated that the spike proteins of the novel MERSr-CoVs bind to both human and bat DPP4 **(Fig. 34b)**. Moreover, bat cells exogenously expressing human DPP4 support the entry of the retrovirus pseudotyped with BtCoV/li/GD/2014-422 spike, while the pseudovirus fails to enter cells that do not express DPP4. The results demonstrate that the spike protein of the newly identified MERSr-CoV recognizes the human DPP4 receptor.

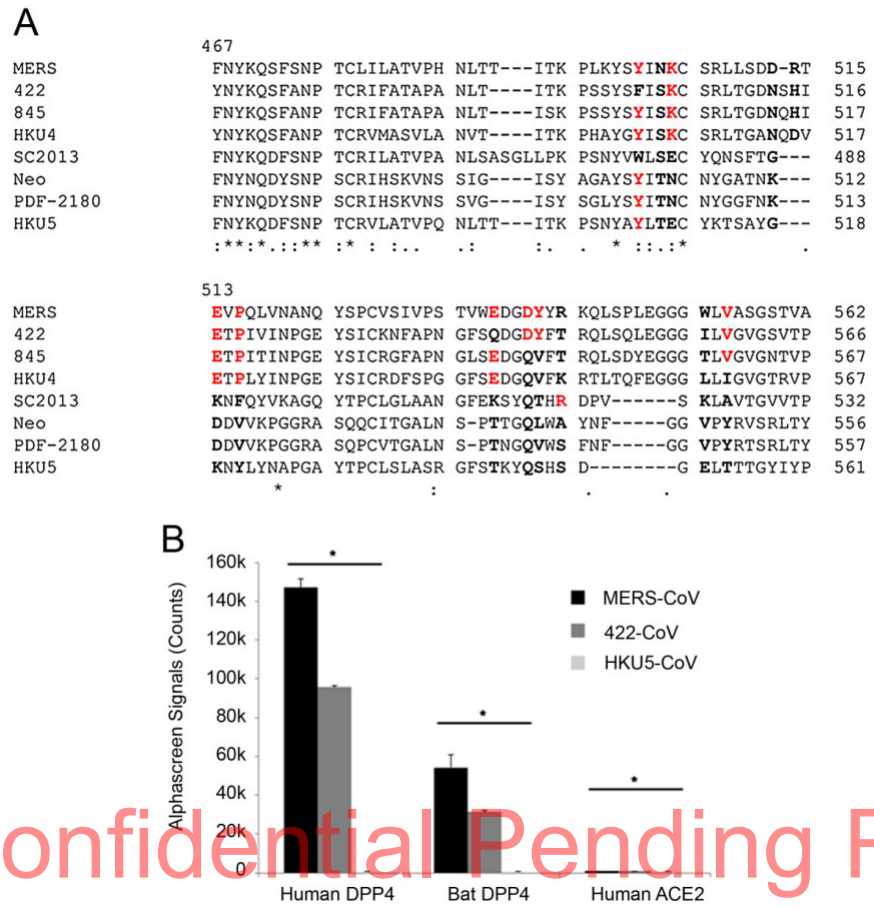





***Figure 34.*** *BtCoV/li/GD/2014-422 RBD analysis (a) and DPP4-binding assay (b)*

### *In Vivo* Infection of Human ACE2 (hACE2) Expressing Mice with SARSr-CoV S Protein variants

Using the reverse genetic methods we previously developed, infectious clones with the WIV1 backbone and the spike protein of SHC014, WIV16 and Rs4231, respectively, were constructed and recombinant viruses were successfully rescued. In Year 4, we performed preliminary *in vivo* infection of SARSr-CoVs on transgenic mice that express hACE2. Mice were infected with $10^5$ pfu of full-length recombinant virus of WIV1 (rWIV1) and the three chimeric viruses with different spikes. Pathogenesis of the 4 SARSr-CoVs was then determined in a 2-week course. Mice challenged with rWIV1-SHC014S have experienced about 20% body weight loss by the 6th day post infection, while rWIV1 and rWIV-4231S produced less body weight loss. In the mice infected with rWIV1-WIV16S, no body weight loss was observed **(Fig. 35a)**. 2 and 4 days post infection, the viral load in lung tissues of mice challenged with rWIV1-SHC014S, rWIV1-WIV16S and rWIV1-Rs4231S reached more than $10^6$ genome copies/g and were significantly higher than that in rWIV1-infected mice **(Fig. 35b)**. These results demonstrate varying pathogenicity of SARSr-CoVs with different spike proteins in humanized mice.

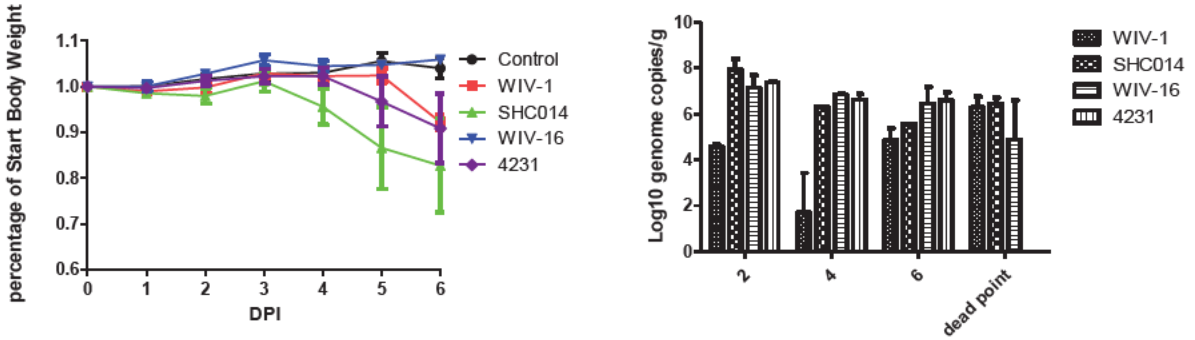



***Figure 35.*** *In vivo infection of SARSr-CoVs in hACE2-expressing mice. (a, left) Body weight change after infection; (b, right) Viral load in lung tissues*

**Additional Year 4 Results for Specific Aim 3:**

**Identification of a HKU2-related Coronavirus of Bat Origin that Caused Fatal Acute Diarrhea in Piglets**

From October 2016, a series of fatal swine diarrhea disease outbreaks occurred in Guangdong province. By May 2017, it had resulted in death of 24,693 piglets across four farms. We identified a novel coronavirus as the etiological agent of the disease by metagenomic analysis, viral isolation and experimental infection, and named this "Swine Acute Diarrhea Syndrome coronavirus (SADS-CoV). During Year 4, we submitted and published a paper on this finding to *Nature* (Zhou *et al.*, 2018). The full-length genome of SADS-CoV shares 95% sequence identity to bat CoV HKU2. However, the S gene sequence identity is only 86%, suggesting that the previously reported HKU2-CoV is not the direct progenitor of SADS-CoV, but that they may have originated from a common ancestor.



Using a SADS-CoV specific qPCR assay based on its RdRp gene, SADS-related coronaviruses (SADSr-CoVs) were detected in rectal swabs of *Rhinolophus* bats collected from 2013 to 2016 in Guangdong. Full-length genome sequencing of 4 bat SADSr-CoVs revealed 96% to 98% overall genome sequence identity between SADSr-CoVs and SADS-CoV. Most importantly, the S protein of SADS-CoV shared more than 98% sequence identity with those of the two SADSr-CoVs (162149 and 141388), compared to 86% with HKU2-CoV **(Fig. *36a*)**. The phylogeny of S1 protein sequence showed strong co-evolutionary relationships with bat alphacoronavirus and their hosts, with swine SADS-CoV more closely related to SADSr-CoVs from *Rhinolophus affinis* than strains from *Rhinolophus sinicus* in which HKU2-CoV was found **(Fig. 36b)**. Analysis of the 33 SADS-CoV full genome sequences we were able to characterize from pigs suggests that viruses from the four farms may have been transmitted from their reservoir hosts independently. These findings highlight the importance of identifying coronavirus diversity and distribution in bats to mitigate future outbreaks that threaten livestock and public health.

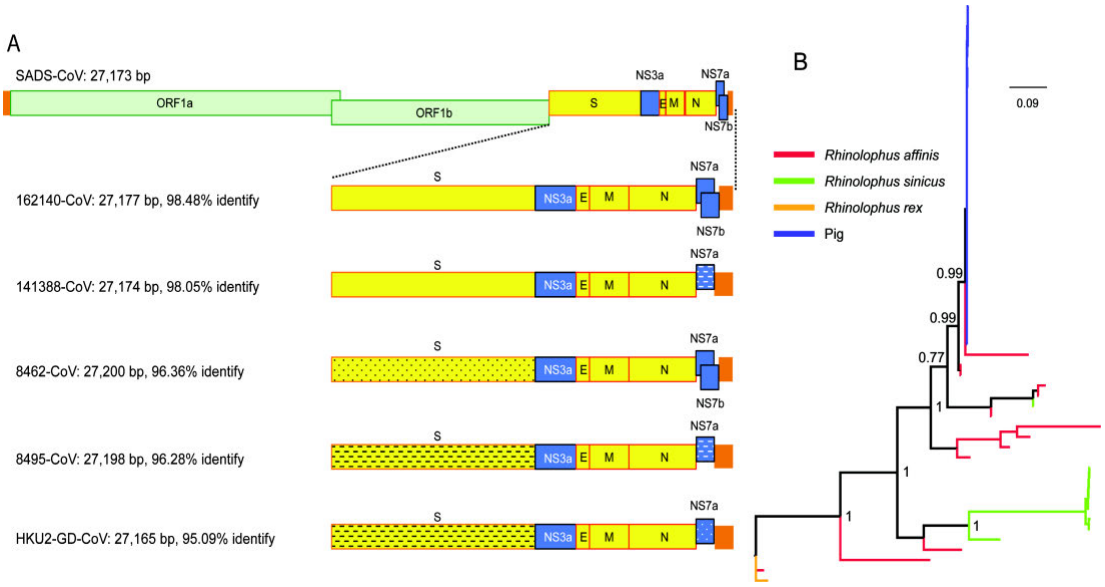



***Figure 36.*** *Genome organization and comparison (a) and Phylogenetic analysis of S1 protein (b) of SADS-CoV and bat SADSr-CoVs*

**Intra-Farm Transmission Model to Understand to Predict Future Transmission and Outbreak**



To better unders and ampl fication dynamics and assess the potent al for future transmission resulting in large outbreaks, we developed an intra-farm, age-structured, stochas ic transmission model for SADS-CoV **(Fig. 37)**. We developed multiple versions of this model to represent different hypotheses of disease transmission mechanisms and fit them to time-series data of reported deaths on multiple SADS-infected farms.

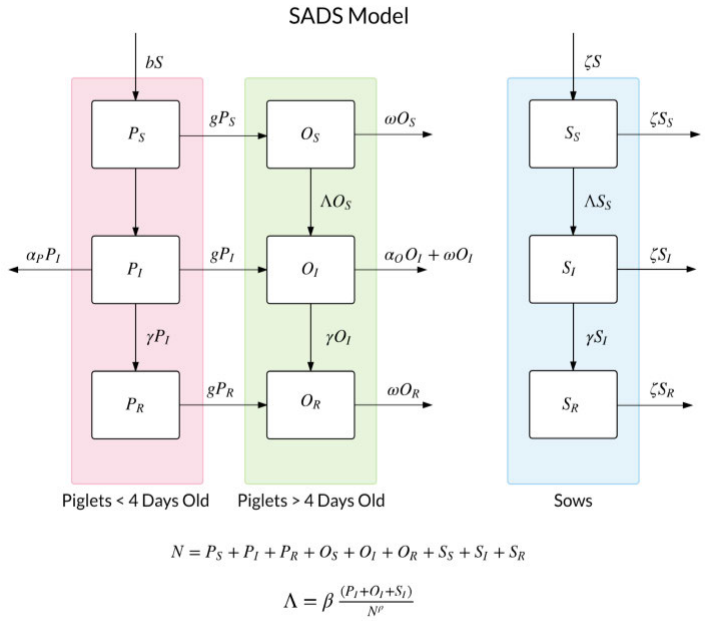



***Figure 37:*** *Schematic of intra-farm transmission mode.*

Our first model structure, which assumed equal mixing of animals across farms **(Fig. 38)** showed that age structure alone was insufficient to generate the temporal pattern of reported deaths on SADS-infected farms. Our second model structure **(Fig. 39)** represented individual barns on a farm as a series of pig-virus meta-populations. This structure was sufficient to re-create the dynamics of the series of rapid "mini-epidemics" that progressed in SADS-infected farms.

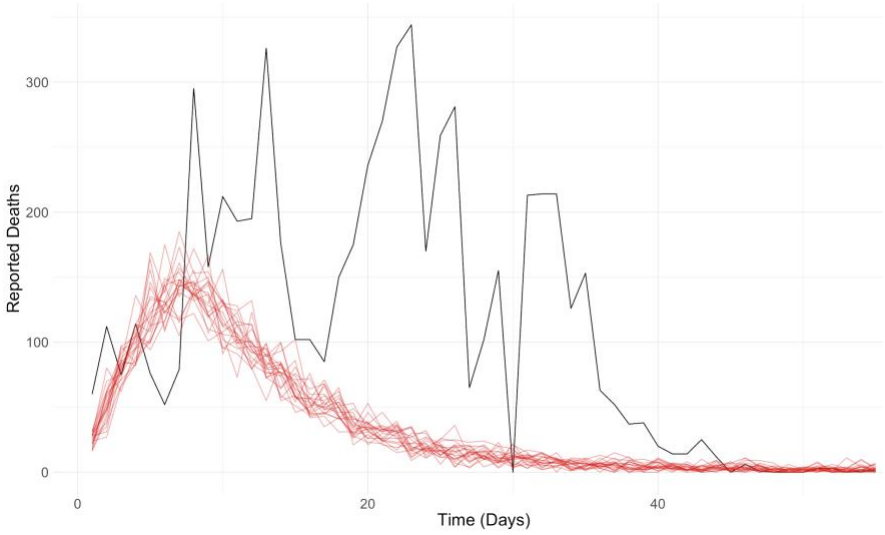



***Figure 38:*** *Best-fit simulations (red) from an equal-mixing transmission model and actual reported death time series (black) on a SADS-infected farm.*



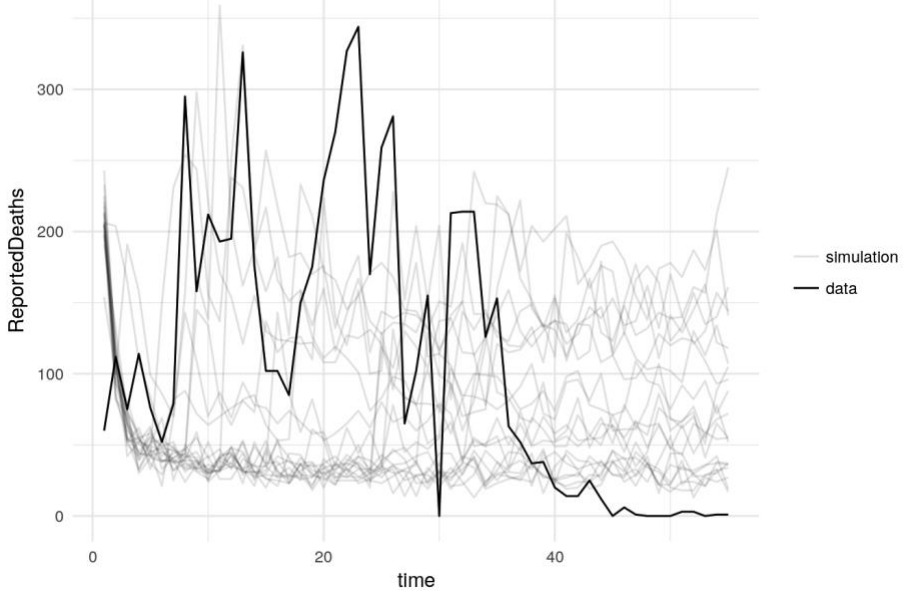



***Figure 39:*** *Best-fit simulations (grey) from an metapopulation transmission model and actual reported death time series (black) on a SADS-infected farm.*

Specific Goals Not Meet

- The wild animal farm survey was piloted in early Y4, with data collected from seven wild animal farms, it was postponed due to the emergence of SADS-CoV where our group had focused on instead in Y4, but will be resumed in Y5 to continue collecting and analyzing data.
- The passive hospital surveillance has been piloted will continue in Year 4 to collect and test for CoVs.

**B. 4 What opportunities for training and professional development has the project provided?**

1. Conference and University lectures: We provided human subject research trainings to chief physicians and nurses at local clinics, staff from Yunnan Institute of Endemic Diseases Control and Prevention, students from Dali College and Wuhan University for both qualitative and quantitative research.

2. Agency and other briefing: Dr. Guangjian Zhu was invited by the Guangdong Institute of Applied Nature Resources, Guangdong Academy of Sciences to provide training to 8 field team members regarding biosafety and PPE use, bats and rodents sampling. Dr. Zhengli Shi participated in the US National Science Foundation-funded EcoHealthNet (grant to EcoHealth Alliance – Epstein PI) that provides research exchange opportunities to undergraduate and graduate-level students.

3. Public outreach: PI Daszak, and Co-investigators Shi, Epstein, and Olival presented the results of this project to the public via interviews with national central and local television, social media, newspaper and journals in China and the US.

## C. PRODUCTS

### C.1 PUBLICATIONS

**Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?**

Yes

**Publications Reported for this Reporting Period**

| Public Access Compliance | Citation |
|---|---|
| Complete | Luo CM, Wang N, Yang XL, Liu HZ, Zhang W, Li B, Hu B, Peng C, Geng QB, Zhu GJ, Li F, Shi ZL. Discovery of Novel Bat Coronaviruses in South China That Use the Same Receptor as Middle East Respiratory Syndrome Coronavirus. Journal of virology. 2018 July 1;92(13). PubMed PMID: 29669833; PubMed Central PMCID: PMC6002729; DOI: 10.1128/JVI.00116-18. |
| Complete | Field HE. Evidence of Australian bat lyssavirus infection in diverse Australian bat taxa. Zoonoses and public health. 2018 September;65(6):742-748. PubMed PMID: 29785730; PubMed Central PMCID: PMC6249124; DOI: 10.1111/zph.12480. |
| Complete | Eskew EA, Olival KJ. De-urbanization and Zoonotic Disease Risk. EcoHealth. 2018 December;15(4):707-712. PubMed PMID: 30120670; PubMed Central PMCID: PMC6265062; DOI: 10.1007/s10393-018-1359-9. |
| Complete | Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nature reviews. Microbiology. 2019 March;17(3):181-192. PubMed PMID: 30531947; PubMed Central PMCID: PMC7097006; DOI: 10.1038/s41579-018-0118-9. |
| Complete | Li HY, Zhu GJ, Zhang YZ, Zhang LB, Hagan EA, Martinez S, Chmura AA, Francisco L, Tai H, Miller M, Daszak P. A qualitative study of zoonotic risk factors among rural communities in southern China. International health. 2020 February 12;12(2):77-85. PubMed PMID: 32040190; PubMed Central PMCID: PMC7017878; DOI: 10.1093/inthealth/ihaa001. |



### C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

**Nothing to report**

### C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

### C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

**Have inventions, patent applications and/or licenses resulted from the award during the reporting period?** No

**If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization?** No

### C.5 OTHER PRODUCTS AND RESOURCE SHARING

**Nothing to report**

## D. PARTICIPANTS

### D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

| Commons ID | S/K | Name | Degree(s) | Role | Cal | Aca | Sum | Foreign Org | Country | SS |
|---|---|---|---|---|---|---|---|---|---|---|
| (b) (6) | Y | DASZAK, PETER | BS,PHD | PD/PI | | | (b) (6), (b) (4) | | | NA |
| (b) (6) | N | Chmura, Aleksei | BS,PHD | Non-Student Research Assistant | | | | | | NA |
| (b) (6) | N | Ross, Noam Martin | PhD | Co-Investigator | | | | | | NA |
| (b) (6) | Y | Olival, Kevin J. | PHD | Co-Investigator | | | | | | NA |
| (b) (6) | Y | Zhang, Shu-yi | PHD | Co-Investigator | | | | East China Normal University | CHINA | NA |
| | N | ZHU, GUANGJIAN | PHD | Co-Investigator | | | | East China Normal University | CHINA | NA |
| | N | GE, XINGYI | PHD | Co-Investigator | | | | Wuhan Institute of Virology | CHINA | NA |
| | N | KE, CHANGWEN | PHD | Co-Investigator | | | | Center for Disease Control and Prevention of Guangdong Province | CHINA | NA |
| | Y | ZHANG, YUNZHI | PHD | Co-Investigator | | | | Yunnan Provincial Institute of Endemic Diseases Control & Prevention | CHINA | NA |
| (b) (6) | N | EPSTEIN, JONATHAN H | MPH,DVM,BA,PHD | Co-Investigator | | | | | | NA |
| (b) (6) | N | SHI, ZHENGLI | PhD | Co-Investigator | | | | Wuhan Institute of Virology | CHINA | NA |



**Glossary of acronyms:**
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

### D.2 PERSONNEL UPDATES

#### D.2.a Level of Effort

Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?

No

D.2.b New Senior/Key Personnel

Are there, or will there be, new senior/key personnel?

No

D.2.c Changes in Other Support

Has there been a change in the active other support of senior/key personnel since the last reporting period?

No

D.2.d New Other Significant Contributors

Are there, or will there be, new other significant contributors?

No

D.2.e Multi-PI (MPI) Leadership Plan

Will there be a change in the MPI Leadership Plan for the next budget period?

NA

## E. IMPACT

**E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?**

Not Applicable

**E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?**

NOTHING TO REPORT

**E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?**

Not Applicable

**E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?**

| Dollar Amount | Country |
|---|---|
| $201,422 | CHINA |

## F. CHANGES

| |
|---|
| **F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE**<br>Not Applicable |
| **F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM**<br>NOTHING TO REPORT |
| **F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS**<br>**F.3.a Human Subjects**<br>No Change |
| **F.3.b Vertebrate Animals**<br>No Change |
| **F.3.c Biohazards**<br>No Change |
| **F.3.d Select Agents**<br>No Change |

## G. SPECIAL REPORTING REQUIREMENTS

### G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

### G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

### G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

### G.4 HUMAN SUBJECTS

| Sub-Project ID: | Study ID | Study Title: | Delayed Onset | Clinical Trial | NCT | NIH-Defined Phase 3 | ACT |
|---|---|---|---|---|---|---|---|
| | 58010 | Understanding the Risk of Bat Coronavirus Emergence-PROTOCOL-001 | NO | NO | | NO | |

### G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

**Are there personnel on this project who are newly involved in the design or conduct of human subjects research?**

No

### G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)



**Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?**

No

### G.7 VERTEBRATE ANIMALS

**Does this project involve vertebrate animals?**

Yes

### G.8 PROJECT/PERFORMANCE SITES

| Organization Name: | DUNS | Congressional District | Address |
|---|---|---|---|
| **Primary:** EcoHealth Alliance, Inc. | 077090066 | NY-010 | 460 West 34th Street<br>17th Floor<br>New York NY 100012317 |
| Wuhan Institute of Virology | 529027474 | | Xiao Hong Shan, No. 44<br>Wuchang District<br>Wuhan NONE |
| East China Normal University | 420945495 | | 3663 Zhongshan Beilu<br>Shanghai NONE |
| ECOHEALTH ALLIANCE | 077090066 | | ECOHEALTH ALLIANCE, INC.<br>460 W 34TH ST |

| | | | |
|---|---|---|---|
| | | | NEW YORK NY 100012320 |

**G.9 FOREIGN COMPONENT**

**Organization Name:** Wuhan Institute of Virology
**Country:** CHINA
**Description of Foreign Component:**
Principal Laboratory for all Research in China as per section G8 (above) and detailed in our Specific Aims

**Organization Name:** Wuhan School of Public Health
**Country:** CHINA
**Description of Foreign Component:**
Principal Coordinating Team for all project field work as per section G8 (above) and detailed in our Specific Aims

**G.10 ESTIMATED UNOBLIGATED BALANCE**

**G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?**

No

**G.11 PROGRAM INCOME**

**Is program income anticipated during the next budget period?**

No

**G.12 F&A COSTS**

**Is there a change in performance sites that will affect F&A costs?**

No

## Section 1 - Basic Information (Study 58010)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Understanding the Risk of Bat Coronavirus Emergence-PROTOCOL-001

1.2. Is this study exempt from Federal Regulations * ❍ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

| | | |
|---|---|---|
| 1.4.a. Does the study involve human participants? | ● Yes | ❍ No |
| 1.4.b. Are the participants prospectively assigned to an intervention? | ❍ Yes | ● No |
| 1.4.c. Is the study designed to evaluate the effect of the intervention on the participants? | ❍ Yes | ● No |
| 1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome? | ❍ Yes | ● No |

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

## Section 2 - Study Population Characteristics (Study 58010)

2.1. Conditions or Focus of Study

2.2. Eligibility Criteria

| | | |
|---|---|---|
| 2.3. Age Limits | Min Age: | Max Age: |
| 2.4. Inclusion of Women, Minorities, and Children | | |
| 2.5. Recruitment and Retention Plan | | |
| 2.6. Recruitment Status | Not yet recruiting | |
| 2.7. Study Timeline | | |

**Inclusion Enrollment Reports**

| IER ID# | Enrollment Location Type | Enrollment Location |
|---|---|---|
| IER 58010 | Foreign | |

## Inclusion Enrollment Report 58010

Using an Existing Dataset or Resource* : ❍ Yes ● No

Enrollment Location Type* : ❍ Domestic ● Foreign

Enrollment Country(ies): CHN: CHINA

Enrollment Location(s):

Comments:

**Planned**

| Racial Categories | Ethnic Categories | | | | Total |
|---|---|---|---|---|---|
| | Not Hispanic or Latino | | Hispanic or Latino | | |
| | Female | Male | Female | Male | |
| American Indian/ Alaska Native | 0 | 0 | 0 | 0 | 0 |
| Asian | 1230 | 1230 | 0 | 0 | 2460 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 | 0 | 0 |
| White | 0 | 0 | 0 | 0 | 0 |
| More than One Race | 0 | 0 | 0 | 0 | 0 |
| **Total** | 1230 | 1230 | 0 | 0 | 2460 |



**Cumulative (Actual)**

| Racial Categories | Ethnic Categories | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | Not Hispanic or Latino | | | Hispanic or Latino | | | Unknown/Not Reported Ethnicity | | | |
| | Female | Male | Unknown/ Not Reported | Female | Male | Unknown/ Not Reported | Female | Male | Unknown/ Not Reported | |
| American Indian/ Alaska Native | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Asian | 980 | 616 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1596 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| White | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| More than One Race | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total** | 980 | 616 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1596 |

## Section 3 - Protection and Monitoring Plans (Study 58010)

3.1. Protection of Human Subjects

3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site? ❍ Yes ❍ No ❍ N/A

If yes, describe the single IRB plan

3.3. Data and Safety Monitoring Plan

3.4. Will a Data and Safety Monitoring Board be appointed for this study? ❍ Yes ❍ No

3.5. Overall structure of the study team

## Section 4 - Protocol Synopsis (Study 58010)

4.1. Brief Summary

4.2. Study Design

4.2.a. Narrative Study Description

4.2.b. Primary Purpose

4.2.c. Interventions

| Type | Name | Description |
|---|---|---|

4.2.d. Study Phase

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ● No

4.2.e. Intervention Model

4.2.f. Masking ❍ Yes ❍ No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation

4.3. Outcome Measures

| Type | Name | Time Frame | Brief Description |
|---|---|---|---|



4.4. Statistical Design and Power

4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ❍ Yes ❍ No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan

## A. COVER PAGE

| | |
|---|---|
| **Project Title:** Understanding the Risk of Bat Coronavirus Emergence | |
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| **Human Subjects:** Yes<br>HS Exempt: No<br>Exemption Number:<br>Phase III Clinical Trial: | **Vertebrate Animals:** Yes |
| **hESC:** No | **Inventions/Patents:** No |

## B. ACCOMPLISHMENTS

### B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Zoonotic coronaviruses are a significant threat to global health, as demonstrated with the emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, and the recent emergence Middle East Respiratory Syndrome (MERS-CoV). The wildlife reservoirs of SARS-CoV were identified by our group as bat species, and since then hundreds of novel bat-CoVs have been discovered (including >260 by our group). These, and other wildlife species, are hunted, traded, butchered and consumed across Asia, creating a largescale human-wildlife interface, and high risk of future emergence of novel CoVs.
To understand the risk of zoonotic CoV emergence, we propose to examine 1) the transmission dynamics of bat-CoVs across the human-wildlife interface, and 2) how this process is affected by CoV evolutionary potential, and how it might force CoV evolution. We will assess the nature and frequency of contact among animals and people in two critical human-animal interfaces: live animal markets in China and people who are highly exposed to bats in rural China. In the markets we hypothesize that viral emergence may be accelerated by heightened mixing of host species leading to viral evolution, and high potential for contact with humans. In this study, we propose three specific aims and will screen free ranging and captive bats in China for known and novel coronaviruses; screen people who have high occupational exposure to bats and other wildlife; and examine the genetics and receptor binding properties of novel bat-CoVs we have already identified and those we will discover. We will then use ecological and evolutionary analyses and predictive mathematical models to examine the risk of future bat-CoV spillover to humans. This work will follow 3 specific aims:

Specific Aim 1: Assessment of CoV spillover potential at high risk human-wildlife interfaces. We will examine if: 1) wildlife markets in China provide enhanced capacity for bat-CoVs to infect other hosts, either via evolutionary adaptation or recombination; 2) the import of animals from throughout Southeast Asia introduces a higher genetic diversity of mammalian CoVs in market systems compared to within intact ecosystems of China and Southeast Asia; We will interview people about the nature and frequency of contact with bats and other wildlife; collect blood samples from people highly exposed to wildlife; and collect a full range of clinical samples from bats and other mammals in the wild and in wetmarkets; and screen these for CoVs using serological and molecular assays.

Specific Aim 2: Receptor evolution, host range and predictive modeling of bat-CoV emergence risk. We propose two competing hypotheses: 1) CoV host-range in bats and other mammals is limited by the
phylogenetic relatedness of bats and evolutionary conservation of CoV receptors; 2) CoV host-range is limited by geographic and ecological opportunity for contact between species so that the wildlife trade disrupts the 'natural' co-phylogeny, facilitates spillover and promotes viral evolution. We will develop CoV phylogenies from sequence data collected previously by our group, and in the proposed study, as well as from Genbank. We will examine co-evolutionary congruence of bat-CoVs and their hosts using both functional (receptor) and neutral genes. We will predict host-range in unsampled species using a generalizable model of host and viral ecological and phylogenetic traits to explain patterns of viral sharing between species. We will test for positive selection in market vs. wild-sampled viruses, and use data to parameterize mathematical models that predict CoV evolutionary and transmission dynamics. We will then examine scenarios of how CoVs with different transmissibility would likely emerge in wildlife markets.



Specific Aim 3: Testing p edict ons of CoV inter-species transmission. We will test our models of host range ( e. emergence potent al) experimentally using reverse genetics, pseudovirus and receptor binding assays, and virus infection experiments in cell culture and humanized mice. With bat-CoVs that we've isolated or sequenced, and using live virus or pseudovirus infection in cells of different origin or expressing different receptor molecules, we will assess potential for each isolated virus and those with receptor binding site sequence, to spill over. We will do this by sequencing the spike (or other receptor binding/fusion) protein genes from all our bat-CoVs, creating mutants to identify how significantly each would need to evolve to use ACE2, CD26/DPP4 (MERS-CoV receptor) or other potential CoV receptors. We will then use receptor-mutant pseudovirus binding assays, in vitro studies in bat, primate, human and other species' cell lines, and with humanized mice where particularly interesting viruses are identified phylogenetically, or isolated. These tests will provide public health-relevant data, and also iteratively improve our predictive model to better target bat species and CoVs during our field studies to obtain bat-CoV strains of the greatest interest for understanding the mechanisms of cross-species transmission.

### B.1.a Have the major goals changed since the initial competing award or previous report?

No

### B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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### B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

**For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?**

No

### B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

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**B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?**

1.Conference and University Lectures: PI Daszak, and Co-investigators Shi, Epstein, Olival, and Zhang gave invited University and Conference lectures including Avoiding Catastrophe Meeting at Concordia Univ., Harvard Univ. Columbia Univ., National Academy of Sciences, World Humanitarian Summit in Turkey, NEIDL Symposium in Boston, Global Pandemic Policy Summit at Texas A&M Univ., One Health EcoHealth Congress in Australia, WHO briefing, Rockefeller Planetary Health meeting, 17th International Bats Conference, China National Global Virome Project Initiative Meeting, and others that included specific discussion of the current project and results.

2.Agency and other briefings: PI Daszak and Co-investigator Shi introduced this project to potential collaborators within Rockefeller Foundation, WHO, FAO, International Collaboration Bureau of Chinese Academy of Sciences, Beijing Genomic Institute, National Natural Science Foundation of China, Institute of Pathogen Biology, Chinese Academy of Medical Science & Peking Union Medical College, and Chinese CDC.

3.Public outreach: PI Daszak and Co-investigator Shi presented this work to members of NSF, NIH, U.S. CDC, the State of Forestry Administration of China, and the general public at the China National Virome Project Initiative Meeting hosted by Chinese CDC and Chinese Academy of Sciences (2017); Co-investigator Olival presented this work at the NYC Medtech Forum to the public (2016); Research Technician Dr. Guangjian Zhu presented this work at the China Conservation Expo to the conservation groups in China (2016). Co-Investigator Y-Z Zhang presented this project to the provincial infectious disease hospital Kunming No.3 People's Hospital in Yunnan province (2016).

**B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?**

Specific Aim 1: Assessment of CoV spillover potential at high risk human-wildlife interfaces.

•To commence the analysis of data collected from the integrated biological behavioral surveillance questionnaires from Yunnan, Guangxi, and Guangdong provinces, linking to the viral and serological testing results of biological samples.

•Following the successful pilot of wildlife trade network research in Lipu, Guilin, Guangxi province in Year 3, we will continue the Wild Animal Farms Survey in Guangxi, and expand to Yunnan and Guangdong in Year 4, with Institutional Review Board approvals from both Yunnan Institute of Endemic Diseases Control and Prevention and Hummingbird #2016-55, to:

−Generate a network model of wildlife trade
−Model trade flows in the wildlife farmer networks to identify locations of high potential for viral recombination
−Update survey instrument for "second wave" network interviews



•We will continue the passive hospital surveillance with anonymized, surveillance data collection from acutely ill hospital in-patients who 1) satisfy syndromic eligibility criteria; 2) have complete medical records; 3) non normative laboratory confirmed diagnostic results; and suspected acute viral infection.

Research has been successfully piloted in four hospitals in Yunnan province: 1) Dali College Affiliated Hospital; 2) Dali Prefecture Hospital; 3) Kunming No. 3 People's Hospital, and 4) Chuxiong Prefecture Hospital, 120 biological samples have been collected, with approval from the Institutional Review Boards of the School of Public Health of Wuhan University and Hummingbird IRB

Specific Aim 2: Receptor evolution, host range and predictive modeling of bat-CoV emergence risk

•The genomic characterization of SL-CoVs in Year 3 was focused on Rhinolophus sinicus in Yunnan, our plan for Year 4 is to obtain complete S gene, RdRp gene or full-length genome sequences of more SL-CoVs from a broader range of bat species identified all over China and conduct a more comprehensive evolution study on SL-CoVs in bats.

•To search for the receptor of SL-CoV with deletions in the homologous region of SARS-CoV RBD (i.e. Rp3, Rs672), and SL-CoVs which has been demonstrated to be unable to utilize bat ACE2 (i.e. Rs4231) whose receptors may be some molecules other than ACE2.

•To conduct population genetics study of Rhinolophus sinicus ACE2s, which includes: the amplification of ACE2 genes from Rhinolophus sinicus samples of different origin, test of the usage efficiency of Rhinolophus sinicus ACE2s of different origins by SL-CoVs and kinetics study on the binding of SL-CoV RBD to different Rhinolophus sinicus ACE2s.

•Phylogeographic study of bat-CoV to better understand the geographic distribution and evolution of bat-CoV genetic diversity in south China.

•Phylogeographic study of bat host (Rhinolophus) species to assess the connectivity of bat populations and infer their historical movements and demographic history to improve our understanding of CoV transmission among bat populations in southern China.

•Cophylogenetic analyses of bat host and CoV phylogenies to assess frequency of cross-species transmission. Comparison of Alpha- and Beta-CoV cophylogenetic patterns building on Year 3 analyses using published sequences.

Specific Aim 3: Testing predictions of CoV inter-species transmission.

•Using the reverse genetic method, we will construct chimeric viruses with the backbone of MERS-CoV and the S genes from diverse newly identified bat MERS-related coronaviruses, and examine the pathogenicity of bat MERS-related coronaviruses on cell and animal levels.

•The animal infection experiments are planned to be conducted in following years to study the pathogenicity of diverse SL-CoVs and MERS-related CoV that we identified in Chinese bats.

•Surveillance of infection in human populations by bat-borne CoVs in Guangxi and Guangdong provinces in previously identified areas with human populations of high risk of exposure to bats. PCR and ELISA will be used, respectively, for detection of viral nucleic acids and antibodies against the viral nucleocapsid protein or spike protein.

**Year 3 Report:** Understanding the Risk of Bat Coronavirus Emergence

**Award Number:** 5R01AI110964-04

**B.2 What was accomplished under these goals?**

***SUMMARY***

The results of the 3rd year of our R01 work are detailed below. They include:

- Initial analysis of behavioral risk qualitative research in Yunnan and wildlife market observational data in Guangdong, that suggests a reduction in wildlife hunting, trade and consumption may be underway in southern China.
- Results from a behavioral risk survey of over 1,000 people in two provinces of southern China that assesses exposure to wildlife and prior bouts of unusual illness, with concurrent taking of samples to test for evidence of exposure to SL-CoVs.
- The finding of serological evidence of spillover of bat SARS-like CoVs in 6 people in Yunnan
- Testing of over 1,000 bat samples to identify diverse alpha- and betacoronaviruses
- Full genome characterization of 26 alphacoronaviruses.
- Receptor binding domain sequences from 37 new bat SL-CoVs that shows S proteins re more diverse than previously thought.
- Host-virus co-phylogeographic analysis of a diverse group of >1,300 bat CoVs showing that these viruses have a larger host range, weaker host specificity and higher frequency of cross-genera transmission than previously thought.
- Use of our reverse genetics system to identify 3 more novel SL-CoVs with potential to directly infect people.



***Specific Aim 1: Assessment of CoV spillover potential at high risk human-wildlife interfaces***

During Year 3 we began analyzing the qualitative research that was conducted in Year 2. In addition, we developed a digital application for a community-based integrated biological behavioral surveillance system and rolled this out in two provinces. The tool aims to identify specific animal exposure risk factors associated with biological evidence of exposure to SARS-like CoV (i.e. seropositive status).

**Qualitative Research**

Interviews conducted in Yunnan province during Year 2 were transcribed and translated into English. A total of 23 individuals (12 women; 11 men) were interviewed in rural regions where wildlife trade routes have been documented. Yunnan province was specifically selected for study because they have large wildlife populations, a diversity of wildlife species and numerous live animal markets. Individuals who were 18 years of age or older and who were able to provide informed consent were eligible to participate. The study was approved by the Institutional Review Boards of the School of Public Health at Wuhan University and Hummingbird IRB #2014-23.

Participants were recruited primarily through local contacts that have been developed as part of wildlife conservation and health research that has been ongoing in these regions in China for the past decade. Contacts including wildlife conservationists and researchers, local government health outreach workers and wildlife farmers facilitated introductions and provided referrals. To achieve a sample with sufficient representation of categories of interest, participants were recruited using purposive sampling, which provides minimum quotas in terms of sex, age and wildlife exposure setting (e.g., live animal market, forest preserve).

Educational attainment varied widely in the population; however, the majority of study participants reported limited schooling, primary education or less. This was further reflected in the occupational distribution of study participants (*Fig. 1*), while there was two respondents who reported more professional occupations, a doctor and an accountant, half (50%) were unskilled laborers or farmers, either agricultural or animal. There were one individuals who self-identified as animal farmers, farming wildlife, bamboo rat, civet, or nutria.

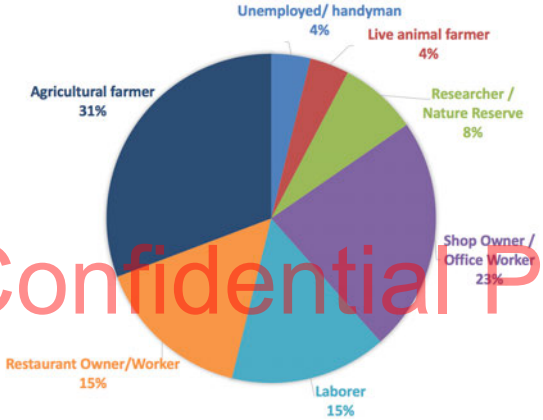





*Figure 1. Occupation of Qualitative Research Participants (n=23) in Yunnan and Guangxi Provinces*

Thematic analysis provided the framework with which to code and analyze data from the ethnographic interviews and focus group. Five core themes were identified to form the basis for this: (1) human-animal contact, (2) unusual illness experience and response, (3) socioeconomics and daily living, (4) biosafety and (5) human environments and movement/travel. Individual interviews and field notes were studied to ensure familiarity with the data set in its entirety and to confirm narrative consistency within individual interviews prior to coding. Using these themes and a coding keyword guide allowed for a directed and consistent coverage of the domains that were the focus of the actual interviews. Qualitative data were re-examined to develop additional theoretical categories or typologies. This analysis aims to assess perceptions, knowledge and participation in the wildlife trade, as well as barriers to participation and observed changes over time. The data were coded for factors associated with wildlife consumption, socioeconomic drivers of wildlife trade, conservation and legal efforts, the prevalence and types of wildlife observed, and wildlife exposures that could transmit disease to humans (*Table 1*).

*Table 1. Topics covered in Ethnographic Interviews*

| Theme Discussed in Ethnographic Interview | No. of Respondents (n=23) | (%) |
|---|---|---|
| **Work/Job Functions** | 22 | 96% |
| **Water & Food** | 22 | 96% |
| **Sanitation** | 22 | 96% |
| **Hygiene** | 22 | 96% |
| **Perceptions/Knowledge** | 22 | 96% |
| **Home Life** | 21 | 91% |
| **Education** | 20 | 87% |
| **Medical Care Treatment** | 20 | 87% |
| **Direct Contact with Animals** | 20 | 87% |
| **Travel** | 19 | 83% |
| **Observed Environment** | 19 | 83% |
| **Animal Responsibilities** | 19 | 83% |
| **Household Illness** | 19 | 83% |
| **Indirect Contact with Animals** | 19 | 83% |
| **Daily Routine** | 18 | 78% |
| **Family Economics** | 18 | 78% |
| **Illness from Animals** | 18 | 78% |
| **Animal Health** | 18 | 78% |
| **Animal Products/R tuals with Animal Products** | 16 | 70% |
| **Death** | 14 | 61% |



The data coding and analytic strategy was designed to avoid the need for expensive analytic software programs and to use standard word processing and spreadsheet programs readily available to in-country teams. These teams received training on qualitative data analysis, and they initiated the first phase of analyses.

Analysis focused on wildlife trade and consumption in these two provinces, specifically on how respondents perceive and contact wildlife through the changing landscape around them. The aim was to identify motivations around animal consumption and practices. A number of participants reported that wildlife are purchased as a means to impress others as a symbol of wealth. Participants routinely reported that the cost of wildlife is double or triple that of regular livestock meat. Ironically, others reported that poorer individuals in these communities who continue to eat wildlife are sometimes scorned for their poverty, because this is a habit from an older time within China. Though there is a stigma to this habit, individuals did report opportunistically capturing and consuming wildlife when convenient.

Participants also noted a decrease in wildlife over time: that in their childhood the forests would be full of the sounds of animals and birds, but this occurs no longer. This decrease was attributed to many factors, most commonly infrastructure development. Respondents discussed

the government investing resources to build new roads and renovate local infrastructure with the intention of increasing tourism, and that this has had the impact of reducing forested habitat for wildlife. Hunting and selling of wildlife was not reported by any participant as a cause of observed wildlife depletion. However, participants did attribute a reduction in wildlife hunting and consumption to an increased enforcement of conservation laws. In particular, the story of one ill-fated hunter who killed a monkey—and was caught—was reported by a number of participants from the same village.

Participants observed that the observed decrease in wildlife abundance and increased conservation law enforcement has made it more difficult to make a living from the wildlife trade. Participants reported choosing alternative forms of money making, indicating that only those people who belong to low socioeconomic classes continue to hunt secretly. The cost-benefit analysis that pits the threat of punitive consequences against the profits to be made through wildlife hunting are only feasible for those 'who have nothing to lose.'

*Table 2: Species Observed in Wet Markets in Guangdong Province from 2015 - 2016*

| Genus species | Common Name |
|---|---|
| ***Prionailurus bengalensis*** | Leopard Cat |
| ***Nyctereutes procyonoides*** | Raccoon Dog |
| ***Sus scrofa*** | Wild Boar |
| ***Lepus sinensis*** | Chinese Hare |
| ***Arctonyx collaris*** | Hog Badger |
| ***Hystrix brachyura*** | Porcupine |
| ***Marmota sp.*** | Marmot |
| ***Rhizomes sinensis*** | Bamboo Rat |
| ***Erinaceus sp.*** | Hedgehog |
| ***Mustela putorius*** | Ferrets |
| ***Muridae*** | Rat (species unknown) |
| ***Myocastor coypus*** | Nutria |
| ***Vulpes sp.*** | Fox |
| ***Mustela sibirica*** | Siberian weasel |
| ***Paguma larvata*** | Masked Palm Civet |
| ***Felis catus*** | Domestic Cat |
| ***Canis lupus familiaris*** | Domestic Dog |
| ***Cervinae*** | Sambar Deer |
| ***Ovis aries*** | Sheep |
| ***Capra sp.*** | Domestic Goat |
| ***Rattus norvegicus*** | Common Rat |



Observations by research staff in live animal markets in Guangzhou found wildlife to be plentiful (*Table 2*), although no bats were seen for sale during the observation period. In contrast, wildlife

was not found in live animal markets at the sites we visited in either Yunnan or Guangxi. This is a change from previous research visits to the same or similar communities, when bats, rodents and wild boar could be found. Locals in Yunnan and Guangxi attribute the change to conservation law enforcement. The success of conservation enforcement may have moved hunting and trapping underground and made the capture of local wildlife less economically feasible than other income generating activities.

**Integrated Biological Behavioral Surveillance in Yunnan and Guangdong Provinces**

To better assess the mechanisms of zoonotic viral spillover, and build on data acquired via ethnographic interview (above) we have designed a structured behavioral questionnaire to measure both exposure and outcome data. This behavioral risk survey assesses exposure to wildlife and bouts of unusual illness over a respondent's lifetime and in the past 12 months. In addition, participants were requested to provide serum to test for previous exposure to SARS-like CoV. The integrated surveillance was pilot-tested in October 2015 among residents living near bat caves or roosts where SL-CoVs have been previously detected in the bat population in Jinning County, Yunnan. After the questionnaire was pilot tested and optimized to fit the research aim, the survey was developed as a digital application (https://www.dropbox.com/s/sv62neywuvl027r/Questionnaire%20Complete.docx?dl=0%). This allows standardization across all field teams and quality control. Four field team leads were trained on behavioral survey data collection, data collection technologies (the digital application) and analysis. The questionnaire was then administered in a follow-up survey in Yunnan province and then in Guangdong province. Surveillance in Guangxi is currently underway.



Of 1089 participants who completed the behavioral questionnaire, 660 (61%) were women and 424 (39%) were men (5 missing for this variable), with a mean age of 50 (range: 10-99). Most reported being farmers (79%) (*Fig. 2*), a majority were long term residents (97%) and 41% had a family income under 3000 RMB annually ($430). Almost three quarters (72%) of the respondents have had only primary level education or less.

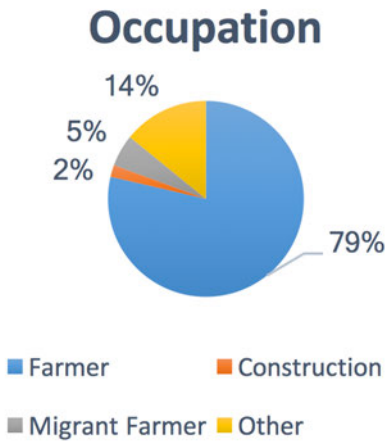



*Figure 2. Occupation of Integrated Biological Behavioral Surveillance Participants in Yunnan and Guangdong Provinces*

Standardized syndromic case definitions informed questions concerning unusual illness experience (e.g. severe acute respiratory infections [SARI], influenza-like illness [ILI], febrile symptoms [Encephalitis]). Lifetime, 12 month, and unusual illnesses experienced in the family for the past 12 months were assessed for all participants. In the past year, SARI was reported by 55 (5.1%) respondents and 14 of those respondents also responded SARI symptoms in family members (*Table 3*).

*Table 3. Unusual Illness Experience In Respondents Lifetime, Past 12 months, Family members*

| Symptoms | Ever | Past 12 months | Family Past 12 months |
|---|---|---|---|
| Severe Acute Respiratory Infections (SARI) | 118 (10.8%) | 55 (5.1%) | 40 (3.7%) |
| Influenza Like Illness (ILI) | 305 (28.0%) | 128 (11.8%) | 142 (13.0%) |
| Encephalitis | 98 (9.0%) | 52 (4.8%) | 30 (2.8%) |
| Hemorrhagic Fever | 2 (0.2%) | 2 (0.2%) | 0 (0.0%) |
| Fever with Diarrhea /Vomiting | 58 (5.3%) | 25 (2.3%) | 21 (1.9%) |
| Fever with Rash | 10 (0.9%) | 7 (0.6%) | 7 (0.6%) |

Type of exposure and species exposed to are shown below (*Table 4*). Poultry was the most commonly contacted animal in almost all categories. Three quarters of respondents reported rodents or shrews entering their home in the past 12 months.



*Table 4: Animal Species Contact by Type of Contact*

| | Pets | Handled | Raised | In house | Cooked/ handled | Eaten raw/ under-cooked | Found dead collected | Scratched/ bitten | Slaughtered | Hunted/ trapped |
|---|---|---|---|---|---|---|---|---|---|---|
| **Rodents/Shrews** | 0 | 33 | 5 | 834 | 38 | 2 | 1 | 1 | 28 | 26 |
| **Bats** | 0 | 5 | 0 | 180 | 8 | 0 | 0 | 1 | 5 | 5 |
| **Non-human primates** | 0 | 1 | 3 | 7 | 4 | 0 | 0 | 0 | 1 | 1 |
| **Birds** | 3 | 19 | 8 | 497 | 39 | 3 | 0 | 0 | 12 | 12 |
| **Carnivores** | 1 | 16 | 7 | 100 | 36 | 0 | 0 | 0 | 19 | 10 |
| **Ungulates** | 0 | 5 | 12 | 23 | 50 | 0 | 0 | 0 | 8 | 1 |
| **Poultry** | 5 | 514 | 843 | 134 | 719 | 5 | 8 | 6 | 425 | 7 |
| **Goats/Sheep** | 0 | 16 | 38 | 4 | 80 | 1 | 0 | 0 | 17 | 0 |
| **Swine** | 3 | 210 | 494 | 43 | 533 | 47 | 1 | 1 | 147 | 2 |
| **Cattle/Buffalo** | 0 | 12 | 77 | 10 | 102 | 5 | 1 | 0 | 11 | 1 |
| **Dogs** | 342 | 40 | 303 | 252 | 62 | 0 | 0 | 22 | 16 | 2 |
| **Cats** | 163 | 10 | 137 | 275 | 18 | 0 | 0 | 11 | 1 | 0 |

Animal exposures among those who reported unusual illness experiences in the past 12 months were evaluated, focusing on three high interest syndromes: SARI, ILI, and encephalitis. Of the 55 respondents who reported SARI symptoms, 49 reported: raising animals; animals in the home; preparing recently killed animals and buying live animals; 50% reported slaughter. Among the 16 respondents who reported ILI symptoms, 12 (75%) reported handling/preparing recently killed animals, 11 (69%) handling live animals or having animals in the home, 10 (63%) reported slaughtering/killing animals or buying live animals at wet market, 9 (56%) raised live animals, 7 (44%) reported a pet, and 1 (6%) reported animal feces near food or eating animal touched or damaged food, hunting, or eating raw/undercooked animal products. Among the four respondents who reported encephalitis symptoms, 3 (75%) reported hunting, handling or raising animals, 2 (50%) reported animals in the home, 1 (25%) reported having animals as pets, slaughtering/killing animals, or having bought live animals at a wet market.

*Table 5. Self-Reporting Symptoms of Syndromes and Sociodemographic and Animal Contact.*

| | SARI Positive *n=55* | | ILI Positive *n=128* | | Encephalitis Positive *n=52* | |
|---|---|---|---|---|---|---|
| **Sociodemographics** | n | % | n | % | n | % |
| **Mother Primary education or less** | 54 | 98.2% | 121 | 94.5% | 50 | 96.2% |
| **Primary education or less** | 45 | 81.8% | 94 | 73.4% | 38 | 73.1% |
| **Female** | 32 | 58.2% | 74 | 57.8% | 29 | 55.8% |
| **Income <3000RMB** | 30 | 54.5% | 45 | 35.2% | 23 | 44.2% |
| **Travel (past 12m)** | 30 | 54.5% | 69 | 53.9% | 34 | 65.4% |
| **Children < 5 yrs in Household** | 15 | 27.3% | 38 | 29.7% | 17 | 32.7% |
| **Household member with same syndrome** | 14 | 25.5% | 46 | 35.9% | 10 | 19.2% |
| **Respondent age <35** | 6 | 10.9% | 24 | 18.8% | 14 | 26.9% |
| **Animal Exposures** | n | % | n | % | n | % |
| **Come in home** | 50 | 90.9% | 117 | 91.4% | 50 | 96.2% |
| **Raise animals** | 49 | 89.1% | 113 | 88.3% | 48 | 92.3% |
| **Prepare/cook recently killed** | 37 | 67.3% | 95 | 74.2% | 35 | 67.3% |
| **Handle live** | 36 | 65.5% | 72 | 56.3% | 38 | 73.1% |
| **Slaughtered** | 31 | 56.4% | 57 | 44.5% | 34 | 65.4% |
| **Animals as Pets** | 23 | 41.8% | 55 | 43.0% | 28 | 53.8% |
| **Buy Animals at Wet Market** | 16 | 29.1% | 49 | 38.3% | 4 | 7.7% |
| **Shared water source** | 9 | 16.4% | 13 | 10.2% | 12 | 23.1% |
| **Feces in/near food** | 8 | 14.5% | 9 | 7.0% | 8 | 15.4% |
| **Consume raw/undercooked** | 7 | 12.7% | 10 | 7.8% | 9 | 17.3% |
| **Scratch/bite** | 4 | 7.3% | 2 | 1.6% | 4 | 7.7% |
| **Consume food damaged by animals** | 3 | 5.5% | 5 | 3.9% | 2 | 3.8% |
| **Hunt or Trap** | 2 | 3.6% | 4 | 3.1% | 7 | 13.5% |
| **Collect dead wildlife** | 1 | 1.8% | 1 | 0.8% | 1 | 1.9% |
| **Consume sick animals** | 0 | 0.0% | 1 | 0.8% | 0 | 0.0% |

We examined the sociodemographic attributes and the types of contacts that were reported in those who reported SARI, ILI, or encephalitis-like symptoms in the past year (see *Table 5*). Over 65% of respondents these syndromes and also reported raising animals, animals coming in the home, or preparing meat or organs from a recently killed animal. A quarter of those who reported symptoms consistent with that of encephalitis were under the age of 35.

Respondents were asked about the source of their unusual illnesses. None reported any kind of animal exposure as a potential source of infection and 11% did not have any idea what may have caused their previous infection, despite the fact that a majority of respondents who reported SARI, ILI, or encephalitis symptoms also reported animal exposures (Table 5). Just over 30% of respondents reported purchasing live animals from a wet market in the past year. Over half (582; 53%) of respondents were worried about disease or disease outbreaks in animals at wet markets and 56% of people believe that animals spread disease. However, those who had purchased animals from markets in the last 12 months reported a great deal of behavior change being undertaken. In particular, respondents reported buying live animals less often 33%, only buying farmed wildlife 32% or buying meat at the supermarket 30% (*Table 6*). For those who participated in animal slaughter or were scratched or bitten in the past year, only 48 respondents (9.9%) reported visiting a doctor.

*Table 6: Behavior Change at Wet Market in the last 12 months*

| Behavior | n | % |
|---|---|---|
| Wash hands | 119 | 33.4% |
| Buy live animals less often | 119 | 33.4% |
| Buy only farmed wildlife | 113 | 31.7% |
| Sometimes shop for meat at supermarket | 107 | 30.1% |
| Wear gloves | 7 | 1.9% |
| Wear a mask | 5 | 1.4% |



**Serological Evidence of Bat SARS-Like CoV Infection in Humans**

Along with the behavioral survey questionnaire, respondents were also asked to provide a biological sample to assess SARS CoV spillover at the high-risk location where the questionnaire has been implemented.

A sensitive and specific ELISA method was developed using the recombinant bat SL-CoV Rp3 NP protein to detect SL-CoV IgG antibodies. Six (2.8%) serum samples from 218 village residents who lived closely to the bat colonies in Yunnan where we isolated SL-CoV WIV1 and WIV16 were positive for SARS-like CoV antibodies (*Fig. 3*). The 6 ELISA positive samples were further confirmed as anti-SL-CoV NP IgG positive by western blot using recombinant Rp3-NP as antigen (*Fig. 4*).

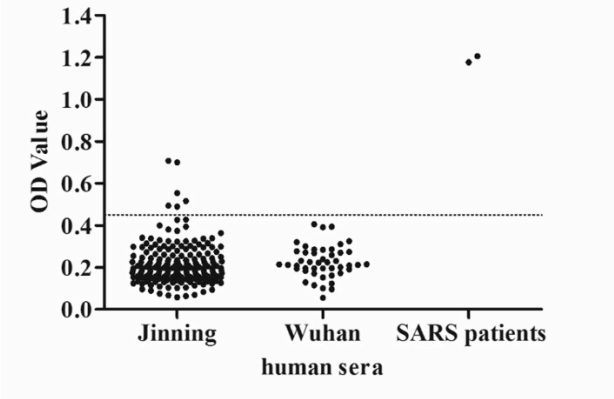



*Figure 3. Serum samples from Jinning, Wuhan, and SARS patients were screened for reactivity of Rp3-NP. Bar in the diagram indicates optical density (OD) cutoff value (0.45) based on healthy blood donors in Wuhan.*

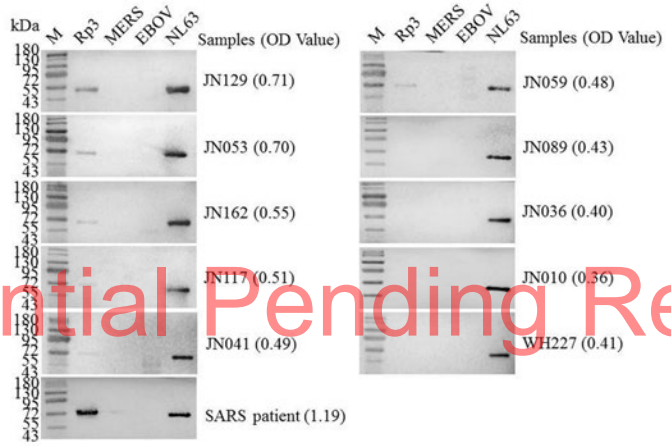





*Figure 4. Western blot analysis of reactivity of human sera to Rp3-NP.*

**Linking Serological Findings with Respondent Questionnaire Data**

Of the 6 respondents in Jinning, Yunnan with serological evidence of SL-CoV infection, 4 had handled animals, 3 had raised or cooked meat from recently killed animals, 2 found animal feces near food stuffs, and 1 slaughtered or hunted an animal. Three of the individuals had contact with poultry in the past twelve months and 2 had contact with either birds, swine or buffalo. One individual reported having contact with a bat. Responses to the questionnaire show that in the last twelve months all of the respondents who have positive testing results, had animals in their dwelling and had contact with rodents or shrews. All 6 of the respondents had reported purchasing an animal from a wet market in the past twelve months.

In addition, 215 oral swabs and 212 rectal swabs collected from human participants in Jinning and Yunnan province were tested for CoV RNA, and no positive results were found. 534 oral swabs, 526 rectal swabs from Xishuangbanna, Yunnan province; and 419 oral swabs, 412 rectal swabs from Ruyuan and Zengcheng, Guangdong province are being tested for CoV.

***Specific Aim 2: Receptor evolution, host range and predictive modeling of bat-CoV spillover risk***

**Bat CoV PCR Detection and Sequencing from Live-Sampled Bat Populations**

We collected 893 rectal swab samples, 167 fecal samples and 33 blood samples from at least 17 bat genera in Yunnan, Guangdong, Guangxi, Hubei and Tibet provinces (*Table 7*) in Year 3. During this year, overall 1060 samples were tested for CoV RNA and 130 (12.3%) were positive (*Table 8*).

*Table 7. Bat samples collected for CoV surveillance in Year 3*

| Date of Sampling | Sampling Locations | Rectal swab | Fecal pellet | Blood specimen |
|---|---|---|---|---|
| **May 11th 2016** | Mengla, Yunnan | 32 | -- | 9 |
| **May 16th 2016** | Jingna, Yunnan | 16 | 114 | 13 |
| **May 22nd 2016** | Lufeng, Yunnan | | 53 | -- |
| **June-July, 2016** | Shixing county, Shaoguan, Guangdong | 113 | -- | -- |
| **July 2016** | Qingzhangshan, Shaoguan, Guangdong | 101 | -- | -- |
| **July 10th 2016** | Ruyuan, Guangdong | 16 | -- | -- |
| **July 11th 2016** | Chengjia, Nanling, Guangdong | 26 | -- | -- |
| **July 2016** | Huadu, Guangzhou, Guangdong | 29 | -- | -- |
| **August 6th 2016** | Lengshuitang vil age, Guilin, Guangxi | 135 | -- | -- |
| **August 6 n 2016** | Nanxishan Park, Guilin, Guangxi | 31 | -- | -- |
| **August 9th 2016** | Lanwu village, Ruyuan, Guangdong | 53 | -- | -- |
| **August 10th 2016** | Liangkou twon, Conghhua, Guangdong | 32 | -- | -- |
| **August 13th 2016** | Jinning, Yunnan | 34 | -- | -- |
| **August 14th 2016** | Lufeng, Yunnan | 25 | -- | -- |
| **August 16th 2016** | Jingna, Yunnan | 33 | -- | -- |
| **August, 2016** | Menghai, Yunnan | 125 | -- | -- |
| **August 21st 2016** | Yaoqu village, Mengla, Yunnan | 30 | -- | -- |
| **September, 2016** | Wuhan, Hubei | 36 | -- | -- |
| **September, 2016** | Motuo, Tibet | 26 | -- | 11 |
| **Total** | | **893** | **167** | **33** |



Genetically diverse alphacoronaviruses related to bat coronavirus 1A/1B, HKU7, HKU6 and HKU2 were identified in *Miniopterus*, *Myotis* and *Rhinolophus* bats, respectively. A novel alphacoronavirus related to human coronavirus NL63 was detected in *Tylonycteris robustula* in Yunnan. SARS-like coronaviruses were detected in 14 Chinese horseshoe bats (*Rhinolophus sinicus*) in Yunnan and Guangdong. Betacoronaviruses related to HKU5 were found in *Pipistrellus abramus* from Hubei, while two lineages of HKU4-related viruses were identified in two species of *Tylonycteris* bats in Yunnan (*Fig. 5*).

Table 8. CoV testing results for bat samples collected in Year 3

| Species | Yunnan | Guangdong | Guangxi | Hubei | Tibet | Total |
|---|---|---|---|---|---|---|
| ***Rousettus spp.*** | 1/34 | | | | 6 | 1/40 |
| ***Aselliscus stoliczkanus*** | 31 | | | | | 31 |
| ***Rhinoluphus spp.*** | 16/41 | 11/136 | 6/60 | | 5 | 33/242 |
| ***Hipposideros spp.*** | 17 | 1/126 | 6 | | 8 | 1/157 |
| ***Myotis spp.*** | 7 | 6/34 | 7/69 | 1 | | 13/111 |
| ***Chaerephon spp.*** | 8 | | | | | 8 |
| ***Megaderma spp.*** | 2 | | | | 1 | 3 |
| ***Ia io*** | 1 | | | | | 1 |
| ***Tylonycteris spp.*** | 32/124 | 8 | | | | 32/132 |
| ***Pipistrellus spp.*** | 1 | 45 | | 5/35 | 2 | 5/83 |
| ***Eonycteris spelaea*** | 1/29 | | | | | 1/29 |
| ***Nyctalus velutinus*** | | 2 | | | | 2 |
| ***Coelops spp.*** | | 2 | | | | 2 |
| ***Miniopterus spp.*** | | 9/17 | | | | 9/17 |
| ***Taphozous melanogopon*** | | | 31 | | | 31 |
| ***Cynopterus sphinx*** | | | | | 3 | 3 |
| ***Murina spp.*** | | | | | 1 | 1 |
| **Fecal pellets** | 35/167 | | | | | 35/167 |
| **Sub-total** | **85/462** | **27/370** | **13/166** | **5/36** | **0/26** | **130/1060** |

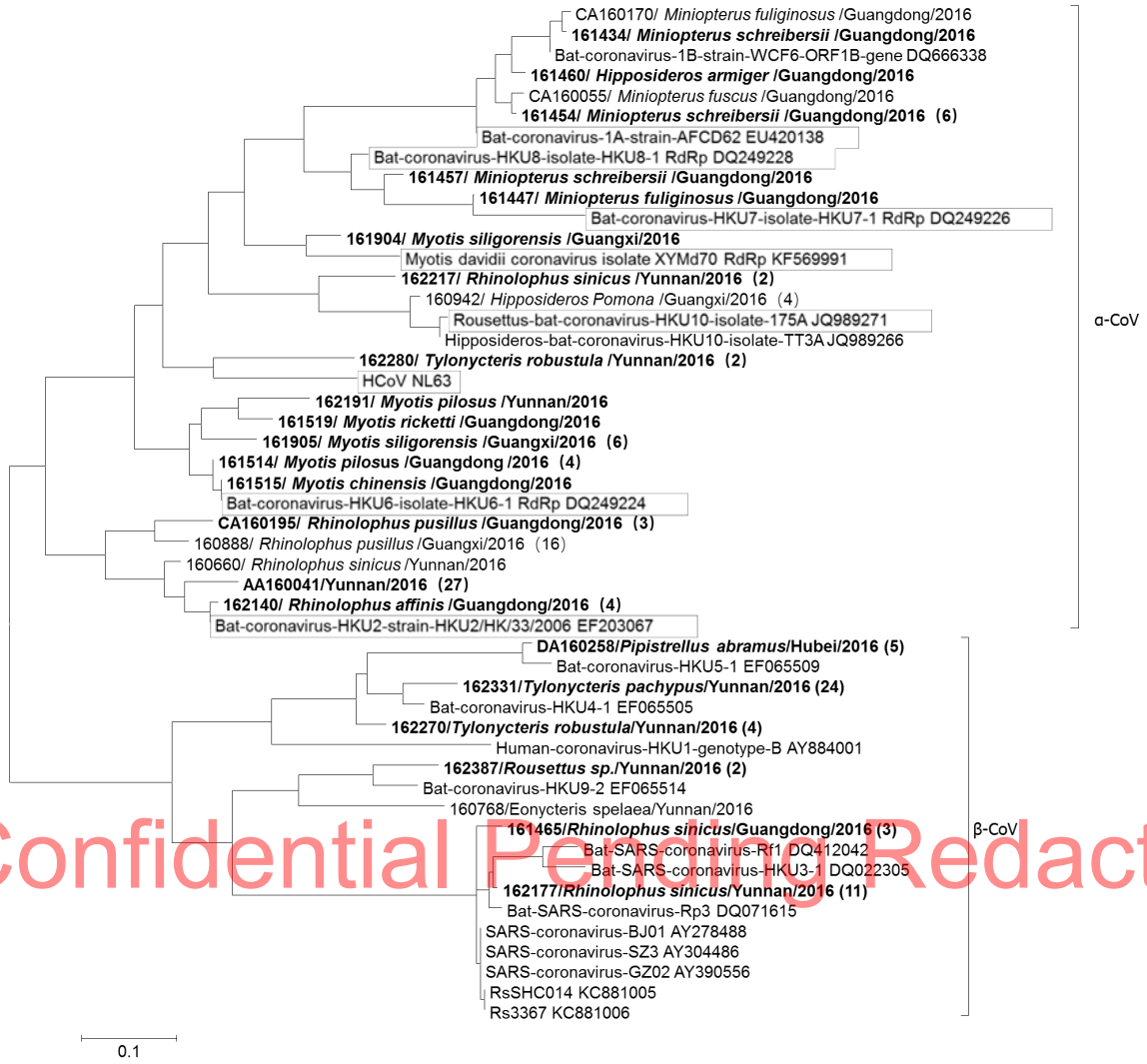





*Figure 5. Phylogenetic analysis of partial RdRp gene of CoV (440-nt partial sequence).*

**Genomic Characterization of Novel Bat Alpha- Coronaviruses**

We generated full-length genome sequences of 26 novel alphacoronaviruses from multiple *Hipposidoeros*, *Rhinolophus* and *Hypsugo* bat species. These alphacoronaviruses grouped into 4 different lineages, including HKU10-like CoVs and 3 novel species according to criteria generated by the International committee of Taxonomy of Viruses (ICTV) (*Fig. 6*). Strains belonging to the novel lineage from *Rhinolophus* share highly similar genome structures with each other but are distinct from all previously sequenced alphacoronaviruses. Putative 3b and 3c genes were identified at the upstream of the E gene, and a 7b gene at the downstream of the N gene was a homologue to *Rhinolophus* bat SARS-like CoV 7a gene. These results expand the understanding of genetic diversity of bat alphacoronaviruses.

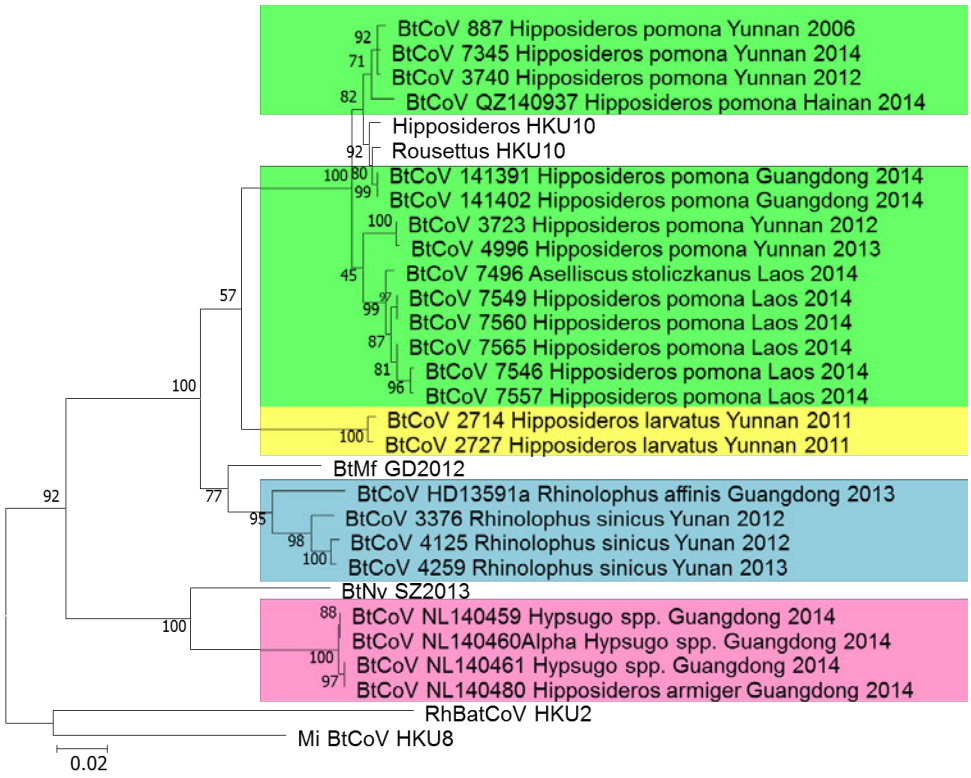



*Figure 6. Phylogenetic analysis based on full-length RdRp gene sequence of alpha-CoVs*



**Genetic D versity of Receptor-B nding Domain (RBD) of SARS-Like Coronavirus in Chinese Bats**

RBD sequences from 37 newly identified SL-CoV from various horseshoe bat species and *Hipposideros* bat species in Yunnan, Guangdong, Guangxi, Hubei and Hunan provinces were amplified and sequenced in Year 3. Phylogenetic analysis revealed that SL-CoV circulating in bat populations in China are highly diverse in the RBD region (*Fi.g 7*). Some strains possessed an RBD sequence distinct from all currently known bat SL-CoVs and formed a new cluster in the phylogenetic tree. However, except for a few strains from Yunnan, most of these SL-CoVs contained nucleotide deletions and were relatively distant to SARS-CoV in the RBD region. These findings suggest that the S gene of SL-CoVs in Chinese bats is even more genetically diverse than expected.

The genomic characterization of SL-CoVs in Year 3 was focused on *Rhinolophus sinicus* in Yunnan, our plan for Year 4 is to obtain complete S gene, RdRp gene or full-length genome sequences of more SL-CoVs from a broader range of bat species identified all over China and conduct a more comprehensive study of the evolution of SL-CoVs in bats.

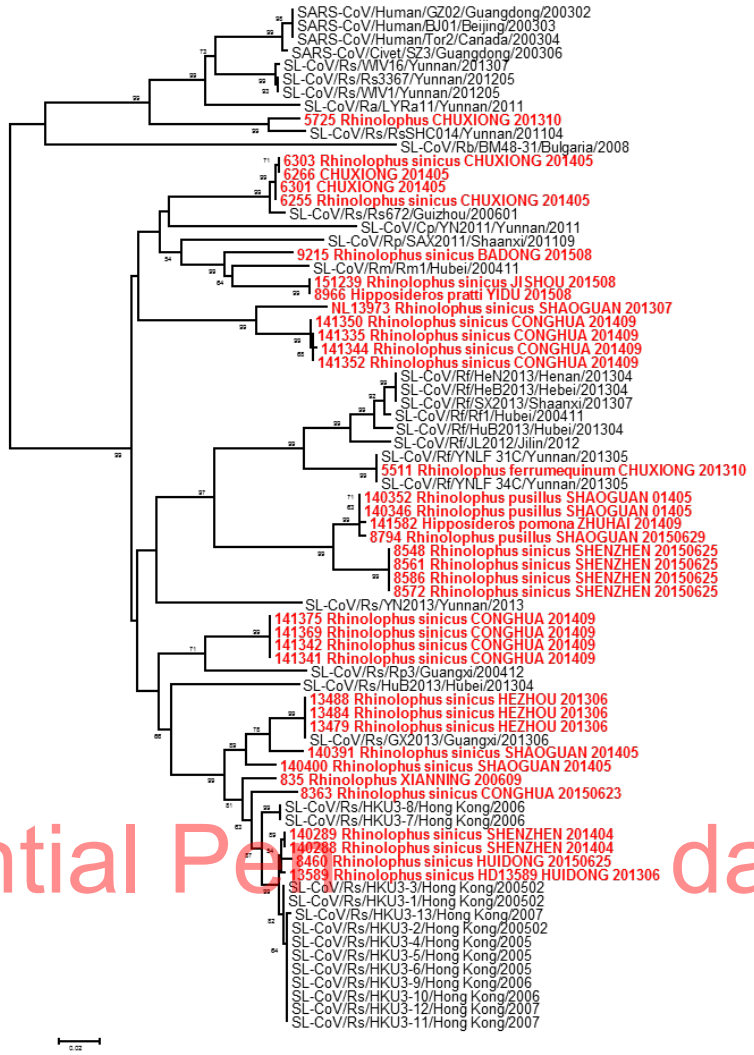





*Figure 7. Phylogenetic analysis of the RBD region of the S gene of bat SL-CoVs detected in China (newly identified sequences were marked in red).*

**Bat Coronavirus Host-virus Phylogeography in China**

To analyze the extent to which different bat species and genera are host to similar bat-CoVs, we reconstructed viral phylogenetic relationships and mapped host-species associations onto these phylogenies. Our dataset includes all CoV RdRp sequences isolated from bat specimens collected by our team from 2008-2015 (Alpha-CoVs: n = 491 – Beta-CoVs: n = 326), including those collected under prior NIAID funding (1 R01 AI079231), and funding from Chinese Federal Agencies. All Chinese bat CoV RdRp sequences available in GenBank were also added to our dataset (Alpha-CoVs: n = 226 – Beta-CoVs: n = 206). Phylogenetic trees were reconstructed for Alpha- and Beta-CoVs separately using Bayesian inference and Maximum Likelihood (ML) approaches. RAxML was used to perform ML analysis and Bayesian analyses were performed with MrBayes 3.2.6.

Beta-CoV sequences clustered into four main genetic lineages: B (SARS-CoV and SARS-like CoVs), C (MERS-CoV), D and a potential new lineage related to lineage B (*Fig. 8*). An important phylogenetic structure is observed within lineages C and D. Alpha-CoV sequences clustered into numerous closely related and less-differentiated lineages (*Fig. 9*).

We observed significant CoV lineage sharing among bat genera in our phylogenetic trees. Importantly SARS-like CoVs (SL-CoVs in lineage B) have been detected in Hipposideridae bats in addition to Rhinolophidae bats which were thought to be the putative natural host taxa of SL-CoV (*Fig. 8*). We found additional bat genera that also hosted CoVs in this clade (*Fig. 8*), expanding potential host targets for novel SL-CoV discovery. CoVs closely related to Bat coronavirus HKU9 (lineage D), which were thought to be specific to pteropodid bats, have also been detected in hipposiderid and vespertilionid bats (*Fig. 8*). Important lineage sharing across several bat families has also been observed among most Alpha-CoV lineages (*Fig. 9*). We used host DNA barcoding to confirm these findings - host mitochondrial sequences were generated to confirm the host species identity for most samples.

These results indicate a larger host range, weaker host specificity and higher frequency of cross-genera transmission for most bat CoV lineages than previously thought. These findings will have important implication in our understanding of bat CoV emergence and spillover risk in China. In Year 4 we will expand these analyses to include more explicit co-evolutionary analyses to identify the frequency and timing of host switching events for each major clade.

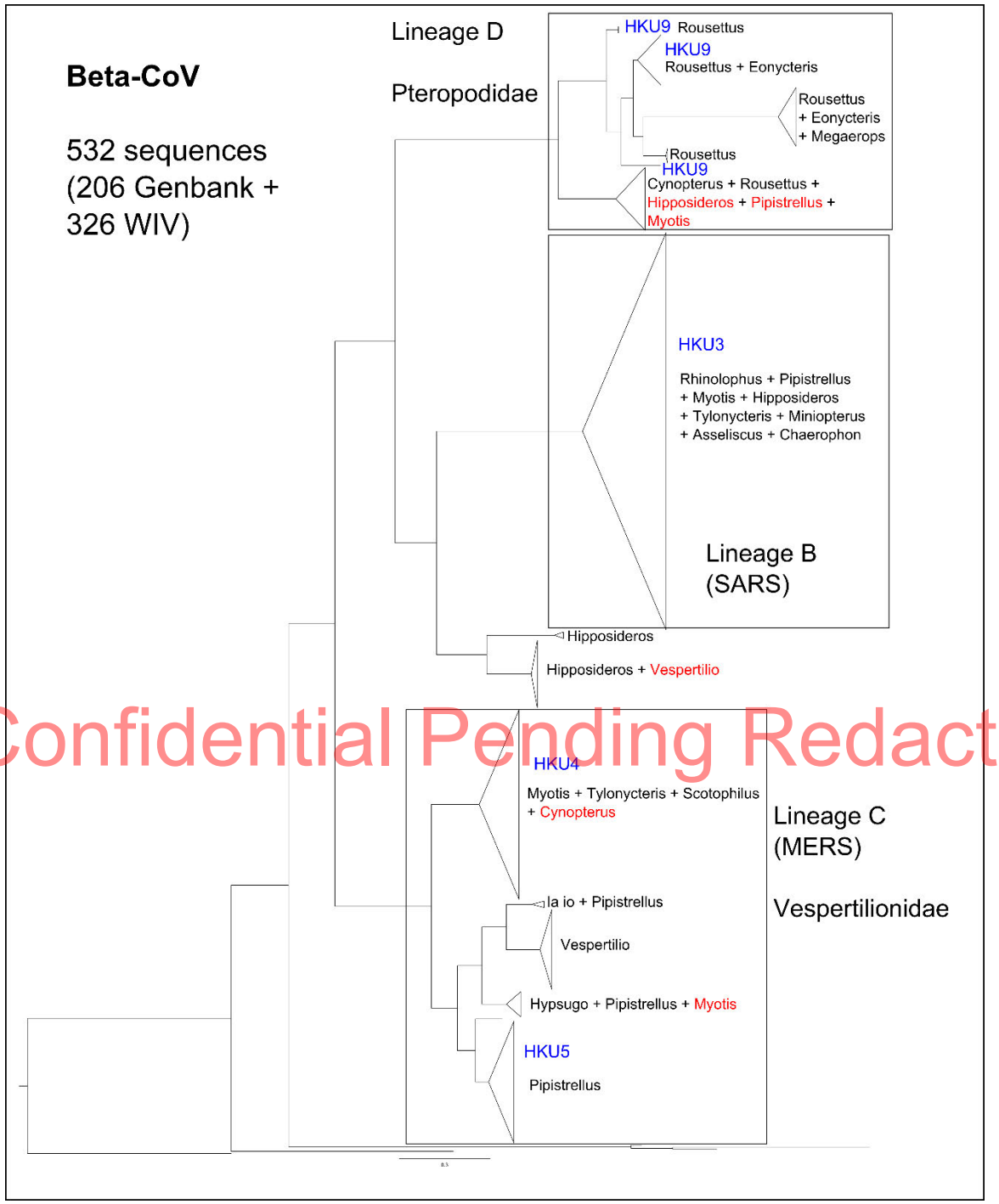





*Figure 8. Maximum Likelihood tree of partial RdRp gene sequences of Beta-CoVs. Bat host genera are indicated along each lineage. Bat genera listed in red correspond to minor and potential new bat hosts and may represent cross-genera/family transmission events.*

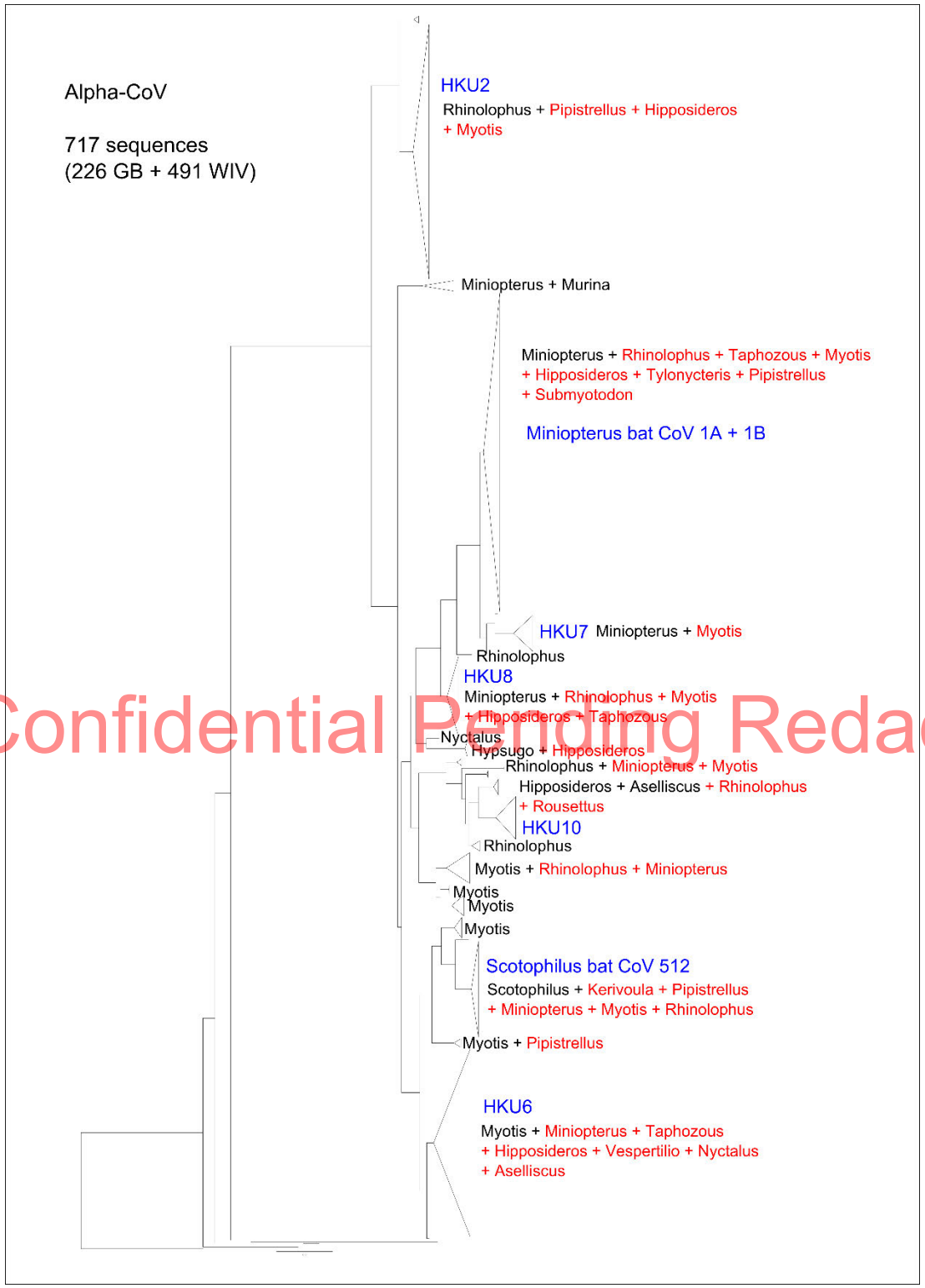





*Figure 9. Maximum Likelihood tree of partial RdRp gene sequences of Alpha-CoVs. Bat host genera are indicated along each lineage. Bat genera listed in red correspond to minor and potential new bat hosts and may represent cross-genera/family transmission events.*

**Global analysis of bat viral sharing to identify key host species**

We curated and analyzed a global dataset of bat host–virus associations to better understand the frequency, and connectivity of viral sharing among bats. We also used this to examine the importance of cave-roosting bats species in harboring and sharing viruses with non cave-roosting species, and to identify specific hosts that are central in the network (*Fig. 10*). Cave roosting bat species are host to most CoVs found in bats (orange). We identified global patterns of viral coinfection based on the number of connections between each virus in the network (Fig. 10). We will expand this approach to our China-CoV specific field data in Year 4.

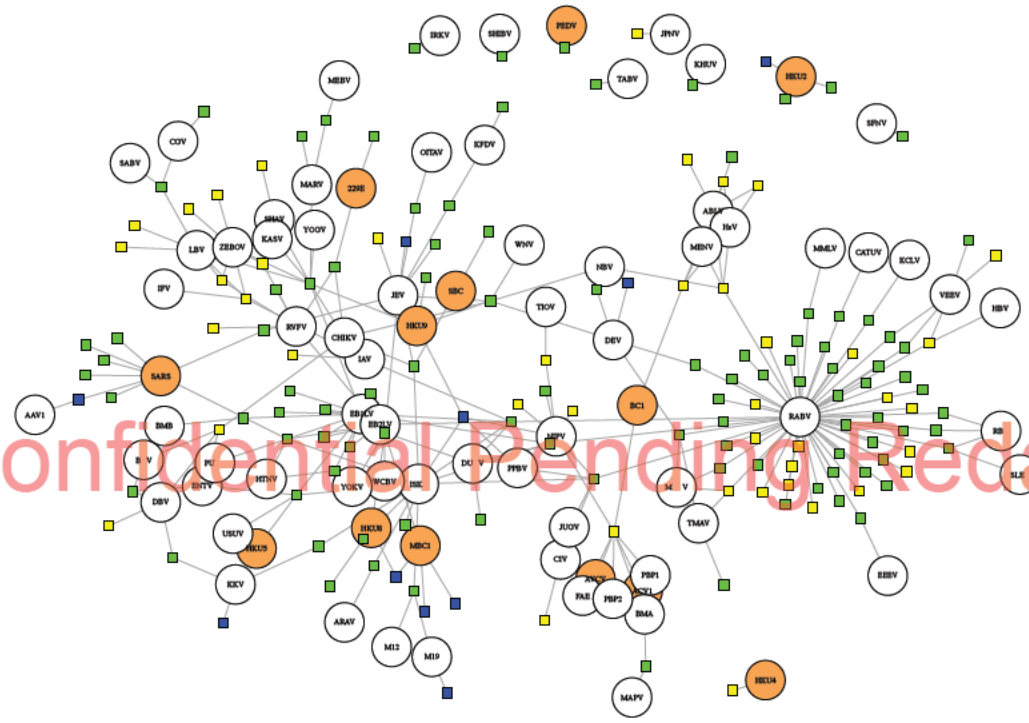





*Figure 10. An analysis of global bat virus sharing using data from the published literature combined with field data. Network analysis includes 152 bat host species and 80 ICTV recognized viral species, with 273 host-viral associations. Unique viruses are represented in circles with known CoVs shown in orange, and each square represents a unique bat species. Green squares = facultative cave-roosting bat species; Blue squares = obligate cave-roosting species; Yellow squares = non cave-roosting species. Viruses are linked in the network based on host species that have been observed harboring the same virus – as detected using PCR or viral isolation.*

***Specific Aim 3: Testing predictions of CoV inter-species transmission***

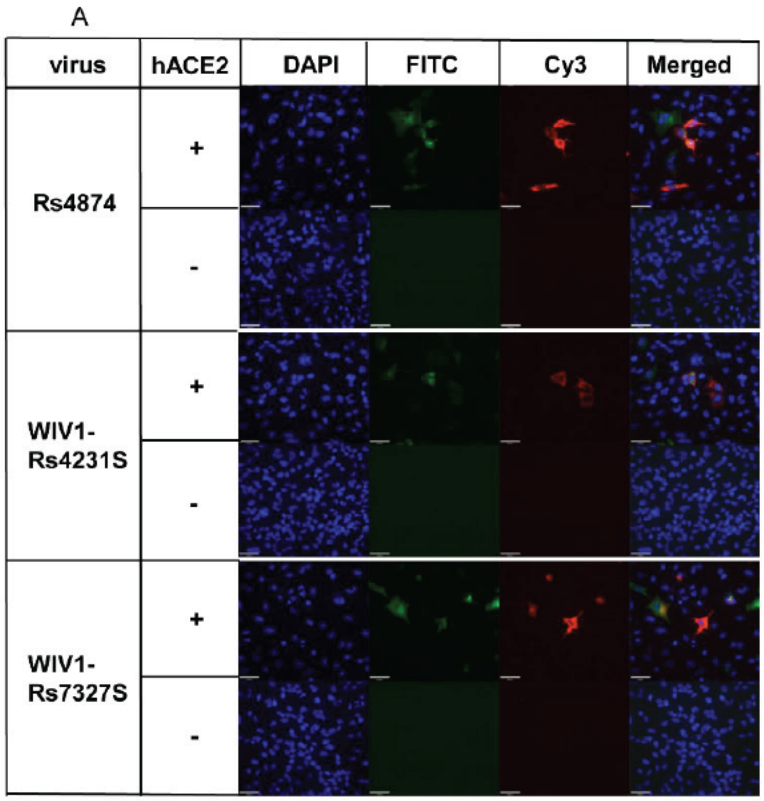
In Year 3 we established an effective and economic reverse genetics system for bat SL-CoV which can be applied to efficiently rescue SL-CoVs that are difficult to culture. This can be used to explore the functions of newly identified SL-CoV genes, as well as to assess pathogenesis of novel bat SL-CoVs. Using this system, we demonstrated that the unique ORFx in WIV1 and WIV16 is a functional gene involving modulation of the host immune response but not essential for *in vitro* viral replication (Zeng et al, 2016, J Virol).

**Identification of Three Novel SL-CoVs with Potential for Direct Transmission to Humans**
In Y2, we conducted full-length genome sequencing of 11 novel SL-CoVs detected in a single bat habitat in Yunnan province, which included strains highly similar to human/civet SARS-CoV in the most variable genes (N-terminal domain and RBD in the S gene, ORF8 and ORF3) (under revision). Based on recombination analysis, we hypothesized that the direct progenitor of the pandemic SARS-CoV may originated from this location after sequential recombination events at multiple genomic positions.

Among the 11 newly identified SL-CoVs, three different strains namely Rs4874, Rs7327 and Rs4231 contained no deletions in the RBD region but their RBD sequences varied from each other. Rs4874 has an S gene almost identical to that of WIV16. Rs7327's S protein varies from that of WIV1 and WIV16 at three aa residues in the receptor-binding motif, including one contact residue (aa 484) with human ACE2. Rs4231 shares similar NTD sequence with WIV1 and WIV16, but has a distinct RBD sequence. In Year 3, we successfully isolated Rs4874 from the single fecal sample. Using the reverse genetic system we previously developed, we constructed two chimeric viruses with the WIV1 backbone replaced with the S gene of Rs7327 and Rs4231, respectively. Vero E6 cells were respectively infected with Rs4874, WIV1-Rs4231S and WIV1-Rs7327S, and efficient virus replication was detected by immunofluorescence assay in all infections. To assess the usage of human ACE2 by the three novel SL-CoVs, we conducted virus infectivity studies using HeLa cells with or without the expression of human ACE2. All viruses replicated efficiently in the human ACE2-expressing cells. The results were further confirmed by quantification of viral RNA using real-time RT-PCR (*Fig.11*).



These finding suggests that diverse variants of SL-CoV S protein without deletions in their RBD are able to use human ACE2 as receptor for cell entry. Diverse SL-CoVs capable of direct transmission to humans are circulating in bats in southwestern China, which represents a potential risk of emergence given the opportunity to spillover to other animals and/or human populations.





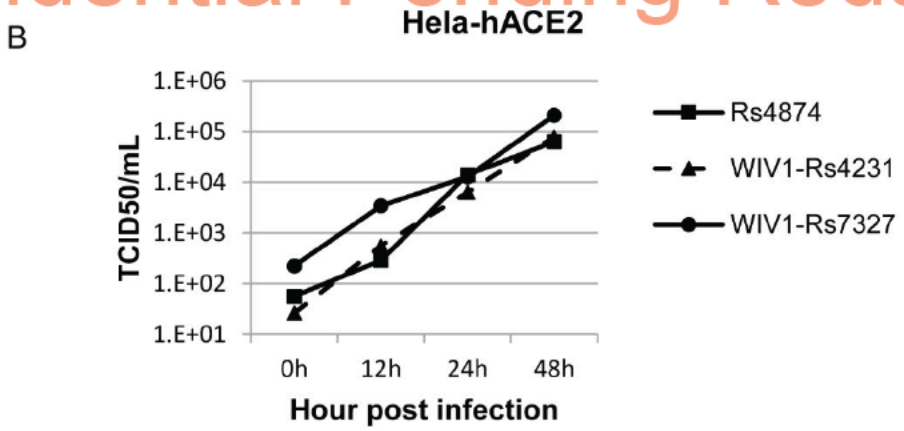




*Figure 11. Analysis of receptor usage by immunofluorescence assay (A) and real-time PCR (B).*

***Additional Year 3 items for Specific Aim 3:***

- The full-length infectious cDNA clone of MERS-CoV has been successfully constructed. The full-length S gene of 12 different novel bat MERS-related coronaviruses have been amplified and cloned into the T-vectors. In Y4, we aim to use the reverse genetic method, and construct chimeric viruses with the backbone of MERS-CoV and the S genes from

diverse newly identified bat MERS-related coronaviruses, to examine the pathogenicity of bat MERS-related coronaviruses on cell and animal levels.

- Establishment of animal infection models for bat SL-CoV and MERS-related CoV: Mice with human ACE2 have been imported to China and have been bred for one generation in Wuhan Institute of Virology. Transgenic mice that express human DPP4 have also been constructed and are being bred. The animal infection experiments are planned to be conducted in following years to study the pathogenicity of diverse SL-CoVs and MERS-related CoV that we identified in Chinese bats.

*Specific Goal Not Meet*

- Observations and animal sampling at wildlife markets were not done in Year 3 because the stricter law enforcement and subsequent cautiousness of traders make it difficult to access to wild animal in markets. Instead, we piloted the wild animal farm survey and will be focusing on it in Year 4, with evidence from pre-investigations that shows most wild animal farms serve as transit points during the wildlife trade.
- The passive hospital surveillance has been piloted in Year 3 and will continue in Year 4 to collect and test samples for SL-CoV and other viral families
- Cophylogenetic analyses of bat host and CoV phylogenies to assess patterns of evolutionary congruence and frequency of cross-species transmission to be continued in Year 4
- Animal infection experiments of SL-CoVs and MERS-related CoV were not done in Year 3, as this is planned as part of work in Year 4.



*Significant Oral Presentations*

1. Daszak P. Plenary talk, One Health-EcoHealth Congress, Melbourne, Dec. 2016
2. Daszak P. 2nd annual Global Pandemic Policy Summit, Scowcroft Ctr, Texas A&M Univ.
3. Daszak P. Global Health Security Agenda side event, UN World Humanitarian Summit: FAO/WHO/USAID/Global He@lth 2030 Innovation Task Force; Istanbul, Turkey.
4. Daszak P. Symposium at École du Val-de-Grâce, Paris
5. Daszak P. Plenary, Institute of Zoology symposium on Bushmeat and disease risks, London.
6. Daszak P. Duke University Provost's Forum on Conservation and Health
7. Olival KJ. The 17th International Bat Research Conference "Assessing the Risk of Disease Emergence from Bat Hunting: Overview and Implications for Risk Mitigation". Durban, South Africa, 2016
8. Daszak P. American Public Health Association Annual Meeting 2016 "Preliminary Results from An Innovative One Health Behavioral Surveillance System". Denver, 2016

**B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?**

We presented this work to the chief physicians, nurses, and directors from county-level clinics in Guangdong and Yunnan provinces during the implementation of Integrated Biological Behavioral Surveillance in Chuxiong and Guangzhou. All the research staff were trained and re-trained for the biosafety and PPE use for human biological sampling.

11 graduate students from School of Public Health of Wuhan University and Wuhan Institute of Virology of CAS were trained for laboratory and field biosafety and PPE use, behavioral data collection methodologies and technologies, and data analysis.

Research Technician Dr. Guangjian Zhu was invited by the Institute of Pathogen Biology, Chinese Academy of Medical Science & Peking Union Medical College to provide training to 10 field team members regarding biosafety and PPE use, bats and rodents sampling.

## C. PRODUCTS

### C.1 PUBLICATIONS

**Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?**

Yes

**Publications Reported for this Reporting Period**

| Public Access Compliance | Citation |
|---|---|
| Non-Compliant | (b) (4) |
| Complete | Zeng LP, Gao YT, Ge XY, Zhang Q, Peng C, Yang XL, Tan B, Chen J, Chmura AA, Daszak P, Shi ZL. 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. 2016 July 15;90(14):6573-82. PubMed PMID: 27170748; PubMed Central PMCID: PMC4936131. |
| Complete | Olival KJ, Willoughby AR. Prioritizing the 'Dormant' Flaviviruses. EcoHealth. 2017 March;14(1):1-2. PubMed PMID: 28194584; PubMed Central PMCID: PMC5386397. |

### C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

**Nothing to report**

### C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT



### C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

**Have inventions, patent applications and/or licenses resulted from the award during the reporting period?**

No

### C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

## D. PARTICIPANTS

### D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

| Commons ID | S/K | Name | Degree(s) | Role | Cal | Aca | Sum | Foreign Org | Country | SS |
|---|---|---|---|---|---|---|---|---|---|---|
| (b) (6) | Y | DASZAK, PETER | BS,PHD | PD/PI | (b) (6) | | | | | NA |
| | N | KE, CHANGWEN | PHD | Co-Investigator | | | | Center for Disease Control and Prevention of Guangdong Province | CHINA | NA |
| (b) (6) | N | Ross, Noam Martin | PhD | Co-Investigator | | | | | | NA |
| | N | SHI, ZHENGLI | PhD | Co-Investigator | | | | Wuhan Institute of Virology | CHINA | NA |
| | N | OLIVAL, KEVIN J | PHD | Co-Investigator | | | | | | NA |
| | N | ZHANG, YUNZHI | PHD | Co-Investigator | | | | Yunnan Provincial Institute of Endemic Diseases Control & Prevention | CHINA | NA |
| | N | ZHU, GUANGJIAN | PHD | Co-Investigator | | | | East China Normal University | CHINA | NA |
| | N | GE, XINGYI | PHD | Co-Investigator | | | | Wuhan Institute of Virology | CHINA | NA |
| | N | EPSTEIN, JONATHAN H | MPH,DVM,BA,PHD | Co-Investigator | | | | | | NA |
| | N | CHMURA, ALEKSEI A | BS | Non-Student Research Assistant | | | | | | NA |
| | N | ZHANG, SHUYI | PHD | Co-Investigator | | | | East China Normal University | CHINA | NA |



**Glossary of acronyms:**
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

### D.2 PERSONNEL UPDATES

**D.2.a Level of Effort**

| |
|---|
| Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?<br><br>No |
| D.2.b New Senior/Key Personnel<br><br>Are there, or will there be, new senior/key personnel?<br><br>No |
| D.2.c Changes in Other Support<br><br>Has there been a change in the active other support of senior/key personnel since the last reporting period?<br><br>No |
| D.2.d New Other Significant Contributors<br><br>Are there, or will there be, new other significant contributors?<br><br>No |
| D.2.e Multi-PI (MPI) Leadership Plan<br><br>Will there be a change in the MPI Leadership Plan for the next budget period?<br><br>NA |

## E. IMPACT

**E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?**

Not Applicable

**E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?**

NOTHING TO REPORT

**E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?**

Not Applicable

**E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?**

| Dollar Amount | Country |
|---|---|
| 213239 | CHINA |

## F. CHANGES

| |
|---|
| **F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE**<br>Not Applicable |
| **F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM**<br>NOTHING TO REPORT |
| **F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS**<br>**F.3.a Human Subjects**<br>No Change |
| **F.3.b Vertebrate Animals**<br>No Change |
| **F.3.c Biohazards**<br>No Change |
| **F.3.d Select Agents**<br>No Change |

## G. SPECIAL REPORTING REQUIREMENTS

### G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

### G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

### G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

### G.4 HUMAN SUBJECTS

**G.4.a Does the project involve human subjects?**

Yes

**Is the research exempt from Federal regulations?**

No

**Does this project involve a clinical trial?**

No

**G.4.b Inclusion Enrollment Data**

Report Attached: Understanding the Risk of Bat Coronavirus Emergence-PROTOCOL-001



**G.4.c ClinicalTrials.gov**

**Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?**

No

### G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

**Are there personnel on this project who are newly involved in the design or conduct of human subjects research?**

No

### G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

**Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?**

No

### G.7 VERTEBRATE ANIMALS

**Does this project involve vertebrate animals?**

Yes

### G.8 PROJECT/PERFORMANCE SITES

| Organization Name: | DUNS | Congressional | Address |
|---|---|---|---|

| | | District | |
|---|---|---|---|
| **Primary:** EcoHealth Alliance, Inc. | 077090066 | NY-010 | 460 West 34th Street<br>17th Floor<br>New York NY 100012317 |
| Wuhan Institute of Virology | 529027474 | | Xiao Hong Shan, No. 44<br>Wuchang District<br>Wuhan |
| Wuhan University School of Public Health | 549376772 | 00-000 | 115 Donghu Road<br>Wuhan nullnull |

**G.9 FOREIGN COMPONENT**

**Organization Name:** Wuhan Institute of Virology
**Country:** CHINA
**Description of Foreign Component:**
Principal Laboratory for all Research in China as per section G8 (above) and detailed in our Specific Aims

**Organization Name:** Wuhan School of Public Health
**Country:** CHINA
**Description of Foreign Component:**
Principal Coordinating Team for all project field work as per section G8 (above) and detailed in our Specific Aims

**G.10 ESTIMATED UNOBLIGATED BALANCE**

**G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?**

No

**G.11 PROGRAM INCOME**



**Is program income anticipated during the next budget period?**

No

**G.12 F&A COSTS**

**Is there a change in performance sites that will affect F&A costs?**

No

Inclusion Enrollment Report

**Inclusion Data Record (IDR) #:** 166195

**Using an Existing Dataset or Resource:** No

**Delayed Onset Study ?:** No

**Clinical Trial:** No

**Enrollment Location:** Foreign

**NIH Defined Phase III Clinical Trial:** No

**Study Title:** Understanding the Risk of Bat Coronavirus Emergence-PROTOCOL-001

## Planned Enrollment

**Planned Enrollment Total:** 2,460

**NOTE:** Planned enrollment data exists in the previous format; the PD/PI did not enter the planned enrollment information in the modified format and was not required to do so. Only the total can be provided.

## Cumulative Enrollment

| Racial Categories | Ethnic Categories | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | Not Hispanic or Latino | | | Hispanic or Latino | | | Unknown/Not Reported Ethnicity | | | |
| | Female | Male | Unknown/ Not Reported | Female | Male | Unknown/ Not Reported | Female | Male | Unknown/ Not Reported | |
| American Indian/Alaska Native | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| Asian | 708 | 459 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **1167** |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| Black or African American | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| White | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| More than One Race | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| Unknown or Not Reported | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| **Total** | **708** | **459** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **1167** |

**From:** Hallett, Adrienne (NIH/OD) [E]
**To:** Tabak, Lawrence (NIH/OD) [E]
**Subject:** FW: COVID origins - Follow-up to June 28, 2021 briefing
**Date:** Friday, July 30, 2021 10:14:00 AM

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From Alan:

As a follow-up to the June 28, 2021 briefing with Dr. Tabak and Dr. Lauer, we would appreciate responses to the following:

1. According to an August 21, 2020 article in Nature, https://www.nature.com/articles/d41586-020-02473-4, Dr. Peter Daszak of EcoHealth Alliance stated:

"The NIH have told us not to work on this project. Obviously, we're not going to break any NIH rules. But we have an ongoing collaboration, 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. So we need to carry on with that work."

Dr. Tabak said during the briefing that if we sent him an article indicating that EcoHealth Alliance had unpublished research on bat coronaviruses in China, then the NIH would consider making a request to EcoHealth Alliance to produce the unpublished research. Will the NIH make such a request to EcoHealth Alliance?

2. Dr. Tabak stated that the only animals that were involved in NIH-supported research at the Wuhan Institute of Virology were mice. Were the mice involved in the research humanized mice?

**From:** Lauer, Michael (NIH/OD) [E]
**To:** Hallett, Adrienne (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Simon, Dina (NIH/OD) [C]; Burrus-Shaw, Cyndi (NIH/OD) [E]; Showe, Melanie (NIH/OD) [E]
**Cc:** Casselle, Julia (NIH/OD) [E]; Lohmann, Larry (NIH/OD) [E]; Everett, Chris (NIH/OD) [E]; Lauer, Michael (NIH/OD) [E]
**Subject:** Re: 6.28 Briefing Packet
**Date:** Sunday, June 27, 2021 12:55:32 PM
**Attachments:** E&C WIV Response Briefing 6.28.pdf

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This is enormously helpful helpful, Adrienne, thanks so much.
Mike

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**From:** "Hallett, Adrienne (NIH/OD) [E]" <(b) (6)
**Date:** Friday, June 25, 2021 at 9:29 AM
**To:** "Tabak, Lawrence (NIH/OD) [E]" <(b) (6) "Lauer, Michael (NIH/OD) [E]" <(b) (6) "Simon, Dina (NIH/OD) [C]" <(b) (6) "Burrus-Shaw, Cyndi (NIH/OD) [E]" (b) (6) , "Showe, Melanie (NIH/OD) [E]" <(b) (6)
**Cc:** "Casselle, Julia (NIH/OD) [E]" <(b) (6) "Lohmann, Larry (NIH/OD) [E]" <(b) (6) "Everett, Chris (NIH/OD) [E]" <(b) (6)
**Subject:** 6.28 Briefing Packet
One fact to note: Diane Cutler is on detail to the Committee from the HHS OIG office. She is planning to attend the briefing.

**House Committee on Energy and Commerce Briefing Materials**

**Logistics:**

| | |
|---|---|
| DATE: | Monday, June 28, 2021 |
| TIME: | 3:30 – 4:30 pm |
| COORDINATES: | BY Video Format TBD |
| PURPOSE: | NIH Bipartisan Briefing with E&C Committee re EcoHealth |
| ATTENDEES: | Lawrence Tabak<br>Michael Lauer<br>House E&C Committee Staff<br>Alan Slobodin (Minority)<br>Bijuan "BJ" Koohmaraie (Minority)<br>Diane Cutler (Minority)<br>Kevin McAloon (Majority, tentative)<br>Chris Knauer (Majority, tentative)<br>Larry Lohmann (NIH OLPA)<br>Kelsey Mellette (HHS/ASL)<br>Jenn Schmalz (HHS/ASL)<br>Anne Tatem (HHS/ASL, tentative)<br>Kimberly Espinosa (HHS/ASL, tentative) |

**Background:**

- On March 18, 2021, E&C's Ranking Member Cathy McMorris Rodgers (R-WA), along with two subcommittee Ranking Members (Reps. Guthrie and Griffiths), sent Dr. Collins a letter to investigate the origins of COVID-19.
    - The letter is 11 pages long with 49 questions and sub-questions.
    - NIH sent a narrative response to this letter on May 21, 2021 and offered a briefing.
- On June 10, 2021, E&C's Ranking Member, along with 25 Republican Members, sent Dr. Collins a follow-up letter with 10 additional questions regarding the origins of COVID-19.
- Note: Diane Cutler is on detail to the Committee from the HHS OIG office.

**Recommendations:**

- The compliance actions the letter asks about are being formally contested so we are advised by OGC:

(b) (5)

**Run of Show:**

- HHS ASL staff will open the call and make introductions.
- They will then reiterate the parameters for the call.
    - The briefing is in response to the first letter.
    - The response to the letter from June 10, 2021 is in process.
    - The Call has a hard stop at 1 hour.
- HHS will then hand it over to Dr. Tabak and Dr. Lauer.
- Dr Tabak will open and proceed through the grant timeline (attached).
- Dr. Tabak and Dr. Lauer proceed through the questions from the letter with committee staff.
- Open for Q&A.

**Background/Briefing Materials:**

- Timeline
- March 18, 2021 letter from E&C
- May 21, 2021 response
- June 10, 2021 letter from E&C
- Staff profiles

**Timeline:**

At the April 17, 2020 White House coronavirus task force briefing, President Trump announced that the administration would "end that grant very quickly" referring to the 2R01AI110964-06 NIH grant (or "the grant") of which your letter requests information.

On April 19, 2020, NIH sent a letter to the EcoHealth Alliance, the institutional awardee of the grant, ordering the suspension of funds to the Wuhan Institute of Virology ("WIV"), one of the grants sub-recipients.

On April 24, 2020 NIH sent a second letter to EcoHealth Alliance, terminating the grant.

On May 20, 2020, NIH sent a letter to the University of California, Irvine, suspending all activities related to RF1 MH120020-01, Genetically engineered anterograde monosynaptic viral tracers for multi-species neural circuit analysis, Dr. Xiangmin Xu (Contact PI), for which the Wuhan Institute of Virology is a subaward participant, awarded by the National Institute of Mental Health (NIMH).

In June 2020, NIAID awarded grants to new centers for research in emerging infectious diseases; one of the 11 grants was awarded to EcoHealth Alliance.

On July 8, 2020, NIH sent a letter to EcoHealth Alliance (attached), indicating the grant was going to be reinstated. However, funding and activities were suspended pending complete, accurate, and satisfactory return of answers, material, and information regarding a number of specific concerns about biosafety practices at its sub-recipient WIV. Furthermore, EcoHealth Alliance was instructed to correct its repeated noncompliance due to its failure to report all sub-awards in the Federal Subaward Report System. EcoHealth Alliance had been directed in NIH Notices of Award to generate these reports as required by the Transparency Act sub-award and executive compensation reporting requirement of 2 C.F.R. Part 170.

The July 8 letter to EcoHealth Alliance indicated that the suspension of the grant was taken in accordance with 45 C.F.R. § 75.371, which permits suspension of award activities in cases of non-compliance, and the NIH Grants Policy Statement, Section 8.5.2, which permits NIH to take immediate action to suspend a grant when necessary to protect the public health and welfare. This action is not appealable under 42 C.F.R. §50.404 and the NIH GPS Section 8.7.

On August 14, 2020, EcoHealth Alliance responded by letter declining to address any of the seven specific concerns NIH requested in the July 8 letter. The grant has been reinstated with all funding and activities suspended pending EcoHealth Alliance's answers to the government's safety and compliance concerns. As this matter is still pending, no further documentation can be provided at this time.

On October 23, 2020, NIH sent a letter to EcoHealth Alliance in response to their response to suspension. The letter noted that EcoHealth not currently having a subrecipient relationship with WIV and not issuing subawards to WIV at the time of suspension did not absolve EcoHealth of any past non-compliance with the terms and conditions of award for grant R01AI110964.

In April of 2021, EcoHealth Alliance submitted documents in response to the October letter.

On June 11, 2021, the HHS OIG initiated an audit into the EcoHealth Alliance grant and all actions related to it.

FRANK PALLONE, JR., NEW JERSEY
CHAIRMAN

CATHY McMORRIS RODGERS, WASHINGTON
RANKING MEMBER

ONE HUNDRED SEVENTEENTH CONGRESS

Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115
Majority (202) 225-2927
Minority (202) 225-3641

March 18, 2021

The Honorable Francis Collins, M.D., Ph.D.
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

Dear Dr. Collins,

We write to request information, assistance, and needed-leadership from the National Institutes of Health (NIH) to advance an independent, scientific investigation into the origins of the COVID-19 pandemic.

The COVID-19 pandemic has been the worst public health crisis in the U.S. in about a hundred years. Over a year has passed since the deadly virus reached our shores and yet, the origin of the virus has yet to be determined. An independent, expert investigation of the origin of COVID-19 is of paramount importance to public health and biosecurity. As noted by Stanford Medical School Professor David Relman:

> A more complete understanding of the origins of COVID-19 clearly serves the interests of every person in every country on this planet. It will limit further recriminations and diminish the likelihood of conflict; it will lead to more effective responses to this pandemic, as well as efforts to anticipate and prevent the next one. It will also advance our discussions about risky science. And it will do something else: Delineating COVID-19's origin story will help elucidate the nature of our very precarious coexistence within the biosphere.[1]

Recently, the World Health Organization (WHO) attempted to investigate the origin of COVID-19. The WHO said that this investigative mission would be guided by the science, be

[1] David A. Relman, *Opinion: To stop the next pandemic, we need to unravel the origins of COVID-19*, PNAS (Nov. 2020), *available at* https://www.pnas.org/content/117/47/29246.

"open-minded," and "not exclude[e] any hypothesis."[2] Unfortunately, China did not provide complete access or independence for the critical WHO mission. On February 13, 2021, National Security Advisor Jake Sullivan issued the following statement:

> We have deep concerns about the way in which the early findings of the COVID-19 investigation were communicated and questions about the process used to reach them. It is imperative that this report be independent, with expert findings free from intervention or alteration by the Chinese government. To better understand this pandemic and prepare for the next one, China must make available its data from the earliest days of the outbreak.[3]

Because of rising tensions between the U.S. and China, the WHO scrapped plans for an interim report.[4] An international group of science experts, including specialists in virology, microbiology, and zoology, asked for a new review.[5]

The NIH, as a premier scientific institution, must lead in order to foster a transparent, independent, and science-based investigation into the origin of the COVID-19 pandemic. Such an effort must meet the WHO's stated goals of an open-minded investigation that does not exclude any plausible hypothesis.[6] In addition, the NIH is well-positioned to gather and provide information through oversight of its grants and other federal awards. Thus, the NIH is in a unique position to investigate the possibility that the pandemic stemmed from a laboratory accident or leak, especially regarding the Wuhan Institute of Virology (WIV).

NIH raised concerns over a possible link between WIV and the COVID-19 outbreak during its review of federal awards to EcoHealth Alliance, a global environmental health nonprofit organization dedicated to protecting wildlife and public health from the emergence of disease. Of the $13.7 million in federal awards that NIH authorized for EcoHealth Alliance, 17

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[2] Smriti Mallapaty, *Where did COVID come from? WHO investigation begins but faces challenges*, NATURE (Nov. 11, 2020), *available at* https://www.nature.com/articles/d41586-020-03165-9.

[3] The White House, Statement of National Security Advisor Jake Sullivan (Feb. 13, 2021), *available at* https://www.whitehouse.gov/briefing-room/statements-releases/2021/02/13/statement-by-national-security-advisor-jake-sullivan/.

[4] Betsy McKay, Drew Hinshaw and Jeremy Page, *WHO Investigators to Scrap Plans for Interim Report on Probe of Covid-19 Origins*, THE WALL STREET JOURNAL (Mar. 4, 2021), *available at* https://www.wsj.com/articles/who-investigators-to-scrap-interim-report-on-probe-of-covid-19-origins-11614865067?mod=latest_headlines

[5] Jaime Metzl, et al, *Call for a Full and Unrestricted International Forensic Investigation into the Origins of COVID-19* (March 4, 2021), *available at* https://s.wsj.net/public/resources/documents/COVID%20OPEN%20LETTER%20FINAL%20030421%20(1).pdf. The co-organizer of the letter and a WHO advisor on human genome editing, Jaime Metzl, PhD, said there is an eighty-five percent chance the pandemic started with an accidental leak from the WIV or Wuhan CDC laboratory, *available at* https://jamiemetzl.com/origins-of-sars-cov-2/. ("I have no definitive way of proving this thesis but the evidence is, in my view, extremely convincing. If forced to place odds on the confidence of my hypothesis, I would say there's an 85% chance the pandemic started with an accidental leak from the Wuhan Institute of Virology or Wuhan CDC and a 15% chance it began in some other way (in fairness, here is an article making the case for a zoonotic jump "in the wild"). If China keeps preventing a full and unrestricted international forensic investigation into the origins of the pandemic, I believe it is fair to deny Beijing the benefit of the doubt.")

[6] Washington Post Editorial Board, *We're still missing the origin story of this pandemic. China is sitting on the answers*, THE WASHINGTON POST (Feb. 5, 2021), *available at* https://www.washingtonpost.com/opinions/2021/02/05/coronavirus-origins-mystery-china/?arc404=true.

projects sponsored by the National Institute of Allergy and Infectious Disease (NIAID) have provided over $7.9 million in federal awards for research of viral emergence from bats in Southeast Asia.[7] EcoHealth Alliance passed some of its funding to the WIV, and in 2020, NIH made efforts to obtain information from EcoHealth Alliance about WIV related to concerns about the origins of COVID-19. In April 2020, NIH wrote to EcoHealth Alliance and Columbia University about an NIH-funded project entitled, "Understanding the Risk of Bat Coronavirus Emergency:"

> It is our understanding that one of the sub-recipients of the grant funds is the Wuhan Institute of Virology ('WIV'). It is our understanding that WIV studies the interaction between corona viruses and bats. The scientific community believes that the coronavirus causing COVID-19 jumped from bats to humans likely in Wuhan where the COVID-19 pandemic began. There are now allegations that the current crisis was precipitated by the release from WIV of the coronavirus responsible for COVID-19. Given these concerns, we are pursuing suspension of WIV from participation in Federal programs. It is in the public interest that NIH ensure that a sub-recipient has taken all appropriate precautions to prevent the release of pathogens that it is studying. This suspension of the sub-recipient does not affect the remainder of your grant assuming that no grant funds are provided to WIV following receipt of this email during the period of suspension.[8]

In January 2021, the U.S. Department of State issued a fact sheet about the activity at the WIV.[9] Among other revelations, it reported the following:

- The U.S. government has reason to believe that several researchers inside the WIV became sick in autumn 2019, before the first identified case of the outbreak, with symptoms consistent with both COVID-19 and common seasonal illnesses. This raises questions about the credibility of WIV senior researcher Shi Zhengli's public claim that there was "zero infection" among the WIV's staff and students of SARS-CoV-2 or SARS-related viruses.[10]

- Starting in at least 2016, WIV researchers conducted experiments involving RaTG13, the bat coronavirus identified by the WIV in January 2020 as the closest sample to SARS-CoV-2 (96.2 percent similar).[11] There was no indication that this research was suspended at any time prior to the COVID-19 outbreak.

- The WIV has a published record of conducting "gain-of-function" research to engineer chimeric viruses.[12] But the WIV has not been transparent or consistent about its record of

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[7] NIH RePORTER, *Research Portfolio Online Reporting Tools* (queried Mar. 4, 2021), *available at* https://reporter.nih.gov/search/qlYUeI9DIk2JfWUdCcWxcA/projects/charts.
[8] Mark Moore, *NIH investigating Wuhan lab at center of coronavirus pandemic*, NEW YORK POST (Apr. 28, 2020), *available at* https://nypost.com/2020/04/28/nih-investigating-wuhan-lab-at-center-of-coronavirus-pandemic/.
[9] U.S. Department of State, *Fact Sheet: Activity at the Wuhan Institute of Virology*, Office of the Spokesperson (Jan. 15, 2021), *available at* https://2017-2021.state.gov/fact-sheet-activity-at-the-wuhan-institute-of-virology//index.html.
[10] *Id.*
[11] *Id.*
[12] *Id.*

studying viruses similar to the COVID-19 virus, including "RaTG13," which was sampled from a cave in Yunnan Province in 2013 after several miners died of SARS-like illness.[13]

- WHO investigators must have access to the records of the WIV's work on bat and other coronaviruses before the COVID-19 outbreak. As part of a thorough inquiry, they must have a full accounting of why the WIV altered and then removed online records of its work with RaTG13 and other viruses.[14]

- Despite the WIV presenting itself as a civilian institution, the U.S. has determined that the WIV has collaborated on projects with China's military.[15] The WIV has engaged in classified research, including laboratory animal experiments, on behalf of the Chinese military since at least 2017.[16]

- The U.S. and other donors who funded or collaborated on civilian research at the WIV have a right and obligation to determine whether any of our research funding was diverted to secret Chinese military projects at the WIV.[17]

Notably, the State Department's former lead investigator who oversaw the Task Force into the COVID-19 virus origin stated recently that he not only believes the virus escaped from the WIV, but that it may have been the result of research that the Chinese military, or People's Liberation Army, was doing on a bioweapon.[18]

Accordingly, it is imperative to determine not only where SARS-CoV-2 originated, but also how and if NIH's funding and research to projects at the WIV could have contributed to SARS CoV-2. To assist our requests and inquiry, please provide the following by April 19, 2021:

1. An assessment from a classified U.S. Defense Intelligence Agency (DIA) report included the possibility that the origins of SARS CoV-2 could have emerged accidentally from a laboratory in Wuhan, China due to unsafe laboratory practices.[19] The DIA report cited U.S. government and Chinese researchers who found "about 33 percent of the original 41 identified cases did not have direct exposure" to the market.[20] That, along with what is known of the WIV's work in past few years, raised reasonable suspicion that the

[13] *Id.*
[14] *Id.*
[15] *Id.*
[16] *Id.*
[17] *Id.*

[18] Jennifer Griffin, Former top State Dept. investigator says COVID-19 outbreak may have resulted from bioweapons research accident, Fox News (March 13, 2021), *available at* https://www.foxnews.com/world/top-state-official-coronavirus-bioweapon-accident

[19] Fred Guterl, Naveed Jamali and Tom O'Connor, *The Controversial Experiments ad Wuhan Lab Suspected of Starting the Coronavirus Pandemic*, NEWSWEEK (Apr. 27, 2020), *available at* https://www.newsweek.com/controversial-wuhan-lab-experiments-that-may-have-started-coronavirus-pandemic-1500503.
[20] *Id.*

pandemic may have been caused by a lab error, not a wet market.[21] Further, a WHO inspector on the recent mission noted that "we know not all of those first 174 early COVID-19 cases visited the market, including the man diagnosed in December 2019 with the earliest onset date."[22] What information does the NIH have on the earliest COVID-19 cases?

2. According to an editorial on February 23, 2021, in *The Wall Street Journal* by former Secretary of State Mike Pompeo and Miles Yu, "[China's] army of scientists claim to have discovered almost 2,000 new viruses in a little over a decade."[23] How many of these discovered viruses does the NIH have information on and were any of these viruses discovered at the WIV?

3. According to *The Wall Street Journal* editorial mentioned in the previous question, some have alleged that the WIV's virus-carrying animals were sold as pets and may even show up at local wet markets.[24] Is the NIH aware of these allegations? If so, please provide any information the NIH has related to these allegations.

4. Please provide all information that NIH has about laboratory accidents and/or biosafety practices at the WIV since January 1, 2015.

5. Please provide all information that NIH has from NIH staff, grantees, sub-grantees, contractors, or subcontractors about communications and events at the WIV from August 2019 to the present.

6. Please provide all information that NIH has from NIH staff, grantees, sub-grantees, contractors, or subcontractors about their communications with China-based NIH, Chinese National Science Foundation, CDC, and China CDC about events at the WIV from August 2019 to the present.

<u>State Department Cables</u>

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[21] *Id.*

[22] Dominic Dwyer, I was the Australian doctor on the WHO's COVID-19 mission to China. Here's what we found about the origins of the coronavirus, THE CONVERSATION (Feb. 21, 2021), *available at*https://www.theguardian.com/commentisfree/2021/feb/22/i-was-on-the-whos-covid-mission-to-china-heres-what-we-found. *See also* Jeremy Page and Drew Hinshaw, *China Refuses to Give WHO Raw Data on Early Covid-19 Cases*, THE WALL STREET JOURNAL (Feb. 12, 2021), *available at* https://www.wsj.com/articles/china-refuses-to-give-who-raw-data-on-early-covid-19-cases-11613150580#:~:text=BEIJING%E2%80%94Chinese%20authorities%20refused%20to,over%20the%20lack%20of%20detail. ("Chinese authorities refused to provide World Health Organization investigators with raw, personalized data on early Covid-19 cases that could help them determine how and when the coronavirus first began to spread in China, according to WHO investigators who described heated exchanges over the lack of detail. The Chinese authorities turned down requests to provide such data on 174 cases of Covid-19 that they have identified from the early phase of the outbreak in the Chinese city of Wuhan in December 2019. Investigators are part of a WHO team that this week completed a monthlong mission in China aimed at determining the origins of the pandemic.")

[23] *Id.*

[24] Mike Pompeo and Miles Yu, *NIH Presses U.S. Nonprofit for Information on Wuhan Virology Lab*, THE WALL STREET JOURNAL (Feb. 23, 2021), available at https://www.wsj.com/articles/chinas-reckless-labs-put-the-world-at-risk-11614102828.

7. What information does NIH have about the WIV's responses to the 2018 U.S. Department of State cables (attached to this letter) regarding safety concerns?

8. The April 2018 cable from the U.S. Department of State stated that the WIV planned to invite University of Texas Medical Branch Galveston (UTMBG) researchers to do research in Wuhan's labs. Please provide any information NIH received that indicates whether the WIV invited UTMBG researchers, and whether UTMBG researchers conducted any research in Wuhan's labs.

    a. If there was such research, please provide information and any documents related to this research.

9. Why was it pertinent to the NIH investigation that the "nonprofit [EcoHealth Alliance] must provide the "WIV's responses to the 2018 Department of State cables regarding safety concerns"?[25]

    a. Did EcoHealth Alliance provide this information? If so, how did NIH use the information to further its investigation?

<u>EcoHealth Alliance, Columbia University Health Sciences</u>

10. Was the 2019 NIH federal award to EcoHealth Alliance reviewed and approved by the HHS Potential Pandemic Pathogen Care and Oversight (P3CO) committee?[26]

    a. If so, please provide the documentation with the committee's decision.

    b. Please also provide the names of the individuals who were members of the committee at the time.

11. Please provide all correspondence and communications between NIH and EcoHealth Alliance, since January 1, 2020, related to federal funding involving the WIV. The documentation should include, but not be limited to, correspondence between NIH and EcoHealth Alliance dated sometime in April 2020, on July 8, 2020, and sometime in August 2020.

12. In April 2020, NIH suspended a 2019 federal award to EcoHealth Alliance, in part, because NIH did not believe the work aligned with "program goals and agency priorities."[27] Please specify the work that was done by the EcoHealth Alliance that did

[25] Meredith Wadman, *NIH imposes 'outrageous' conditions on resuming coronavirus grant targeted by Trump*, SCIENCEMAG (Aug. 19, 2020), *available at* https://www.sciencemag.org/news/2020/08/nih-imposes-outrageous-conditions-resuming-coronavirus-grant-targeted-trump.
[26] National Institutes of Health, *Notice Announcing the Removal of the Funding Pause for Gain-of-Function Research Project* (Dec. 19, 2017), *available at* https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-071.html.
[27] *Id.*

not align with the agency's program goals and priorities, and when that work was conducted.

a. Was an evaluation of EcoHealth Alliance's work and whether it aligned with the agency's program goals and priorities conducted by the NIH before the award was issued? If yes, please provide any related documentation. If not, why not?

13. In April 2020 correspondence with EcoHealth Alliance, NIH wrote that it "received reports that the Wuhan Institute of Virology…has been conducting research at its facilities in China that pose serious bio-safety concerns."[28] What are the sources for those reports to NIH and what were the specific allegations reported?

14. Why did the NIH request that EcoHealth Alliance provide a sample of the pandemic coronavirus that the WIV used to determine its genetic sequence for SARS CoV-2?[29]

    a. Why is this information important to NIH's investigation?

    b. Has NIH obtained the sample and if so, what evaluations have been done, and for what purpose?

    c. If NIH has not yet obtained the sample, what are the planned studies and evaluations NIH will conduct with the sample when it is obtained?

15. What is the nature of NIH's concerns about purported restrictions at the WIV including "diminished cell-phone traffic in October 2019, and the evidence that there may have been roadblocks surrounding the facility from October 14-19, 2019[,]" about the WIV lab or virus origin?[30]

    a. What is the basis of information to NIH about the purported restrictions at the WIV?

    b. What are the other purported restrictions at the WIV in October 2019?

16. After terminating EcoHealth Alliance's 2019 project entitled "Understanding the Risk of Bat Coronavirus Emergence," the NIH later offered to reinstate the EcoHealth Alliance funding in July 2020 if EcoHealth Alliance agreed to meet certain conditions.[31]

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[28] Betsy McKay, *NIH Presses U.S. Nonprofit for Information on Wuhan Virology Lab*, THE WALL STREET JOURNAL (Aug. 19. 2020), *available at* https://www.wsj.com/articles/nih-presses-u-s-nonprofit-for-information-on-wuhan-virology-lab-11597829400.
[29] Meredith Wadman, *NIH imposes 'outrageous' conditions on resuming coronavirus grant targeted by Trump*, SCIENCEMAG (Aug. 19, 2020), *available at* https://www.sciencemag.org/news/2020/08/nih-imposes-outrageous-conditions-resuming-coronavirus-grant-targeted-trump.
[30] *Id.*
[31] Betsy McKay, *NIH Presses U.S. Nonprofit for Information on Wuhan Virology Lab*, THE WALL STREET JOURNAL (Aug. 19. 2020), *available at* https://www.wsj.com/articles/nih-presses-u-s-nonprofit-for-information-on-wuhan-virology-lab-11597829400.

a. Please provide all of the information presented to NIH from EcoHealth Alliance in response to NIH's conditions for reinstatement.

b. What actions did NIH take based upon the information received? How has the information been used in NIH's investigation?

c. One condition for the federal award reinstatement was for EcoHealth Alliance to arrange for an outside inspection of the WIV and its records, "with specific attention to addressing the question of whether WIV staff had SARS-CoV-2their possession prior to December 2019."[32] Why is it pertinent to the NIH's investigation if staff at WIV had SARS-CoV-2 in their possession prior to December 2019? What is the potential significance if the staff did have the virus in their possession prior to December 2019?

d. What information does NIH have that was used for the basis of requesting that the EcoHealth Alliance "must 'explain the apparent disappearance' of a scientist who worked in the Wuhan lab," and on social media was rumored to be "patient zero" of the pandemic?[33]

i. What is the potential significance about the whereabouts of this scientist and the photo being removed from the website?

17. Please provide all correspondence and communications between NIH and Columbia University related to federal funding involving the WIV, including email correspondence in April 2020 between Dr. Michael Lauer, Deputy Director of extramural research, and Naomi Schrag of Columbia University.

a. In an April 2020 email, Dr. Lauer advised Naomi Schrag of Columbia University that it would be helpful for NIH "to know about all China-based participants in this work since the Type 1 grant started in 2014 - who they were and how much money they received."[34] Why did NIH request that Columbia University provide information about all of the China-based participants?

i. What is the pertinence of the timeframe starting in 2014 for the requested information?

ii. Did Columbia University provide the NIH with the requested information about all of the China-based participants from all grantees since 2014? If so, please provide the information1. If not, why not?

<u>Federal Funding Records</u>

[32] *Id.*
[33] *Id.*
[34] Meredith Wadman and Jon Cohen, *NIH's axing of bat coronavirus grant a 'horrible precedent' and might break rules, critics say*, SCIENCEMAG (Apr. 30, 2020), *available at* https://www.sciencemag.org/news/2020/04/nih-s-axing-bat-coronavirus-grant-horrible-precedent-and-might-break-rules-critics-say.

18. Please provide ledgers or any accounting for dispersion of all NIH federal funding awards that EcoHealth Alliance has sent to the WIV, including through contracts, grants, donations, cooperative agreements, staffing, or any other support or means. In addition, please provide the results and outcomes from the funding and support.[35]

19. What is the total amount of NIH federal funding per year from 2017 through 2021 that has directly or indirectly supported the WIV scientists or research through grant recipients, including to EcoHealth Alliance; Wildlife Trust, Inc.; Columbia University Health Sciences; Trustees of Columbia University; University of North Carolina Chapel Hill; Vanderbilt University; University of Virginia; and Oregon Health and Science University?[36]

20. According to a report in *The Washington Post* on April 14, 2020, the WIV issued a news release in English about the final visit from U.S. Embassy scientist diplomats in Beijing, which occurred on March 27, 2018.[37] Does the NIH have a copy of this news release? If so, please provide a copy.

21. For NIH award recipients that have provided support to the WIV since January 1, 2012, please provide annual reports, trip reports related to the WIV, documentation of any survey or field trips by the WIV, and interim data summaries from the WIV.

22. Please provide copies of all grantee annual reports, progress reports, projects, studies, and observations since 2014 where foreign sites for all Type 1 and Type 2 awards have been documented as involving the WIV.

23. Please provide copies of all grantee annual reports, progress reports, projects, studies, and observations since 2014 for NIH domestic grantee awards with a foreign component involving the WIV.

24. Please provide the name(s) of the NIH program manager(s) or officer(s) responsible for overseeing the grants to EcoHealth Alliance and time period(s) of responsibility.

25. Please provide the name(s) of the NIH Scientific Review Officers responsible for reviewing and approving any NIH financial awards to EcoHealth Alliance and any other funding recipients that supported the WIV.

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[35] Betsy McKay, *NIH Presses U.S. Nonprofit for Information on Wuhan Virology Lab*, THE WALL STREET JOURNAL (Aug. 19. 2020), *available at* https://www.wsj.com/articles/nih-presses-u-s-nonprofit-for-information-on-wuhan-virology-lab-11597829400.

[36] National Institutes of Health, Research Portfolio online Reporting Tools, NIH RePorter *available at* https://report.nih.gov/ (last accessed March 6, 2020).

[37] Josh Rogin, *Opinion: State Department cables warned of safety issues at Wuhan lab studying bat coronaviruses*, THE WASHINGTON POST (Apr. 14, 2020), *available at* https://www.washingtonpost.com/opinions/2020/04/14/state-department-cables-warned-safety-issues-wuhan-lab-studying-bat-coronaviruses/.

26. According to an editorial in *The Wall Street Journal*, the WIV housed tens of thousands of bat samples and laboratory animals in 2019.[38] Please provide any information the NIH has on the number of bat samples and animals at the WIV.

    a. Did any NIH scientists who are fluent in Mandarin review the Chinese scientific literature on the WIV research related to coronaviruses that is dated before February 1, 2020?

27. Does the NIH have the unpublished sequences of bat coronaviruses that were maintained in the WIV database before December 30, 2019, or before the database was removed from the internet?[39] Does NIH have the full sequences of the eight viruses sampled in the Yunnan province on an EcoHealth Alliance bat-virus sampling trip in 2015?

    a. Please provide NIH's analysis if the sequences have been analyzed.

    b. If NIH does not have the sequences, can NIH get this information from the EcoHealth Alliance or from other NIH-funded sources?

28. Please provide the original version of "Origin and cross-species transmission of bat coronaviruses in China" that was submitted to *Nature* by EcoHealth Alliance on October 6, 2019, published August 25, 2020, and funded in part by NIAID (award number R01AI110964).[40] If NIH does not have the October 6, 2019 report, can NIH obtain it from EcoHealth Alliance for this response? If so, please provide the report.

29. Have NIH, EcoHealth Alliance, or other NIH award recipient(s) been denied permission or access to results of any WIV research, which indirectly received financial support from NIH awards? If so, please provide the date(s), individuals involved, and circumstances of each denial.

We request that the NIH provide the requested documents and information in a coordinated response from all stakeholders and the appropriate divisions within NIH, including but not limited to subject matter experts from NIH's Division of Security and Emergency Response, the Office of Management Assessment, the Center for Scientific Review, the National Institute of Allergy and Infectious Diseases, and the Office of Extramural Research. After the requested information has been provided, we ask that the NIH provide a briefing to the Minority Committee staff to discuss the information that the NIH has related to the origins of SARS-CoV-2, including any potential links to the WIV. Finally, we request that you appoint an NIH working group representing an appropriate diversity of scientific disciplines to collect data and

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[38] Mike Pompeo and Miles Yu, *NIH Presses U.S. Nonprofit for Information on Wuhan Virology Lab*, THE WALL STREET JOURNAL (Feb. 23, 2021), *available at* https://www.wsj.com/articles/chinas-reckless-labs-put-the-world-at-risk-11614102828.

[39] Washington Post Editorial Board, *We're still missing the origin story of this pandemic. China is sitting on the answers*, THE WASHINGTON POST (Feb. 5, 2021), *available at* https://www.washingtonpost.com/opinions/2021/02/05/coronavirus-origins-mystery-china/?arc404=true.

[40] Latinne, A., Hu, B., Olival, K.J. et al,. *Origin and cross-species transmission of bat coronaviruses in China*, Nature (Aug. 25, 2020), *available at* https://www.nature.com/articles/s41467-020-17687-3#Ack1.

information related to COVID-19 origins (including the WIV), and that the NIH working group coordinate and consult with foreign scientific agencies involved in similar work.

Your assistance with this request is greatly appreciated. If you have any questions, please contact Alan Slobodin or Diane Cutler of the Minority Committee staff.

Sincerely,

Cathy McMorris Rodgers
Republican Leader
Committee on Energy and Commerce

Brett Guthrie
Republican Leader
Subcommittee on Health

H. Morgan Griffith
Republican Leader
Subcommittee on Oversight and Investigations

Attachment

Cc: The Honorable Frank Pallone, Chairman
The Honorable Diana DeGette, Chair, Subcommittee on Oversight and Investigations
The Honorable Anna Eshoo, Chair, Subcommittee on Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

May 21, 2021

The Honorable Cathy McMorris Rodgers
U.S. House of Representatives
Washington, DC 20515

Dear Representative McMorris Rodgers:

Thank you for your letter regarding the National Institutes of Health's (NIH) support for biomedical research related to SARS-CoV-2, "gain of function" (GOF) research, and the NIH grant to the EcoHealth Alliance. As Principal Deputy Director of NIH, I am pleased to respond to your inquiry.

Neither NIH nor the National Institute of Allergy and Infectious Diseases has ever approved any grant that would have supported GOF research on coronaviruses that would have increased their transmissibility or lethality for humans.

Some scientists use the term GOF research broadly to refer to *any* modification of a biological agent that confers new or enhanced activity to that agent. In some cases, this research is performed to give new properties to agents to allow them to grow and be studied in the lab; for example, the agent may be modified so that it can be studied in research animals. However, not all research that some label as GOF research entails the same level of risk. The subset of GOF research that is anticipated to enhance the *transmissibility* and/or *virulence* of potential pandemic pathogens, which could make them more dangerous to humans, has been the subject of substantial scrutiny and deliberation.

In 2017, the U.S. Department of Health and Human Services (HHS) issued its Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens (HHS P3CO Framework). The HHS P3CO Framework is intended to guide HHS funding decisions on proposed research that is reasonably anticipated to create, transfer, or use Potential Pandemic Pathogens (PPPs) resulting from the enhancement of a pathogen's transmissibility or virulence in humans (enhanced PPP) and seeks to preserve the benefits of life sciences research involving enhanced PPPs while minimizing potential biosafety and biosecurity risks.

As your letter notes and has been publicly stated, NIH awarded a grant to EcoHealth Alliance Inc., a research organization based in New York City, in June 2014. The application was subjected to rigorous peer review and did not propose research to enhance any coronavirus to be more transmissible or virulent.

The research proposed in the grant application sought to understand how bat coronaviruses evolve naturally in the environment to become transmissible to the human population. This

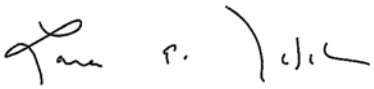
included studying viral diversity in bat reservoirs, surveying people who work in live animal markets or other jobs with high exposure to wildlife for evidence of bat-coronavirus infection, and analyzing data to predict which newly discovered viruses pose the greatest threat to human health. To support its work, EcoHealth made sub-awards to the Wuhan Institute of Virology and other institutions based in East Asia where coronaviruses tend to emerge and are prevalent. NIH is not currently funding the Wuhan Institute of Virology.

I would be happy to further discuss this grant, and this issue, at your convenience. NIH is committed to upholding the highest standards within the conduct of science and the oversight of federal funding.

In conclusion, NIH strongly supports the need for further investigation by the World Health Organization (WHO) into the origins of the SARS-CoV-2 coronavirus. Working with a cross-regional coalition of 13 countries, we urge the WHO to begin the second phase of their study without delay.

Thank you again for the opportunity to address these questions. An identical response has been sent to the co-signers of your letter.

Sincerely,



Lawrence A. Tabak, D.D.S., Ph.D.
Principal Deputy Director

cc: The Honorable Frank Pallone
Chairman, House Committee on Energy and Commerce

FRANK PALLONE, JR., NEW JERSEY
CHAIRMAN

CATHY McMORRIS RODGERS, WASHINGTON
RANKING MEMBER

ONE HUNDRED SEVENTEENTH CONGRESS

# Congress of the United States

## House of Representatives

COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115
Majority (202) 225–2927
Minority (202) 225–3641

June 10, 2021

The Honorable Francis Collins, M.D., Ph.D.
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

Dear Dr. Collins:

As the committee of jurisdiction over public health, the Energy and Commerce Committee has authorizing responsibilities over the U.S. National Institutes of Health (NIH). We strongly support a comprehensive investigation into the origins of the COVID-19 pandemic, including the possibility of an accidental laboratory leak.

The Chinese Communist government has not yet allowed Chinese scientists to cooperate with an investigation into COVID-19 origins, and has admitted to destroying samples and records pertinent to such an investigation.[1] Thus, it is imperative we assemble all data and information in U.S. possession about bat coronavirus research experiments and lab safety protocols from all sources outside of China, particularly from EcoHealth Alliance (EHA). EHA is an NIH grantee who has been involved in bat coronavirus research in China and has issued grant subawards to the Wuhan Institute of Virology (WIV). It is also essential to collect information about the WIV, the laboratory that was conducting bat coronavirus experiments located in Wuhan, China, the epicenter of the COVID-19 outbreak. As a federal cognizant grant-making agency that funded bat coronavirus research at the WIV through EHA awards, NIH is in a unique position to publicly share detailed research reports in its possession. Importantly, NIH has full access to EHA records and EHA has refused to cooperate with our inquiry. Therefore, it is critical for NIH to cooperate with our objective fact-finding investigation as we continue to collect data about U.S. funded bat coronavirus research.

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[1] Josh Chin, *China Told Labs to Destroy Coronavirus Samples to Reduce Safety Risks*, The Wall Street Journal (May 16, 2020) *available at* https://www.wsj.com/articles/china-told-labs-to-destroy-coronavirus-samples-to-reduce-biosafety-risks-11589684291/.

Since the Republican committee leaders March 18, 2021 letter to NIH, our investigation has found a number of additional issues that raise very serious concerns about the adequacy of NIH's oversight of grantees. The following newly found issues appear troubling and given the significance of these concerns, we expect the NIH to respond fully and substantively. Minority committee staff is continuing to work with your staff to schedule an NIH briefing. The NIH should be prepared to address these issues at the briefing, in addition to all of the questions from the March 18, 2021 letter that presently remain unanswered.

1. NIH's Award of $2 million to EHA Despite Grant Suspension

On May 25, 2021, a spokesperson for EHA told Fox Business that its NIH funding is frozen and NIH did not give them guidance on when funds will be unfrozen.[2] EHA's representation about their NIH funding was not forthcoming. NIH terminated grant R01AI110964 to EHA entitled, "Understanding the Risk of Bat Coronavirus Emergence" in April 2020.[3] NIH eventually converted the grant termination to a suspension on July 8, 2020, pending EHA's responses to seven requests from NIH related to WIV's actions. NIH could unfreeze the funding if EHA cooperates with NIH's requests, but apparently EHA has not yet done so. Despite EHA's obstruction of NIH requests, NIH gave new financial awards to EHA in June 2020 and August 2020, totaling $2,127,602.[4] By NIH authorizing new funding to EHA, an NIH-suspended grantee, the NIH undercut its July 8, 2020 suspension and has incentivized its grantees to defy NIH oversight with impunity.

2. NIH's Inadequate Oversight of EHA's Other Support

You testified during a May 25, 2021 Congressional hearing that NIH was, "...of course not aware of other sources of funds or other activities they might have undertaken outside of what our approved grant allowed," when asked about NIH grant recipient EHA, and the WIV, an EHA subaward recipient.[5] Pursuant to the NIH Grants Policy, EHA was required to report all "other support," in-kind contributions such as laboratory space, equipment and supplies, and facilities and other resources for all individuals designated as the Principal Investigator (PI) personnel.[6] Per the NIH grants policy, the grant Principal Investigator Dr. Peter Daszak and EHA were required to report its other research funding sources and activities to NIH.[7] Without

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[2] Fox News, *Biden State Department quietly ended team's work probing COVID origin*, State Department (May 25, 2021) *available at* https://www.foxnews.com/politics/biden-state-department-shut-down-team-covid-origin-investigation.

[3] National Institutes of Health, *Understanding the Risk of Bat Coronavirus Emergence*, REPORTER (last accessed June 2, 2021) *available at* https://reporter.nih.gov/search/p1odLH_U1kyZgyOhClrN2w/project-details/9320765#similar-Projects/.

[4] USASpending.gov, *Cooperative agreement numbers U01AI151797 and U01AI153420*, EcoHealth Alliance available at

[5] House Committee on Appropriations, *FY 2022 Budget Request for the National Institutes of Health*, Hearings (May 25, 2021) *available at* https://appropriations.house.gov/events/hearings/fy-2022-budget-request-for-the-national-institutes-of-health.

[6] National Institutes of Health, Other Support, Grants & Funding (last accessed June 1, 2021) available at https://grants.nih.gov/grants/forms/othersupport.htm.

[7] *Id.*

further details or documentation, your testimony bolsters the notion that NIH oversight is largely ignorant of other awards to the grantee.

3. NIH's Inadequate Oversight of EHA's Delinquent Financial Reports

As the prime recipient of NIH grant R01AI110964, EHA gave a total $598,500 in five subaward transactions to the WIV from 2015 to 2019 for the WIV to, "conduct high-quality testing, sequencing, and analyses of field samples; maintenance of cold-chains from field to lab; ensuring quality control of sample storage and testing; collaborating on scientific publications and programmatic reporting."[8] EHA also gave a total of $201,217.10 in two subaward transactions to the Wuhan University School of Public Health (WUSPH) to "conduct targeted site-analyses, human behavioral surveillance including qualitative and quantitative surveys; analyses of data; collaborating on scientific publications and programmatic reporting," from 2016 through 2017.[9]

EHA is required to report its subawards to GSA's FFATA Subaward Reporting System (FSRS) by the end of the month following the month when the subaward was made.[10] For example, when EHA issued a $133,000 subaward to the WIV on May 29, 2015, EHA was required to report that subaward to FSRS by June 30, 2015.[11] USASpending is the U.S. government's open federal spending data source and when the grant number R01AI110964 data is downloaded, details reveal that EHA did not report subawards for that grant until 2020, even though EHA made subawards starting in 2015.[12] EHA reported all seven subaward transactions for R01AI110964 on July 13, 2020, five days following NIH's July 8, 2020 letter to EHA instructing EHA to ensure EHA reported all subaward data to FSRS.[13] Before the year 2020, only one other EHA subaward grant is reported in USASpending.gov, in which three subaward transactions for NIH grant number R56TW009502 are recorded in 2014.[14] EHA's apparent non-compliance of required financial reporting raises concerns about the adequacy of NIH oversight of NIH grants.

4. NIH's Possible Funding of EHA for Duplicative Research in China

EHA received federal funding as both a prime and sub-recipient not only from NIH, but also from the U.S. Agency for International Development (USAID) for its bat coronavirus research. The project descriptions and research articles are so similar that a distinction between the NIH bat coronavirus research objectives and achievements for the awards to EHA are almost interchangeable with EHA's USAID-funded bat coronavirus research objectives and

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[8] *Id.*
[9] *Id.*
[10] USAspending.gov, *Data Sources,* About (last accessed June 1, 2021), *available at* https://www.usaspending.gov/about.
[11] *Id.*
[12] USASpending.gov, *Advanced Search: Recipient – EcoHealth Alliance* (June 1, 2021) *available at* USASpending.gov/.
[13] *Id.*
[14] *Id.* See NIH grant number R56TW009502.

achievements.[15] The NIH grant progress reports will reveal details about the bat coronavirus research that can be compared to the reports from USAID-funded research. In its research funded by the USAID, EHA partnered with the WIV and with East China Normal University.[16] We are very concerned that the NIH and USAID may have funded duplicate projects and that EHA partnered with additional unreported entities in China for NIH-funded research.

5. NIH's Inadequate Reconciliation of EHA's Grant Subawards

As far back as 2005, Peter Daszak of EHA has authored over 20 bat coronavirus and other zoonic pathogen research articles with Dr. Zhengli Shi of the WIV, plus other researchers, about experiments funded by NIH.[17] Their collaborative research has resulted in a 2005 publication entitled "Bats Are Natural Reservoirs of SARS-Like Coronaviruses," funded by NIH.[18] In 2013, they published "Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor," funded by NIH and USAID. [19] Their numerous publications acknowledge NIH as a research sponsor yet the only EHA support to the WIV in USASpending.gov was reported by EHA on July 13, 2020 (see concern number three above).[20] Vanity Fair reported that Dr. Shi "herself listed U.S. government grant support of more than $1.2 million on her curriculum vitae: $665,000 from the NIH between 2014 and 2019; and $559,500 over the same period from USAID."[21] EHA's late and potentially incomplete reporting of the WIV as its sub-award recipient raises questions about EHA's compliance with required financial reporting and also raises concerns about NIH's oversight of grant awards to EHA.

6. NIH's Inadequate Oversight of EHA's Place of Performance Reporting

The Federal Funding Accountability and Transparency Act of 2006 (FFATA) requires that federal award reporting must include the primary location of where the work will be performed, (including the city, state, congressional district, and country).[22] For EHA's NIH awards, China is not listed as the place of performance in USASpending.gov and instead, EHA's

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[15] USASpending.gov, *Advanced Search: Recipient – EcoHealth Alliance* (June 1, 2021) *available at* USASpending.gov/.
[16] USAID PREDICT-1 CONSORTIUM, *Reducing Pandemic Risk, Promoting Global Health*, Final Report (Dec. 2014) *available at* https://ohi.sf.ucdavis.edu/sites/g/files/dgvnsk5251/files/files/page/predict-final-report-lo.pdf.
[17] NIH Reporter, *Anthropogenic change & emerging zoonic paramyxoviruses*, Project Number 5R01TW005869-04 (Budget Start Date June 1, 2005) *available at* https://reporter.nih.gov/search/WMYBIQPE20aG4fAZLFj0lw/project-details/6923645#details, NIH National Library of Medicine, *Advanced Search for 'Shi, Daszak,'* National Center for Biotechnology Information (June 2, 2021) *available at* https://pubmed.ncbi.nlm.nih.gov/?term=Daszak%2C+Shi&sort=date&sort_order=asc&size=200.
[18] NIH National Library of Medicine, *Bats Are Natural Reservoirs of SARS-Like Coronaviruses*, PubMed (Sept.5, 2005) *available at* https://pubmed.ncbi.nlm.nih.gov/16195424/.
[19] Ge, XY., *et al., Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor*, Nature 503, 535–538 (May 16, 2013) *available at* https://doi.org/10.1038/nature12711.
[20] *Id.*
[21] Katherine Eban, The Lab-Leak Theory – Inside the Fight to Uncover COVID-19 Origins, Vanity Fair (June 3, 2021) *available at* https://www.vanityfair.com/news/2021/06/the-lab-leak-theory-inside-the-fight-to-uncover-covid-19s-origins.
[22] PL 109-282, Sept. 26, 2006 *available at* https://www.govinfo.gov/content/pkg/PLAW-109publ282/pdf/PLAW-109publ282.pdf.

primary place of performance is identified as New York.[23] The NIH grant documents, and the financial and progress reports we have requested will contain travel budgets and research details that will confirm the location(s) where EHA actually performed its research. Published research articles about NIH-funded experiments describe EHA's bat coronavirus research and surveillance activities often partnered with the WIV in China. We are very concerned about the discrepancy in EHA's primary place of performance as being New York in USASpending.gov when research articles, publications, and media interviews suggest EHA's primary place of performance is not domestic.[24]

7. NIH's Lack of Visibility into EHA's Grant Subawards

USASpending.gov limits visible data to prime and subaward recipients, and does not disclose funds that are further disbursed subaward recipients.[25] EHA is a subaward recipient of NIH grant funds from the Arizona State University and the Trustees of Columbia University in New York City.[26] As a subaward recipient, EHA does not publicly report when it further distributes subaward funds to other organizations such as the WIV or other recipients in China.[27] NIH questions to EHA in the July 8, 2020 grant suspension letter suggest that NIH lacks information and visibility on sub-grant awards that are either issued or received by EHA.[28]

8. NIH's Inadequate Oversight of EHA's Grant Fund Accounting

In our April 18, 2021 letter to EHA, we raised the issue that EHA reported a $319,570 cash award grant and a $126,792 cash award grant disbursed by wire to China for the purpose of "[u]understanding the risk of bat coronavirus emergence" on its IRS Form 990, calendar year 2016.[29] EHA reported giving $321,700 for coronavirus and emerging diseases to China on its IRS Form 990, calendar year 2015.[30] EHA IRS Form 990's for other years do not include that purpose or identify the WIV as an organization to which funds were paid. With EHA organized as a 501 (c)(3) non-profit organization, its IRS Form 990's are public documents able to be reviewed by NIH. As a non-federal entity that expends more $750,000 or more in federal funds in one year, EHA is required to submit a Single Audit report, previously known as the OMB Circular A-133 audit. The purpose of a Single Audit report is to provide assurance to the Federal Government that a non-federal entity has adequate internal controls in place, and is generally in

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[23] *Id.*
[24] Nidhi Subbaraman, *'Heinous!': Coronavirus researcher shut down for Wuhan-lab link slams new funding restrictions*, Nature (Aug. 21, 2020), *available at* https://www.nature.com/articles/d41586-020-02473-4.
[25] USASpending.gov, *Advanced Search: Recipient - EcoHealth Alliance* (June 1, 2021) *available at* USASpending.gov/.
[26] *Id.*
[27] *Id.*
[28] Internal Revenue Service, EHA 990 final, Schedule F, Parts I and II (May 3, 2017) *available at* https://apps.irs.gov/pub/epostcard/cor/311726494_201606_990_2017090514700974.pdf.
[29] U.S. Energy and Commerce Republicans, *Letter to EcoHealth Alliance*, The COVID-19 Origins Investigation (Apr. 16, 2021) *available at* https://republicans-energycommerce.house.gov/the-covid-19-origins-investigation/.
[30] Internal Revenue Service, *EHA 990 final 2015, Schedule F, Parts I and II* (May 3, 2017) *available at* https://apps.irs.gov/pub/epostcard/cor/311726494_201606_990_2017090514700974.pdf.

compliance with program requirements.[31] In EHA's Single Audit reports for years 2016 to 2020, no payments are evident for EHA funds paid to the WIV.[32]

9. NIH's Inadequate Oversight of Its Funded Researchers in China

The WIV named NIH and EHA on its website as WIV international partner as of and prior to the date of our March 18, 2021 letter to NIH.[33] By March 22, 2021, the WIV had removed NIH as a partner from its website.[34] The NIH has characterized its relationship Chinese scientists as respectable scientific partners.[35] However, within three days following our letter to NIH which inquired about NIH grants to the WIV, the WIV quickly concealed its long-standing relationship with NIH by deleting evidence of its NIH partnership from its website. This action does not seem consistent with NIH's claim that the WIV and its scientists were a respectable scientific partner. It has been reported that some Chinese scientists working with EHA are current or former members of the People's Liberation Army of China.[36] It has also been reported that the Chinese military were conducting research at the WIV.[37] We are concerned that NIH-funded coronavirus research in China may not have undergone proper biodefense risk analysis.

10. NIH's Lack of Cooperation with Congressional Oversight Inquiry

NIH is supposed to be a transparent institution and the grant documents we requested should be a matter of public record.[38] Contrary to your public statement implying that we asked for "pretty sensitive materials, not quite classified, but getting close to that," the grant documents we requested are releasable to the public per NIH's own policy and should have already been provided to us.[39]

As you are aware, the NIH grant documents and progress reports we requested will include details pertinent to our COVID-19 origins investigation, including information about: all research participants and collaborating organizations; location(s) of work performed; instruments, equipment and monies provided to grant sub-recipients; financial accounting

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[31] U.S. Department of Health and Human Services, *Single Audit* (Apr. 25, 2016) *available at* (https://www.hhs.gov/about/agencies/asfr/data-act-program-management-office/single-audit/index.html.
[32] Federal Audit Clearinghouse, *EcoHealth Alliance, Inc and Wildlife Preservation Trust Int. Single Audit Reports 2017-2021* (June7, 2021) *available at* https://facdissem.census.gov/SearchResults.aspx.
[33] Internet Archive Wayback Machine, *Wuhan Institute of Virology, CAS*, Partnerships (Mar. 18, 2021) *available at* https://web.archive.org/web/20210318052528/http://english.whiov.cas.cn/International_Cooperation2016/Partnerships/.
[34] Internet Archive Wayback Machine, *Wuhan Institute of Virology, CAS*, Partnerships (Mar. 22, 2021) *available at* https://web.archive.org/web/20210322053537/http://english.whiov.cas.cn/International_Cooperation2016/Partnerships/
[35] House Committee on Appropriations, *FY 2022 Budget Request for the National Institutes of Health*, Hearings (May 25, 2021) *available at* https://appropriations.house.gov/events/hearings/fy-2022-budget-request-for-the-national-institutes-of-health.
[36] Alexis, Shi Zhengli: Weaponizing Coronaviruses, with Pentagon Funding, at a Chinese Military Lab, https://enviroshop.com/shi-zhengli-weaponizing-coronaviruses-with-pentagon-funding-at-a-chinese-military-lab/
[37] *Id.*
[38] National Institutes of Health, *NIH Grants Policy Statement*, Policy and Compliance (June 1, 2021) *available at* https://grants.nih.gov/policy/nihgps/index.htm.
[39] *Id.*

reports; research techniques and accomplishments; research products such as: technologies, patent applications, data or databases, physical collections, and models; significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents; and budgetary information and project outcomes.[40]

As the federal grant awarding agency, NIH must have the right of access to any of EHA's documents or other records which are pertinent to NIH federal awards.[41] The NIH grants policy states that the Freedom of Information Act (FOIA) and U.S. Department of Health and Human Services regulations require NIH to release certain grant documents and records requested by members of the public, regardless of the intended use of the information.[42] Per NIH policy, NIH will generally release funded applications and progress reports pursuant to a FOIA request.[43] NIH considers most grant-related information in the application or post-award phases as being public information (emphasis added).[44]

In support of this inquiry and the public interest in the origins of the COVID-19 pandemic, please provide written responses to the following by June 24, 2021:

1. We again renew our request for NIH's immediate compliance with our oversight inquiry for production of the grant documents and progress reports forthwith that we first requested on March 18, 2021.

2. What is NIH's policy for awarding funds to organizations when the organization has NIH grant funds in suspended status and are not cooperating NIH requests? If the NIH permits new award funding under these circumstances, please provide the policy, and explain how such funding does not undercut NIH's ability to oversee grantees and does not incentivize grantees to defy NIH's requests for information.

3. Please explain all oversight steps NIH has taken to ensure EHA's full compliance with federal financial subaward reporting requirements for all NIH grants. Please explain if EHA reported to NIH any subaward recipients other than the WIV or the WUSPH for NIH grant R01AI110964. Please provide all financial records of all NIH funds given to Dr. Zhengli Shi of the WIV.

4. For all NIH awards in which EHA was a subrecipient, please provide a financial accounting of EHA's subawards to the WIV or other organizations in China.

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[40] Hugh Hewitt, *Dr. Francis Collis On The U.S. Funding of the Wuhan Lab and Congressional Oversight,* The Hugh Hewitt Show (June 2, 2021) *available at* https://hughhewitt.com/dr-francis-collins-on-the-u-s-funding-of-the-wuhan-lab-and-congressional-oversight/, National Institutes of Health, *Research Performance Progress Report,* Grants & Funding (May 4, 2021) *available at* https://grants.nih.gov/grants/rppr/index.htm.
[41] *Id.*
[42] National Institutes of Health, *NIH Grants Policy Statement*, Policy and Compliance (June 1, 2021) *available at* https://grants.nih.gov/policy/nihgps/index.htm.
[43] *Id.*
[44] *Id.*

5. How does NIH ensure it does not award unapproved duplicate grants for same or similar research already funded by other agencies, to EHA or other NIH grant recipients? For all NIH awards to EHA, please provide accounting information for EHA subawards to recipients in China.

6. Please explain how NIH has reviewed EHA annual Single Audit reports to ensure how EHA has met program and reporting requirements.

7. How does NIH audit the financial reports submitted to the IRS by its 501(c)(3) non-profit organization grant award recipients to ensure NIH awards are accurately reported? How does NIH ensure its grantees do not act as a pass-through or money laundering provider to send U.S. research funding to China?

8. Please explain NIH's policy for ensuring its awardees accurately report the actual place of research performance. For all NIH-funded research, please provide all China site locations where EHA's work was performed.

9. Please explain if EHA reported its other funding or in-kind support, including awards from federal agency, to NIH. Please explain if EHA reported any support from organizations in China.

10. Did NIH perform a biodefense risk analysis for coronavirus research conducted at the WIV as research with potential for dual use of research concern, pandemic pathogen or bioweapon development, as outlined in the HHS *Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens*?[45] Please describe NIH's coordination procedures with the U.S. Intelligence Community that are completed before NIH funds research projects in foreign countries with existing biodefense programs.

Please make arrangements to schedule the briefing for Committee staff by June 24, 2021. If you have any questions, please contact Alan Slobodin or Diane Cutler of the Minority Committee staff. Thank you for your attention to this request.

Sincerely,

Cathy McMorris Rodgers
Republican Leader
Committee on Energy and Commerce

Fred Upton
Republican Leader
Subcommittee on Energy

[45] U.S. Department of Health and Human Services, *Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens*, Science Safety Security (Dec. 2017) *available at* https://www.phe.gov/s3/dualuse/Pages/p3co.aspx.

Bob Latta
Republican Leader
Subcommittee on Communications and Technology

Brett Guthrie
Republican Leader
Subcommittee on Health

David McKinley
Republican Leader
Subcommittee on Environment and Climate Change

H. Morgan Griffith
Republican Leader
Subcommittee on Oversight and Investigations

Gus Bilirakis
Republican Leader
Subcommittee on Consumer Protection and Commerce

Michael C. Burgess, M.D.
Member of Congress

Steve Scalise
Member of Congress

Adam Kinzinger
Member of Congress

Bill Johnson
Member of Congress

Billy Long
Member of Congress

Larry Bucshon, M.D.
Member of Congress

Markwayne Mullin
Member of Congress

Richard Hudson
Member of Congress

Tim Walberg
Member of Congress

Earl L. "Buddy" Carter
Member of Congress

Jeff Duncan
Member of Congress

Gary Palmer
Member of Congress

Neal P. Dunn, M.D.
Member of Congress

John Curtis
Member of Congress

Debbie Lesko
Member of Congress

Greg Pence
Member of Congress

Dan Crenshaw
Member of Congress

John Joyce, M.D.
Member of Congress

Kelly Armstrong
Member of Congress

**Alan Slobodin**
Job Title
**Chief Investigative Counsel, Republican/Staff Director, Republican**

Education

- **George Washington University Law School**
  - JD
  - 1984
- **Temple University-of The Commonwealth System of Higher Education**
  - BBA, business management, magna cum laude
  - 1979

Career History

- **Chief Investigative Counsel, Republican/Staff Director, Republican** House Subcommittee on Oversight and Investigations

January 2021 - Present

- **Chief Investigative Counsel** House Subcommittee on Oversight and Investigations

January 2019 - January 2021

- **Chief Investigative Counsel** House Subcommittee on Oversight and Investigations

December 2017 - January 2019

- **Chief Investigative Counsel** House Subcommittee on Oversight and Investigations

October 2017 - December 2017

- **Chief Investigative Counsel** House Subcommittee on Oversight and Investigations

2014 - October 2017

- **Deputy Chief Counsel** House Subcommittee on Oversight and Investigations

May 2004 - 2013

- **Senior Counsel, Oversight** House Subcommittee on Oversight and Investigations

1995 - April 2004

- **President and General Counsel, Legal Studies Division** Washington Legal Foundation

1989 - 1995

- **Counsel, Republican** House Subcommittee on Constitution, Civil Rights, and Civil Liberties

1986 - 1989

- **Assistant General Counsel** Washington Legal Foundation

1985 - 1986

- **Attorney** Ross, Dixon and Bell LLP

1984 - 1985

**B.J. Koohmaraie**
Job Title
**Chief Counsel, Republican**

Education

- **University of Nebraska College of Law**
  - JD
  - 2014
- **Nebraska Wesleyan University**
  - BS, political science
  - 2011

Career History

- **Chief Counsel, Republican**House Committee on Energy and Commerce

January 2021 - Present

- **Chief Counsel, Republican**House Subcommittee on Oversight and Investigations

February 2021 - Present

- **Coalitions Director/Deputy Chief Counsel**House Committee on Energy and Commerce

June 2020 - January 2021

- **Deputy Chief Counsel**House Subcommittee on Consumer Protection and Commerce

August 2019 - June 2020

- **Counsel**House Subcommittee on Consumer Protection and Commerce

January 2019 - August 2019

- **Counsel**House Subcommittee on Consumer Protection and Commerce

March 2017 - January 2019

- **Assistant Attorney General**Nebraska Office of the Attorney General

September 2014 - February 2017

- **Senior Certified Law Clerk**Nebraska Office of the Attorney General

March 2013 - September 2014

- **Research Assistant**University of Nebraska College of Law

August 2012 - May 2013

- **Regulatory Policy Intern**American Action Forum

May 2012 - August 2012

- **Staff Assistant**Rep. Adrian Smith (R-NE-3)

May 2010 - July 2011

- **Intern** Rep. Adrian Smith (R-NE-3)

April 2010 - May 2010

**Diane Cutler**
Job Title
**U.S. Department of Health and Human Services Office of Inspector General Detailee**

Career History

- **U.S. Department of Health and Human Services Office of Inspector General Detailee** House Committee on Energy and Commerce

January 2021 - Present

- **U.S. Department of Health and Human Services Office of Inspector General Detailee** House Committee on Energy and Commerce

August 2019 - January 2021

**Chris Knauer**
Job Title
**Oversight Staff Director, Democratic**

Education

- **McCourt School of Public Policy**
  - MPP
  - 1990
- **University of California Berkeley**
  - BA
  - 1987

Career History

- **Oversight Staff Director, Democratic** House Subcommittee on Oversight and Investigations

March 2015 - Present

- **Senior Investigator** House Committee on Oversight and Reform

January 2012 - February 2015

- **Investigator** House Committee on Oversight and Reform

January 2011 - January 2012

- **Senior Investigator** House Committee on Oversight and Reform

September 2009 - January 2011

- **Education Coordinator** House Committee on Oversight and Reform

August 2009 - August 2009

- **Senior Investigative Counsel** House Committee on Oversight and Reform

March 2009 - August 2009

- **Senior Investigator/Professional Staff Member** House Committee on Energy and Commerce

March 2007 - February 2009

- **Senior Investigator** House Committee on Energy and Commerce

January 2007 - February 2007

- **Investigator** House Committee on Energy and Commerce

1993 - January 2007

- **Evaluator** U.S. Government Accountability Office

1991 - 1993

**Kevin McAloon**
Job Title
**Oversight Investigator, Democratic**

Education

- **Villanova University**
    - MA, political science
    - 2009
- **Villanova University**
    - BA, political science
    - 2008

Career History

- **Oversight Investigator** House Subcommittee on Oversight and Investigations

January 2019 - Present

- **Professional Staff Member** House Committee on Energy and Commerce

March 2017 - January 2019

- **Senior Communications Analyst** U.S. Government Accountability Office

June 2015 - March 2017

- **Program Analyst Team Leader** U.S. Department of Health and Human Services Office of the Inspector General

February 2008 - May 2015

| | |
|---|---|
| **From:** | Myles, Renate (NIH/OD) [E] |
| **To:** | Tabak, Lawrence (NIH/OD) [E]; Lankford, David (NIH/OD) [E]; Jacobs, Anna (NIH/OD) [E] |
| **Cc:** | Lauer, Michael (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; Wojtowicz, Emma (NIH/OD) [E]; Jorgenson, Lyric (NIH/OD) [E]; Hallett, Adrienne (NIH/OD) [E] |
| **Subject:** | PLEASE REVIEW: Question from the WSJ |
| **Date:** | Tuesday, June 22, 2021 4:47:47 PM |
| **Attachments:** | NIHLetter8July.pdf |

Hi all:

Mike received the below inquiry from the WSJ and we propose responding with the below. Please let us know if you have any concerns.

The questions in the letter should be taken at face value (they are questions, not statements). NIH routinely reviews allegations that raise concerns about possible non-compliance with terms and conditions of NIH grant awards. A safe working environment is a term and condition of award (see the NIH Grant Policy Statement 4). Based on information provided to NIH via various sources, NIH posed the questions in the letter to the grantee to ascertain if safety was being compromised. NIH continues to work with the grantee on this matter.

Thanks,

Renate

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**From:** "Gordon, Michael" < (b) (6)

**Date:** Tuesday, June 22, 2021 at 7:55 AM

**To:** "Lauer, Michael (NIH/OD) [E]" < (b) (6)

**Subject:** Fwd: Question from the WSJ

Dr. Lauer,

I am a reporter for The Wall Street Journal and have a question for you. I would be happy to discuss this by phone or in person, including on a background not-for-attribution basis. I am looking for some guidance on a July 8, 2020 letter you wrote, which has been in the public domain for nearly a year. I am neither a proponent of the lab theory nor a supporter of the zoonotic hypothesis regarding the origins of Covid-19 in China. I am just trying to understand and present the facts as best I can.

In your July 8 letter you described some restrictions at the Wuhan Institute of Virology in 2019. Specifically, you wrote that there was "diminished cell-phone traffic in October 2019" at or near that facility. You also wrote that "there was evidence that there may have been roadblocks surrounding the facility from October 14-19, 2019."

My WSJ colleague, Betsy McKay, wrote in August about this letter, which was addressed to the EcoHealth Alliance. (https://www.wsj.com/articles/nih-presses-u-s-nonprofit-for-information-on-wuhan-virology-lab-11597829400). It has also been distributed on Capitol Hill.

My questions are as follows.

Do you or NIH still stand by the statement that there was diminished cell traffic in and around the WIV in October 2019? What was the source of that information and is it a source in which NIH has confidence? The letter suggests that it is a fact that there was diminished cell phone traffic. To your understanding, is it a fact or merely a possibility? Have you and NIH changed that position based on more recent information? Did EcoHealth Alliance ever provide any information regarding your questions? What about the roadblocks? Is there any similar information on that? I have attached a copy of the letter to this email.

Again, we can talk on a background, not-for-attribution basis if you wish. I am trying to better understand a complicated situation and fully understand that new information may have arisen over the past year and that some prior impressions may have been discomfirmed. I also want to be sure that I am interpreting your letter correctly, and it has been interpreted as stating for a fact that there was disminished cell phone traffic. So I would like to be sure that this is what you intended. I am trying to be very careful about all this. Thanks for your attention, and I would be happy to answer any questions on this request.

Michael Gordon
National Security Correspondent
The Wall Street Journal
(b) (6) (cell, WhatsApp, Signal)
michael.gordon@wsj.com (work email)
MGWSJ@protonmail.com (encrypted email)
Book site: michaelrgordon.com

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892

8 July 2020

Drs. Aleksei Chmura and Peter Daszak
EcoHealth Alliance, Inc.
460 W 34th St
Suite 1701
New York, NY 10001

Re: NIH Grant R01AI110964

Dear Drs. Chmura and Daszak:

In follow-up to my previous letter of April 24, 2020, I am writing to notify you that the National Institute of Allergy and Infectious Diseases (NIAID), an Institute within the National Institutes of Health (NIH), under the Department of Health and Human Services (HHS), has withdrawn its termination of grant R01AI110964, which supports the project *Understanding the Risk of Bat Coronavirus Emergence*. Accordingly, the grant is reinstated.

However, as you are aware, the NIH has received reports that the Wuhan Institute of Virology (WIV), a subrecipient of EcoHealth Alliance under R01AI110964, has been conducting research at its facilities in China that pose serious bio-safety concerns and, as a result, create health and welfare threats to the public in China and other countries, including the United States. Grant award R01AI110964 is subject to biosafety requirements set forth in the NIH Grants Policy Statement (e.g., NIH GPS, Section 4.1.24 "Public Health Security") and the Notice of Award (e.g., requiring that "Research funded under this grant must adhere to the [CDC/NIH Biosafety in Microbiological and Biomedical Laboratories (BMBL)]."). Moreover, NIH grant recipients are expected to provide safe working conditions for their employees and foster work environments conducive to high-quality research. NIH GPS, Section 4. The terms and conditions of the grant award flow down to subawards to subrecipients. 45 C.F.R. § 75.101.

As the grantee, EcoHealth Alliance was required to "monitor the activities of the subrecipient as necessary to ensure that the subaward is used for authorized purposes, in compliance with Federal statutes, regulations, and the terms and conditions of the subaward . . ." 45 C.F.R. § 75.352(d). We have concerns that WIV has not satisfied safety requirements under the award, and that EcoHealth Alliance has not satisfied its obligations to monitor the activities of its subrecipient to ensure compliance.

Moreover, as we have informed you through prior Notices of Award, this award is subject to the Transparency Act subaward and executive compensation reporting requirement of 2 C.F.R. Part

170. To date you have not reported any subawards in the Federal Subaward Reporting System.

Therefore, effective the date of this letter, July 8, 2020, NIH is suspending all activities related to R01AI110964, until such time as these concerns have been addressed to NIH's satisfaction. This suspension is taken in accordance with 45 C.F.R. § 75.371, Remedies for Noncompliance, which permits suspension of award activities in cases of non-compliance, and the NIH GPS, Section 8.5.2, which permits NIH to take immediate action to suspend a grant when necessary to protect the public health and welfare. This action is not appealable in accordance with 42 C.F.R. § 50.404 and the NIH GPS Section 8.7, Grant Appeals Procedures. However, EcoHealth Alliance has the opportunity to provide information and documentation demonstrating that WIV and EcoHealth Alliance have satisfied the above-mentioned requirements.

Specifically, to address the NIH's concerns, EcoHealth must provide the NIH with the following information and materials, which must be complete and accurate:

1. Provide an aliquot of the actual SARS-CoV-2 virus that WIV used to determine the viral sequence.
2. Explain the apparent disappearance of Huang Yanling, a scientist / technician who worked in the WIV lab but whose lab web presence has been deleted.
3. Provide the NIH with WIV's responses to the 2018 U.S. Department of State cables regarding safety concerns.
4. Disclose and explain out-of-ordinary restrictions on laboratory facilities, as suggested, for example, by diminished cell-phone traffic in October 2019, and the evidence that there may have been roadblocks surrounding the facility from October 14-19, 2019.
5. Explain why WIV failed to note that the RaTG13 virus, the bat-derived coronavirus in its collection with the greatest similarity to SARS-CoV-2, was actually isolated from an abandoned mine where three men died in 2012 with an illness remarkably similar to COVID-19, and explain why this was not followed up.
6. Additionally, EcoHealth Alliance must arrange for WIV to submit to an outside inspection team charged to review the lab facilities and lab records, with specific attention to addressing the question of whether WIV staff had SARS-CoV-2 in their possession prior to December 2019. The inspection team should be granted full access to review the processes and safety of procedures of all of the WIV field work (including but not limited to collection of animals and biospecimens in caves, abandoned man-made underground cavities, or outdoor sites). The inspection team could be organized by NIAID, or, if preferred, by the U.S. National Academy of Sciences.
7. Lastly, EcoHealth Alliance must ensure that all of its subawards are fully reported in the Federal Subaward Reporting System

During this period of suspension, NIH will continue to review the activities under this award, taking into consideration information provided by EcoHealth Alliance, to further asses compliance by EcoHealth Alliance and WIV, including compliance with other terms and conditions of award that may be implicated. Additionally, during the period of suspension, EcoHealth Alliance may not allow research under this project to be conducted. Further, no funds from grant R01AI110964 may be provided to or expended by EcoHealth Alliance or any subrecipients; all such charges are unallowable. It is EcoHealth Alliance's responsibility as the

recipient of this grant award to ensure that the terms of this suspension are communicated to and understood by all subrecipients. EcoHealth Alliance must provide adequate oversight to ensure compliance with the terms of the suspension. Any noncompliance of the terms of this suspension must be immediately reported to NIH. Once the original award is reinstated, NIH will take additional steps to restrict all funding in the HHS Payment Management System in the amount of $369,819. EcoHealth Alliance will receive a revised Notice of Award from NIAID indicating the suspension of these research activities and funding restrictions as a specific condition of award.

Please note that this action does not preclude NIH from taking additional corrective or enforcement actions pursuant to 45 CFR Part 75, including, but not limited to, terminating the grant award. NIH may also take other remedies that may be legally available if NIH discovers other violations of terms and conditions of award on the part of EcoHealth Alliance or WIV.

.

Sincerely,

Michael S. Lauer -S

Digitally signed by Michael S. Lauer -S
Date: 2020.07.08 21:43:41 -04'00'

Michael S Lauer, MD
NIH Deputy Director for Extramural Research
Email: (b) (6)

cc: Dr. Erik Stemmy
Ms. Emily Linde

| | |
|---|---|
| **From:** | Myles, Renate (NIH/OD) [E] |
| **To:** | Lankford, David (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Jacobs, Anna (NIH/OD) [E] |
| **Cc:** | Lauer, Michael (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; Wojtowicz, Emma (NIH/OD) [E]; Jorgenson, Lyric (NIH/OD) [E]; Hallett, Adrienne (NIH/OD) [E] |
| **Subject:** | RE: PLEASE REVIEW: Question from the WSJ |
| **Date:** | Tuesday, June 22, 2021 5:36:13 PM |

Thanks, all. We'll clear now.

**From:** Lankford, David (NIH/OD) [E] < (b) (6)
**Sent:** Tuesday, June 22, 2021 5:34 PM
**To:** Myles, Renate (NIH/OD) [E] < (b) (6) Tabak, Lawrence (NIH/OD) [E] < (b) (6) Jacobs, Anna (NIH/OD) [E] < (b) (6)
**Cc:** Lauer, Michael (NIH/OD) [E] < (b) (6) Fine, Amanda (NIH/OD) [E] < (b) (6) Wojtowicz, Emma (NIH/OD) [E] < (b) (6) Jorgenson, Lyric (NIH/OD) [E] < (b) (6) Hallett, Adrienne (NIH/OD) [E] < (b) (6)
**Subject:** RE: PLEASE REVIEW: Question from the WSJ

Anna and I are fine with the response.

David W. Lankford
NIH Legal Advisor
Office of the General Counsel
Public Health Division, NIH Branch
NIH Building 31, Room 2B-50
Bethesda, MD 20892-2111
Telephone: (b) (6)
Fax: (301) 402-1034
E-Mail: (b) (6)


**From:** Myles, Renate (NIH/OD) [E] < (b) (6)
**Sent:** Tuesday, June 22, 2021 4:48 PM
**To:** Tabak, Lawrence (NIH/OD) [E] < (b) (6) Lankford, David (NIH/OD) [E] < (b) (6) Jacobs, Anna (NIH/OD) [E] < (b) (6)
**Cc:** Lauer, Michael (NIH/OD) [E] < (b) (6) Fine, Amanda (NIH/OD) [E] < (b) (6) Wojtowicz, Emma (NIH/OD) [E] < (b) (6) Jorgenson, Lyric (NIH/OD) [E] < (b) (6) Hallett, Adrienne (NIH/OD) [E] < (b) (6)
**Subject:** PLEASE REVIEW: Question from the WSJ

Hi all:

Mike received the below inquiry from the WSJ and we propose responding with the below. Please let us know if you have any concerns.

The questions in the letter should be taken at face value (they are questions, not statements). NIH routinely reviews allegations that raise concerns about possible non-compliance with terms and conditions of NIH grant awards. A safe working environment is a term and condition of award (see the NIH Grant Policy Statement 4). Based on information provided to NIH via various sources, NIH posed the questions in the letter to the grantee to ascertain if safety was being compromised. NIH continues to work with the grantee on this matter.

Thanks,
Renate

---

**From:** "Gordon, Michael" <(b) (6)
**Date:** Tuesday, June 22, 2021 at 7:55 AM
**To:** "Lauer, Michael (NIH/OD) [E]" <(b) (6)
**Subject:** Fwd: Question from the WSJ

Dr. Lauer,
I am a reporter for The Wall Street Journal and have a question for you. I would be happy to discuss this by phone or in person, including on a background not-for-attribution basis. I am looking for some guidance on a July 8, 2020 letter you wrote, which has been in the public domain for nearly a year. I am neither a proponent of the lab theory nor a supporter of the zoonotic hypothesis regarding the origins of Covid-19 in China. I am just trying to understand and present the facts as best I can.
In your July 8 letter you described some restrictions at the Wuhan Institute of Virology in 2019. Specifically, you wrote that there was "diminished cell-phone traffic in October 2019" at or near that facility. You also wrote that "there was evidence that there may have been roadblocks surrounding the facility from October 14-19, 2019."
My WSJ colleague, Betsy McKay, wrote in August about this letter, which was addressed to the EcoHealth Alliance. (https://www.wsj.com/articles/nih-presses-u-s-nonprofit-for-information-on-wuhan-virology-lab-11597829400). It has also been distributed on Capitol Hill.
My questions are as follows.
Do you or NIH still stand by the statement that there was diminished cell traffic in and around the WIV in October 2019? What was the source of that information and is it a source in which NIH has confidence? The letter suggests that it is a fact that there was diminished cell phone traffic. To your understanding, is it a fact or merely a possibility? Have you and NIH changed that position based on more recent information? Did EcoHealth Alliance ever provide any information regarding your questions? What about the roadblocks? Is there any similar information on that? I have attached a copy of the letter to this email.
Again, we can talk on a background, not-for-attribution basis if you wish. I am trying to better understand a complicated situation and fully understand that new information may have arisen over the past year and that some prior impressions may have been discomfirmed. I also want to be sure that I am interpreting your letter correctly, and it has been interpreted as stating for a fact that there was disminished cell phone traffic. So I would like to be sure that this is what you intended. I am trying to be very careful about all this. Thanks for your attention, and I would be happy to answer any questions on this request.

Michael Gordon
National Security Correspondent
The Wall Street Journal
(b) (6) (cell, WhatsApp, Signal)
michael.gordon@wsj.com (work email)
MGWSJ@protonmail.com (encrypted email)
Book site: michaelrgordon.com

# WEEKLY REPORT

June 22, 2021

MEMORANDUM FOR THE CABINET SECRETARY

FROM: Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

SUBJECT: National Institutes of Health (NIH) Weekly Report | Week ending June 25, 2021

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## AMERICAN RESCUE PLAN (ARP) / AMERICAN JOBS PLAN (AJP) / ECONOMY

- N/A

## COVID-19

- **Past Week Accomplishments and Setbacks/Obstacles:**
  - **Novavax Vaccine is Safe and Prevents COVID-19:** On June 14th, the National Institutes of Health (NIH) announced clinical trial results showing that the Novavax investigational vaccine demonstrated 90.4% efficacy in preventing symptomatic COVID-19.[1]
  - **Study of Vaccination During Pregnancy:** Planned for June 23rd, NIH announced the launch of a study to evaluate mothers vaccinated against COVID-19 during and after pregnancy. The study, called MOMI-VAX, is being conducted by the Infectious Diseases Clinical Research Consortium funded by the National Institute of Allergy and Infectious Diseases (NIAID).

- **Next Week – Upcoming Events / Tasks / Developments:**
  - **(CLOSE HOLD) Funding Awards for the Return to School Program:** Tentatively on June 30th, NIH will announce five awards totaling $15 million over two years to projects at five institutions to build evidence on safely returning students,

[1] https://www.nih.gov/news-events/news-releases/us-clinical-trial-results-show-novavax-vaccine-safe-prevents-covid-19

teachers, and support staff to in-person school in areas with vulnerable and underserved populations. These awards complement eight existing awards made on April 15th and expand the racial/ethnic, age, and geographic diversity of the Return to School program. The five institutions are the University of California, Los Angeles, Arizona State University, the University of Hawaii at Manoa, the University of Miami, and the University of Nebraska Medical Center.

## CLIMATE

- N/A

## EQUITY FOR UNDERSERVED COMMUNITIES

- N/A

## SIGNIFICANT EXECUTIVE ORDER (EO) & AGENCY ACTIVITY

- N/A

## APPENDIX

- **Speeches**
  - NIH:
    - NIH Director Dr. Francis Collins' upcoming speeches:
      - July 14th: Brief remarks at the Rapid Acceleration of Diagnostics-Underserved Populations (RADx-UP) Phase II Return to School kick-off meeting with all awarded investigators.
      - Brief pre-recorded remarks for the International 2021 AIDS Society Annual Meeting's HIV Cure and Gene Therapy Forum taking place July 16th-20th.
      - July 31st: Brief pre-recorded welcome remarks for the 34th Cystic Fibrosis Education Conference.
    - On June 14th, NIH Principal Deputy Director Dr. Lawrence Tabak spoke to the Cancer Biology Graduate Program at the University of Pennsylvania's Perelman School of Medicine on NIH's efforts to address structural racism and barriers in the biomedical workforce.

- **Media:**

- NIH:
  - NIH Director Dr. Francis Collins' recent and upcoming media engagements:
    - June 20th: Interview with MSNBC's Ali Velshi on the Delta variant and to encourage Americans to get vaccinated.
    - June 21st: Interview with NPR's Allison Aubrey about vaccination rates and considerations for vaccine boosters.
    - June 28th: Guest on RFD-TV's *Rural Health Matters* to discuss COVID-19 news of the day and take questions from the audience. This call-in show features experts from the University of Nebraska Medical Center discussing the Coronavirus and how it impacts farmers, ranchers, and rural America.

- **Noteworthy public engagement:**
  - NIH:
    - During the month of July, NIH will hold listening sessions on ARPA-H with key stakeholders including patient and patient advocacy groups, disease organizations, and professional societies. In preparation for the listening sessions, tentatively on June 25th, NIH will participate in an information session with OSTP to provide key stakeholders with information on the overall vision, mission, and organization of ARPA-H. ARPA-H is a new science agency proposed by President Biden that would build high-risk, high-reward approaches to drive biomedical discoveries towards rapid adoption by industry and medicine.
    - On July 16th, NIH Director Dr. Francis Collins will join Facts and Faith, a weekly Zoom call, hosted by Virginia Commonwealth University Massey Cancer Center Director Dr. Robert Winn, to provide accurate information about COVID-19, the vaccine, and cancer to African American church leaders throughout Virginia.
    - On June 25th, NIH Principal Deputy Director Dr. Lawrence Tabak will provide opening remarks for the

Artificial Intelligence and Machine Learning (AI/ML) Consortium to Advance Health Equity and Researcher Diversity (AIM-AHEAD) stakeholder forum. Experts in AI/ML from industry and academia have been invited to participate in this meeting, which will provide an overview of AI/ML research initiatives for health disparities and will engage attendees in listening sessions via breakout groups focused on three main topics: research interests, computing infrastructure and resources, and training needs.

- On June 30th, NIH Principal Deputy Director Dr. Lawrence Tabak will participate in a discussion on diversity, equity, and inclusion in the research and development pipeline at Research!America's Reaching the Peak: A Science & Technology Career Summit for early career researchers.

- **Principal level meetings or calls with Members of Congress:**
  - NIH: On June 30th, NIH Director Dr. Francis Collins will brief the Congressional Black Caucus on disparities, equity, systemic racism, and strategies to improve the diversity of the scientific workforce.

- **Noteworthy inquiries from Congressional committees or Members of Congress; scheduled testimony by Secretary or Deputy Secretary:**
  - NIH:
    - On June 14th, National Institute of Environmental Health Sciences (NIEHS) Director Dr. Rick Woychik briefed House and Senate Interior and Environment Appropriations Subcommittee staff on NIEHS superfund-related activities.
    - On June 30th, NIH Deputy Director for Management Dr. Alfred Johnson, NIH Budget Director Neil Shapiro, and NIH Office of Research Facilities Director Daniel Wheeland will provide a status update on current and future projects related to NIH's buildings and facilities for House and Senate L-HHS Appropriations Subcommittee staff.

- (Update) On June 10th, Rep. Cathy McMorris Rodgers (R-WA), Rep. Fred Upton (R-MI), and 24 other representatives wrote to NIH Director Dr. Francis Collins requesting answers to specific questions relating to the origins of COVID-19 and oversight of grant awards. NIH's response is in progress.
- (Update) During the week of June 28th, NIH Principal Deputy Director Dr. Lawrence Tabak is tentatively scheduled to brief House Energy and Commerce Committee staff on grant recipient EcoHealth Alliance.

**From:** Matocha, Martha (NIH/NINR) [E]
**To:** Doswell, Greta (NIH/OD) [E]
**Cc:** McMahon, Christine (NIH/OD) [E]
**Subject:** RE: For Your Review (Due 2pm Tues): Weekly Cabinet Report for OS
**Date:** Tuesday, June 29, 2021 2:12:59 PM
**Attachments:** Draft NIH Agency Weekly Cabinet Report_06.29.2021 v5_MM.docx

Hi Greta – I made one edit, bottom of last page. Martha

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**From:** Doswell, Greta (NIH/OD) [E] <(b) (6)
**Sent:** Tuesday, June 29, 2021 1:43 PM
**To:** Matocha, Martha (NIH/NINR) [E] <(b) (6)
**Cc:** McMahon, Christine (NIH/OD) [E] <(b) (6)
**Subject:** FW: For Your Review (Due 2pm Tues): Weekly Cabinet Report for OS

Hi Martha,

I wanted to keep you updated regarding the Cabinet Report in Christine's absence. The COVAXIN COVID-19 vaccine press release was updated (still waiting to hear on the funding awards for the Return to School Program). Please see page 5 for the revision per Courtney and I added the July 1 UNITE Briefing bullet. Please let me know if you have any edits.
Thanks,
Greta

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**From:** Aklin, Courtney (NIH/OD) [E] <(b) (6)
**Sent:** Tuesday, June 29, 2021 6:13 AM
**To:** McMahon, Christine (NIH/OD) [E] <(b) (6) Burklow, John (NIH/OD) [E] <(b) (6) Lauer, Michael (NIH/OD) [E] <(b) (6)
**Cc:** ES-HHS Reports Team <(b) (6) Harris, Melissa (NIH/OD) [E] <(b) (6)
**Subject:** Re: For Your Review (Due 2pm Tues): Weekly Cabinet Report for OS

Hello Christine,

One modification to the following bullet:

- On July 2nd, 6th, and 7th, NIH will hold listening sessions on ARPA-H with key stakeholders such as patient and patient advocacy groups, disease organizations, and professional societies.

The dates for the ARPA-H listening sessions are changing. The one for July 2 is being rescheduled to a later date in July and there is conversation about pushing the July 6 and 7 ones to the week of July 12. I will check in about the potential new dates and get back to you.

Best,

Courtney

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**From:** "McMahon, Christine (NIH/OD) [E]" <(b) (6)
**Date:** Monday, June 28, 2021 at 2:26 PM
**To:** Courtney Aklin <(b) (6) "Burklow, John (NIH/OD) [E]"
<(b) (6) "Lauer, Michael (NIH/OD) [E]" <(b) (6)
**Cc:** ES-HHS Reports Team <(b) (6) "Harris, Melissa (NIH/OD) [E]"
<(b) (6)
**Subject:** For Your Review (Due 2pm Tues): Weekly Cabinet Report for OS

Good afternoon Courtney, John, and Mike,

Attached for your review please find the proposed NIH submission for this week's Weekly Cabinet Report, which is due to OS COB tomorrow. We would appreciate any comments by 2:00 p.m. tomorrow (Tuesday).

Many thanks!

Christine

Christine McMahon
Executive Secretariat
National Institutes of Health
(b) (6)

# WEEKLY REPORT

June 29, 2021

MEMORANDUM FOR THE CABINET SECRETARY

FROM: Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

SUBJECT: National Institutes of Health (NIH) Weekly Report | Week ending July 2, 2021

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## AMERICAN RESCUE PLAN (ARP) / AMERICAN JOBS PLAN (AJP) / ECONOMY

- N/A

## COVID-19

- **Past Week Accomplishments and Setbacks/Obstacles:**
  - **COVID-19 Prevalence Far Exceeded Early Cases:** On June 22nd, the National Institutes of Health (NIH) announced findings from NIH researchers estimating that there were nearly 17 million undiagnosed cases in the U.S. by mid-July 2020.[1]
  - **Teen Substance Use Steady During Pandemic:** On June 24th, NIH announced findings from an NIH-funded study indicating adolescent marijuana use and binge drinking did not significantly change during the COVID-19 pandemic.[2]
  - **Enhanced Efficacy of India's COVAXIN COVID-19 vaccine:** On June 29th, NIH announced that an NIH-funded adjuvant enhanced the effectiveness of India's COVAXIN COVID-19 vaccine according to interim data from a Phase 3 trial. Adjuvants are substances formulated as part of a vaccine to

[1] https://www.nih.gov/news-events/news-releases/nih-study-suggests-covid-19-prevalence-far-exceeded-early-pandemic-cases
[2] https://www.nih.gov/news-events/news-releases/adolescent-marijuana-alcohol-use-held-steady-during-covid-19-pandemic

boost immune responses and enhance a vaccine's effectiveness.[3]

- **Rapid Antigen Tests on Par with PCR Tests:** On June 30th, NIH announced findings from an NIH-funded study that both rapid antigen tests and PCR tests were equally effective in detecting SARS-CoV-2 infection when tests were given at the same time of day, every three days.
- **White Paper with Important Considerations for Returning to School:** On June 30th, the ABC Science Collaborative, led by investigators from Duke University and funded by the Rapid Acceleration of Diagnostics-Underserved Populations (RADx-UP) Return to School Program, released a white paper titled, "COVID-19 and Schools: The Year in Review and a Path Forward." This document, produced in collaboration with leaders and experts across the country, provides a review of existing evidence and important considerations for returning to school in the fall. The ABC Science Collaborative is a program that pairs scientists and physicians with school and community leaders to help understand the most current and relevant information about COVID-19.
- **Funding Awards for the Return to School Program:** On June 30th, NIH (tentatively) announced five awards totaling $15 million over two years for five institutions to build evidence on safely returning students, teachers, and support staff to in-person school in areas with vulnerable and underserved populations. These awards complement eight existing awards made on April 15th and expand the racial/ethnic, age, and geographic diversity of the Return to School Program. The five institutions are the University of California, Los Angeles; Arizona State University; the University of Hawaii at Manoa; the University of Miami; and the University of Nebraska Medical Center.

## CLIMATE

- N/A

[3] https://www.nih.gov/news-events/news-releases/adjuvant-developed-nih-funding-enhances-efficacy-indias-covid-19-vaccine

## EQUITY FOR UNDERSERVED COMMUNITIES

- **Past Week Accomplishments and Setbacks/Obstacles:**
    - **Artificial Intelligence/Machine Learning (AI/ML) for Health Equity:** NIH is seeking feedback to inform development of a new initiative that aims to leverage AI/ML to mitigate health disparities:
        - On June 21st, NIH published a Request for Information (RFI): Inviting Input to Broaden the Benefits of AI/ML Technologies to Reduce Health Disparities and Inequities and Enhance the Diversity of the AI/ML Workforce.
        - On June 25th, NIH hosted the AI/ML Consortium to Advance Health Equity and Research Diversity (AIM-AHEAD) Stakeholder Forum, which included listening sessions via breakout groups focused on three main topics: research interests, computing infrastructure and resources, and training needs.

## SIGNIFICANT EXECUTIVE ORDER (EO) & AGENCY ACTIVITY

- N/A

## APPENDIX

- **Speeches**
    - NIH:
        - NIH Director Dr. Francis Collins' recent and upcoming speeches:
            - June 22nd: Participation in a livestreamed fireside chat at the US-India Chamber of Commerce Annual Meeting with Dr. Margaret Hamburg and moderated by Dr. Elias Zerhouni on the general topic of lessons learned and the future pathways for COVID-19.
            - August 3rd: Panel presentation at the International Space Station (ISS) Research and Development Conference. NIH's National Center for Advancing Translational Sciences (NCATS) has partnered with the ISS National Lab to collaborate on refining tissue chip technology for biomedical research use on the space station.

        - August 25th: Remarks at the last of three meetings that are part of Phase I of an NIH/Foundation for the National Institutes of Health (FNIH) project to develop evidence-based music therapies for brain disorders of aging.
    - NIH Chief Officer for Scientific Workforce Diversity (SWD) Dr. Marie Bernard's recent speeches:
        - June 29th: Presentation on SWD at a meeting of the Tau Consortium, a collaborative research program that is managed and funded by the Rainwater Charitable Foundation in partnership with other funders.
        - June 29th: Panel presentation at the national conference of the Institutional Research and Academic Career Development Awards, a program funded by the National Institute of General Medical Sciences.
        - June 30th: Panel presentation at a national summit on addressing diversity, equity, inclusion, and anti-racism in 21st century science, technology, engineering, math, and medicine (STEMM) organizations, convened by the National Academies of Sciences, Engineering, and Medicine.

- **Media:**
    - NIH: On June 30th, NIH Director Dr. Francis Collins was a guest on *The Medhi Hasan Show* on Peacock to discuss COVID-19 news of the day.

- **Noteworthy public engagement:**
    - NIH:
        - On June 25th, NIH Director Dr. Francis Collins and Principal Deputy Director Dr. Lawrence Tabak participated in an information session with the White House Office of Science and Technology Policy (OSTP) Director Dr. Eric Lander and OSTP Assistant Director for Biomedical Science Initiatives Dr. Tara Schwetz to provide key stakeholders with information on the overall

vision, mission, and organization of ARPA-H. ARPA-H is a new science agency proposed by President Biden that aims to build high-risk, high-reward approaches to drive biomedical discoveries towards rapid adoption by industry and medicine.
    - NIH will hold listening sessions on ARPA-H with key stakeholders such as patient and patient advocacy groups, disease organizations, and professional societies throughout the month of July.

- **Principal level meetings or calls with Members of Congress:**
    - NIH: On June 28th, NIH Principal Deputy Director Dr. Lawrence Tabak briefed House Energy and Commerce Committee members on grant recipient EcoHealth Alliance.
    - NIH: On July 1st, NIH Principal Deputy Director Dr. Lawrence Tabak and Chief Officer for Scientific Workforce Diversity Dr. Marie Bernard will brief the House and Senate Appropriations Committee on the NIH UNITE Initiative.

- **Noteworthy inquiries from Congressional committees or Members of Congress; scheduled testimony by Secretary or Deputy Secretary:**
    - NIH: On June 24th, the National Heart, Lung, and Blood Institute Director Dr. Gary Gibbons and the National Institute of Environmental Health Sciences Director Dr. Rick Woychik briefed Rep. Josh Harder (D-CA) on climate change research related to asthma.

**From:** McMahon, Christine (NIH/OD) [E]
**To:** Matocha, Martha (NIH/NINR) [E]
**Cc:** Doswell, Greta (NIH/OD) [E]; Katie (NIH/OD) Krolopp [C] ( (b) (6)
**Subject:** NIH Submission: Weekly Cabinet Report
**Date:** Tuesday, June 29, 2021 5:46:00 PM
**Attachments:** NIH Agency Weekly Cabinet Report_06.29.2021.docx

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Hi Martha,

I'm not sure how much longer we want to wait on NICHD. I had expected to get the update at COB, but haven't heard anything back since around 5pm. In the attached final version I included a note for OS that we will provide them with an update on the item tomorrow. A draft email for submitting to OS is below (please confirm the phone number I listed for you). Please send to: (b) (6) and cc: (b) (6)

Thank you!
Christine

———

Hello Perrie, Clare, and Andres,

Attached please find the NIH submission for this week's Cabinet Report.

Please let me know if you have any questions. I can be reached at (b) (6)

Sincerely,
Martha Matocha, Ph.D.
Acting Deputy Director (on detail)
NIH Executive Secretariat

# WEEKLY REPORT

June 29, 2021

MEMORANDUM FOR THE CABINET SECRETARY

FROM: Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

SUBJECT: National Institutes of Health (NIH) Weekly Report | Week ending July 2, 2021

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## CLIMATE

- N/A

[3] https://www.nih.gov/news-events/news-releases/adjuvant-developed-nih-funding-enhances-efficacy-indias-covid-19-vaccine

## EQUITY FOR UNDERSERVED COMMUNITIES

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