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Studie zum

Ursprung der Coronavirus-Pandemie

Leiter der Studie und Verantwortlicher für den Inhalt:

Prof. Dr. Dr. h.c. Prof. h.c. Roland Wiesendanger

Universität Hamburg

Zeitraum der Studie

01.01.2020 – 31.12.2020

Vorwort

Die vorliegende Studie zum Ursprung der Coronavirus-Pandemie wurde im Zeitraum vom 01.01.2020 bis 31.12.2020 an der Universität Hamburg durchgeführt. Erste Zwischenergebnisse dieser Studie wurden am 5. Mai 2020 im Rahmen einer Pressemitteilung bekannt gegeben. Seitdem sind durch internationalen Informationsaustausch weitere wesentliche Erkenntnisse und Dokumente zusammengetragen worden.

Die Studie basiert auf einem interdisziplinären wissenschaftlichen Ansatz, d.h. nicht auf einer ausschließlich fachspezifischen Sichtweise, sowie auf einer umfangreichen Recherche unter Nutzung aller denkbaren Informationsquellen. Hierzu gehören:

- interdisziplinäre sowie fachspezifische wissenschaftliche Literatur basierend auf wissenschaftlicher Begutachtung („Peer review“),
- wissenschaftliche Literatur ohne wissenschaftliche Begutachtung,
- Briefe, Korrespondenz und Kommentare publiziert in der wissenschaftlichen Literatur,
- Artikel in Print- und Online-Medien,
- Berichte im Internet / in sozialen Medien,
- persönliche Kommunikation mit internationalen Kollegen.

Die Quellenangaben zu dieser Studie wurden entsprechend strukturiert, um eine klare Abgrenzung zwischen wissenschaftlicher Primärliteratur (mit und ohne Peer Review) und publizierten Meinungsäußerungen zu erzielen.

Das vorliegende Dokument wurde am 6. Januar 2021 fertig gestellt. Es wurde zunächst ausschließlich in Wissenschaftskreisen verteilt und diskutiert. Am 12. Februar 2021 erfolgte die Freigabe für die Veröffentlichung als Basis einer breit angelegten Diskussion in der Bevölkerung, die angesichts der Bedeutung der Thematik faktenbasiert informiert werden soll und in zukünftige Entscheidungsprozesse einzubeziehen ist.

Ergänzende Informationen und weitere Dokumente können beim Leiter der Studie erfragt werden:

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1 Motivation und wesentliche Ergebnisse der Studie im Überblick

Die gegenwärtige Coronavirus-Pandemie stellt für viele Menschen die größte Herausforderung seit Ende des zweiten Weltkriegs dar. Die weltumspannende Krise ist verbunden mit dem Verlust vieler Menschenleben im Zusammenhang mit einer COVID-19 Erkrankung (innerhalb eines Jahres ca. 1,8 Millionen Sterbefälle laut Statistik der Johns Hopkins University, USA). Einhergehend mit einer beispiellosen wirtschaftlichen Krise gibt es viele, zum Teil noch unübersehbare Konsequenzen für das Leben und den Wohlstand der Menschen - in vielen Fällen sogar für die notwendigsten Lebensgrundlagen, gerade in den ärmsten Ländern der Welt.

Auch wenn sich die gegenwärtige öffentliche Diskussion naturgemäß in erster Linie auf die Bewältigung der Folgen der Pandemie im Gesundheitswesen, in der Wirtschaft sowie in vielen gesellschaftlichen Bereichen konzentriert, so ist die Frage nach dem Ursprung der Pandemie von zentraler Bedeutung: „Wann immer ein neuer Virustyp auftritt, ist es sehr wichtig zu verstehen, woher das neue Virus stammt, das heißt die Quelle der Viren zu identifizieren sowie die Details der Ausbreitung zu studieren, um auf diese Weise wichtige Informationen als Grundlage für gegenwärtige und zukünftige Maßnahmen zu gewinnen“, so die Weltgesundheitsorganisation (World Health Organization, WHO). Die wissenschaftsbasierte Auseinandersetzung mit dieser wichtigen Thematik ist Gegenstand der vorliegenden Studie.

Seit Beginn der Pandemie gibt es zwei verschiedene Erklärungsversuche für deren Ursache:

1) Die zufällige Übertragung von Coronaviren aus dem Tierreich auf den Menschen („Zoonose“), wobei als ursprüngliche Virenquelle ein bestimmter Fledermaustyp in Frage kommt. In Folge einer Virusmutation unter Mitwirkung eines Zwischenwirtstiers hat dann eine Übertragung auf den Menschen stattgefunden, wobei in diesem Zusammenhang einem Tiermarkt im Zentrum der Stadt Wuhan (China), dem Ursprungsort der Coronavirus-Pandemie, eine zentrale Bedeutung zugesprochen wird.

2) Alternativ hierzu wird seit Beginn der Pandemie ein Laborunfall in einem biotechnologischen Hochsicherheitslabor im Zentrum der Stadt Wuhan (unweit des in Verdacht geratenen Tiermarkts) als mögliche Ursache genannt. Dieser Verdacht basiert auf der Tatsache, dass über viele Jahre hinweg risikoreiche Forschung und Genmanipulationen an Coronaviren im Zentrum der Aktivitäten des virologischen Instituts in Wuhan standen, welche durch wissenschaftliche Publikationen in der Fachliteratur belegt sind.

Bis heute gibt es keine wissenschaftlich basierten strikten Beweise für eine der beiden genannten Theorien. In einer solchen Situation sollten Wissenschaftler – unabhängig von der jeweiligen Fachrichtung – eine neutrale Haltung einnehmen und eine ergebnisoffene Diskussion bis zur endgültigen Klärung der entscheidenden Frage nach dem Ursprung der Pandemie führen. Gleichwohl haben sich einige namhafte Virologen sehr frühzeitig auf die erste Theorie, also eine Zoonose, in öffentlichen Stellungnahmen festgelegt. Dies hat dazu geführt, dass führende Vertreter aus Politik und Gesellschaft jüngst vermehrt von einer „Naturkatastrophe“ im Zusammenhang mit der Coronavirus-Pandemie sprachen.

Aber liegt hier tatsächlich eine Naturkatastrophe – vergleichbar einem Erdbeben, einem Tsunami oder einem Vulkanausbruch – zugrunde? Ist die gegenwärtige weltweite Krise tatsächlich die Folge eines Zufalls der Natur – einer zufälligen Mutation eines Coronavirus einer Fledermaus unter Mitwirkung eines Zwischenwirtstieres – oder das Resultat einer Unachtsamkeit eines Wissenschaftlers oder einer Wissenschaftlerin bei der Durchführung hoch risikoreicher Forschung mit weltweitem Pandemie-Potential?

Da für die Beantwortung dieser bedeutungsvollen Frage bislang keine wissenschaftsbasierten Beweise im strikten Sinne vorliegen, können derzeit nur Indizien angeführt werden, welche die eine oder andere Theorie als wahrscheinlicher erscheinen lassen.

Die vorliegende einjährige Studie kommt zu dem Schluss, dass sowohl die Zahl als auch die Qualität der Indizien eindeutig für einen Laborunfall am virologischen Institut der Stadt Wuhan als Ursache der gegenwärtigen Pandemie sprechen. Hierfür wurden wissenschaftsbasierte Analysen der existierenden Fachliteratur sowie unabhängig überprüfbare relevante Dokumente herangezogen, welche im Hauptteil dieser Studie nicht nur zitiert, sondern auch teilweise im Originaltext wiedergegen werden, da das Zielpublikum dieser Studie nicht immer Zugang zu den entsprechenden Literaturquellen hat bzw. nicht die Zeit findet, diese selbst alle aufzurufen.

Einige der wesentlichen Indizien, welche für einen Laborunfall als Ursache der gegenwärtigen Pandemie sprechen und im Rahmen dieser Studie ausführlich dargelegt sowie diskutiert werden, sollen hier eingangs kurz zusammengefasst werden:

- Coronaviren, die ursprünglich auf Fledermäuse zurückgehen, führen nicht so leicht zu Infektionserkrankungen beim Menschen mit der Ausprägung, wie wir es in der derzeitigen Pandemie erleben (sehr hohe Übertragungsrate; Virenbefall nicht nur der Atemwege, sondern auch weiterer Organe; u.a.). Virologen sprechen in diesem Zusammenhang von einer „Anpassungsbarriere“.

- Mutationen von Coronaviren könnten in Zwischenwirtstieren stattgefunden haben und schließlich auf Wildtiermärkten auf den Menschen übertragen worden sein. Allerdings wurde ein solches Zwischenwirtstier im Zusammenhang mit der gegenwärtigen Coronavirus-Pandemie bis heute nicht identifiziert.

- Darüber hinaus ist ein wesentlicher Fakt, dass ein signifikanter Teil der allerersten COVID-19 Patienten in Wuhan gar keinen Kontakt zu dem in Verdacht geratenen Wildtiermarkt hatte. Dies ist durch mehrere wissenschaftliche Originalpublikationen in referierten Fachzeitschriften belegt.

- Es gibt zahlreiche unabhängige Hinweise darauf, dass eine junge Wissenschaftlerin des „Wuhan Institute of Virology“ sich als Erste mit dem neuartigen Coronavirus im Labor infiziert hat und somit am Anfang der COVID-19 Infektionskette stand. Ihr Eintrag auf der Webseite des Instituts wurde gelöscht und sie gilt seit Ende des Jahres 2019 als verschwunden.

- Gemäß zahlreicher Berichte wurden Fledermäuse auf dem in Verdacht geratenen Wildtiermarkt in Wuhan nicht angeboten. Es wurden jedoch über viele Jahre hinweg Fledermausviren von den Wissenschaftlern des „Wuhan Institute of Virology“ in weit entfernten Höhlen einer südchinesischen Provinz eingesammelt und nach Wuhan

gebracht. Dies ist durch mehrere wissenschaftliche Originalpublikationen in referierten Fachzeitschriften belegt.

- Eine Forschergruppe am „Wuhan Institute of Virology“ hat über viele Jahre hinweg nicht nur natürlich vorkommende Coronaviren untersucht, sondern diese gentechnisch manipuliert mit dem Ziel, diese für den Menschen ansteckender und gefährlicher zu machen. Diese so genannte „gain-of-function“ Forschung am „Wuhan Institute of Virology“ ist durch mehrere wissenschaftliche Originalpublikationen in referierten Fachzeitschriften belegt und wurde bereits seit Jahren von vielen Vertretern der Wissenschaft kritisch beurteilt.

- Es existierten Berichte über erhebliche Sicherheitsmängel im „Wuhan Institute of Virology“ bereits vor Ausbruch der Coronavirus-Pandemie. Ein Blick auf die Statistik der dokumentierten Unfälle in biotechnologischen Hochsicherheitslaboren zeigt, dass ein ungewollter Austritt hoch infektiöser Viren aus solchen Laboren in der Vergangenheit nicht selten vorkam, sowohl in China als auch etwa in USA. Darüber hinaus existieren Videoaufnahmen, welche belegen, dass Laborabfälle am „Wuhan Institute of Virology“ nicht ordnungsgemäß entsorgt wurden und dass die Mitarbeiter des Instituts keine ausreichende Schutzkleidung trugen.

- Eine Analyse der Handynutzungsaktivitäten im und um das „Wuhan Institute of Virology“ in der zweiten Hälfte des Jahres 2019 gibt Hinweise darauf, dass es in der ersten Oktoberhälfte 2019 zu einer zeitweisen Unterbrechung des Laborbetriebs sowie zu Absperrungen rund um das Institutsgelände kam. Gleichzeitig gab es erste bestätigte Fälle von COVID-19 Erkrankungen mit Todesfolge in verschiedenen Krankenhäusern der Stadt Wuhan bereits im Oktober 2019. Dies erklärt u.a. auch, warum bereits im November 2019 allererste Fälle von COVID-19 Erkrankungen auch in Europa nachträglich festgestellt wurden (wie etwa durch eine detaillierte Analyse der Lungenaufnahmen eines COVID-19 Patienten in Frankreich).

Auf Grund dieser und vieler weiterer in der vorliegenden Studie dargelegten und auf wissenschaftlichen Originalpublikationen sowie nachprüfbarer Dokumente basierenden Indizien mag es umso überraschender sein, dass zahlreiche Virologen nach wie vor nur eine Zoonose als Ursache der gegenwärtigen Pandemie in allen verfügbaren Medien propagieren. Die vorliegende Studie beschäftigt sich daher abschließend auch mit der Rolle der Wissenschaft im Zusammenhang mit der Frage nach dem Ursprung der derzeitigen Coronavirus-Pandemie.

2 Zentrale Frage nach dem Ursprung der Coronavirus-Pandemie: Naturkatastrophe oder Laborunfall?

In dieser für die Nachkriegsgeneration höchst außergewöhnlichen Zeit der Einschränkung von Grundrechten verursacht durch die Coronavirus-Pandemie stellt sich jeder Einzelne immer häufiger die Frage: Wie gefährlich ist das Corona-Virus wirklich? Überschätzen wir die Gefahr? Werden die Freiheitsrechte der Bürger und Bürgerinnen derzeit zu Unrecht eingeschränkt? Lässt sich der drohende beispiellose Einbruch der Wirtschaft rechtfertigen? Sind die derzeit geltenden Verhaltensregeln angemessen oder sind sie Ausdruck einer übervorsichtigen Reaktion des Staates in einer noch nie dagewesenen Situation seit Kriegsende?

Viele ziehen immer wieder Vergleiche mit der wohlbekannten Grippe heran und verweisen darauf, dass beispielsweise die Grippesaison 2017/18 in Deutschland schätzungsweise ca. 25.000 und in USA ca. 60.000 Menschenleben gefordert hat. Andere wiederum argumentieren, dass ohne staatliche Intervention die Zahl der Todesopfer in Folge einer COVID-19 Erkrankung deutlich höher wäre und dass in diesen Tagen – trotz aller staatlicher Schutzmaßnahmen – die weltweite Zahl der Todesopfer in dieser Pandemie bereits 1,8 Millionen übersteigt (lt. Statistik der Johns Hopkins University, USA).

Was unterscheidet aber denn nun das neuartige Coronavirus SARS-CoV-2 von allen bisher bekannten Coronaviren-Arten und der Vielzahl sonstiger Viren, denen wir während unseres gesamten Lebens ständig ausgesetzt sind? Nach heutigem Stand des Wissens sind folgende Eigenschaften des neuen Coronavirus-Typs außergewöhnlich:

- Coronaviren sind schon lange bekannt und können u.a. gewöhnliche Erkältungskrankheiten beim Menschen auslösen, welche jedoch typischerweise ab Ende April nicht mehr in Erscheinung treten. Auch bei der Grippe, verursacht durch Influenzaviren, flacht die Saison ab Ende März deutlich ab, d.h. selbst bei einer noch so schwerwiegend verlaufenden Grippesaison der Vergangenheit konnte man sich sicher sein, dass die Grippewelle im Frühjahr wieder abklingt. Ein „Shutdown“ des öffentlichen Lebens war dadurch nicht erforderlich. Das neuartige Coronavirus verhält sich jedoch offensichtlich anders und verbreitet sich jeweils auch in denjenigen Ländern der Welt, in denen gerade Sommerzeit herrscht.

- Coronaviren spielten auch bei schwereren Erkrankungen der Vergangenheit eine wichtige Rolle, so etwa bei der SARS-Epidemie im Jahr 2003. Allerdings war diese Art der Coronaviren deutlich weniger ansteckend für den Menschen, so dass die Zahl der Infizierten unter 10.000 und die Zahl der Toten unter 1.000 weltweit blieb. Neue Forschungsergebnisse weisen darauf hin, dass das neuartige Coronavirus SARS-CoV-2 bis zu einem dreifach so großen Abstand von einem Infizierten noch ansteckend sein kann im Vergleich zu früheren SARS-Coronaviren. Ferner kann bei dem neuartigen Coronavirus deutlich leichter eine Infektion beim Aufenthalt mehrerer Personen in einem geschlossenen Raum auftreten, auch wenn ein Mindestabstand von zwei Metern eingehalten wird. Die hohe Ansteckungsgefahr verbunden mit dem neuartigen

Coronavirus-Typ wird wissenschaftlich erklärt durch die sehr gute Adaption des SARS-CoV-2 Virus an menschliche Zellrezeptoren [I.1], so dass das neuartige Coronavirus sehr viel leichter Zugang zu menschlichen Zellen findet und die betreffenden Personen sehr leicht infizieren kann.

- Tatsächlich ist die Adaption des SARS-CoV-2 Virus an menschliche Zellrezeptoren so gut, dass nicht nur (obere) Atemwegsorgane, sondern auch andere innere Organe von diesem neuen Virustyp befallen werden können. Dies führt in einigen Fällen zu einem sehr schwerwiegenden Verlauf der Erkrankung von COVID-19 Patienten, verursacht durch ein Multiorganversagen.

Jeder kann bereits anhand der drei oben aufgeführten Besonderheiten des neuen Virustyps erkennen, dass wir es nicht mit einer für uns gewohnten Viruserkrankung zu tun haben. „Wann immer ein neuer Virustyp auftritt, ist es sehr wichtig zu verstehen, woher das neue Virus stammt, das heißt die Quelle der Viren zu identifizieren sowie die Details der Ausbreitung zu studieren, um auf diese Weise wichtige Informationen als Grundlage für gegenwärtige und zukünftige Maßnahmen zu gewinnen“, so die Weltgesundheitsorganisation (World Health Organization, WHO). Die Frage nach dem Ursprung der derzeitigen Coronavirus-Pandemie gilt zweifellos als besonders bedeutsam im Hinblick auf zukünftige Maßnahmen zur Verringerung der Wahrscheinlichkeit des Ausbruchs vergleichbarer Pandemien.

2.1 Die Wildtiermarkt-Theorie

Basierend auf Berichten in wissenschaftlichen Fachzeitschriften ([I.1]-[I.3]) und in verschiedenen Medien startete die Coronavirus-Pandemie an einem Punkt, der Stadt Wuhan in China, gegen Ende des Jahres 2019. Ein Wildtiermarkt im Zentrum dieser Stadt wurde und wird bis heute am häufigsten als mögliche Quelle der neuartigen Coronaviren genannt. Die genetische Analyse der neuen SARS-CoV-2 Viren, welche von Menschen mit einer COVID-19 Erkrankung entnommen wurden, weist einen hohen Grad der Verwandtschaft zu Coronaviren in Fledermäusen nach [I.1, I.3], ähnlich wie im Falle der bereits bekannten SARS-Viren, welche für die SARS-Epidemie 2003 verantwortlich waren. Es wird spekuliert, dass die Coronaviren über ein anderes Wildtier als Zwischenwirt letztlich auf den Menschen übertragen worden sein könnten. Man spricht in diesem Zusammenhang von einer „Zoonose“. Als mögliche Zwischenwirtstiere wurden seit Beginn der Pandemie u.a. folgende Tierarten ins Gespräch gebracht: Schlangen, Schleichkatzen, Schuppentiere (Pangoline) und Marderhunde [IV.1].

Es gibt zahlreiche wissenschaftlich basierte Fakten, welche gegen diese Theorie sprechen:

1. Fledermäuse selbst wurden auf dem im Verdacht stehenden Wildtiermarkt nicht angeboten.

2. Bis heute ist keines der o.g. Zwischenwirtstiere als Überträger der derzeit kursierenden Coronavirus-Erkrankung nachgewiesen worden. Man könnte allerdings an dieser Stelle noch einwenden, dass es auch im Falle früherer Krankheiten verursacht durch

Coronaviren eine längere Zeit gebraucht hat, um das Zwischenwirtstier zu identifizieren.

3. Ein wesentlich schwerwiegenderes Argument ist, dass ein signifikanter Anteil (34%) der ersten dokumentierten COVID-19 Patienten keinen Kontakt zu dem im Verdacht stehenden Wildtiermarkt hatten [I.2, I.3]. Insbesondere der erste in der wissenschaftlichen Originalliteratur dokumentierte Patient hatte keinen Kontakt zu demjenigen Wildtiermarkt (genauer: „Huanan seafood market“), der kurz nach Ausbrechen der Pandemie von der chinesischen Regierung offiziell als Ursache für die COVID-19 Erkrankungen deklariert wurde. Autoren dieser Studien waren u.a. Ärzte der Kliniken in Wuhan, welche selbst die COVID-19 Patienten in der Frühphase der Pandemie behandelt und epidemiologisch relevante Interviews geführt hatten.

   Nachfolgend ist ein Auszug aus der wissenschaftlichen Originalliteratur [I.2] mit dem wesentlichen Diagramm wiedergegeben. Bei der Zeitschrift „LANCET“ handelt es sich dabei um eine der angesehensten Fachzeitschriften der medizinischen Forschung:

LANCET VOLUME 395, ISSUE 10223, P. 497-506, FEBRUARY 15, 2020

Published online: January 24, 2020. DOI: https://doi.org/10.1016/S0140-6736(20)30183-5

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

Chaolin Huang, Yeming Wang, Xingwang Li, Lili Ren, Jianping Zhao, Yi Hu, Li Zhang, Guohui Fan, Jiuyang Xu, Xiaoying Gu, Zhenshun Cheng, Ting Yu, Jiaan Xia, Yuan Wei, Wenjuan Wu, Xuelei Xie, Wen Yin, Hui Li, Min Liu, Yan Xiao, Hong Gao, Li Guo, Jungang Xie, Guangfa Wang, Rongmeng Jiang, Zhancheng Gao, Qi Jin, Jianwei Wang, and Bin Cao

Summary

Background

A recent cluster of pneumonia cases in Wuhan, China, was caused by a novel betacoronavirus, the 2019 novel coronavirus (2019-nCoV). We report the epidemiological, clinical, laboratory, and radiological characteristics and treatment and clinical outcomes of these patients.

Methods

All patients with suspected 2019-nCoV were admitted to a designated hospital in Wuhan. We prospectively collected and analysed data on patients with laboratory-confirmed 2019-nCoV infection by real-time RT-PCR and next-generation sequencing. Data were obtained with standardised data collection forms shared by WHO and the International Severe Acute Respiratory and Emerging Infection Consortium from electronic medical records. Researchers also directly communicated with patients or their families to ascertain epidemiological and symptom data. Outcomes were also compared between patients who had been admitted to the intensive care unit (ICU) and those who had not.

Findings

By Jan 2, 2020, 41 admitted hospital patients had been identified as having laboratory-confirmed 2019-nCoV infection. Most of the infected patients were men (30 [73%] of 41); less than half had underlying diseases (13 [32%]), including diabetes (eight [20%]), hypertension (six [15%]), and cardiovascular disease (six [15%]). Median age was 49·0 years (IQR 41·0–58·0). 27 (66%) of 41 patients had been exposed to Huanan seafood market. One family cluster was found. Common symptoms at onset of illness were fever (40 [98%] of 41 patients), cough (31 [76%]), and myalgia or fatigue (18 [44%]); less common symptoms were sputum production (11 [28%] of 39), headache (three [8%] of 38), haemoptysis (two [5%] of 39), and diarrhoea (one [3%] of 38). Dyspnoea developed in 22 (55%) of 40 patients (median time from illness onset to dyspnoea 8·0 days [IQR 5·0–13·0]). 26 (63%) of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest CT. Complications included acute respiratory distress syndrome (12 [29%]), RNAaemia (six [15%]), acute cardiac injury (five [12%]) and secondary infection (four [10%]). 13 (32%) patients were admitted to an ICU and six (15%) died. Compared with non-ICU patients, ICU patients had higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα.

…

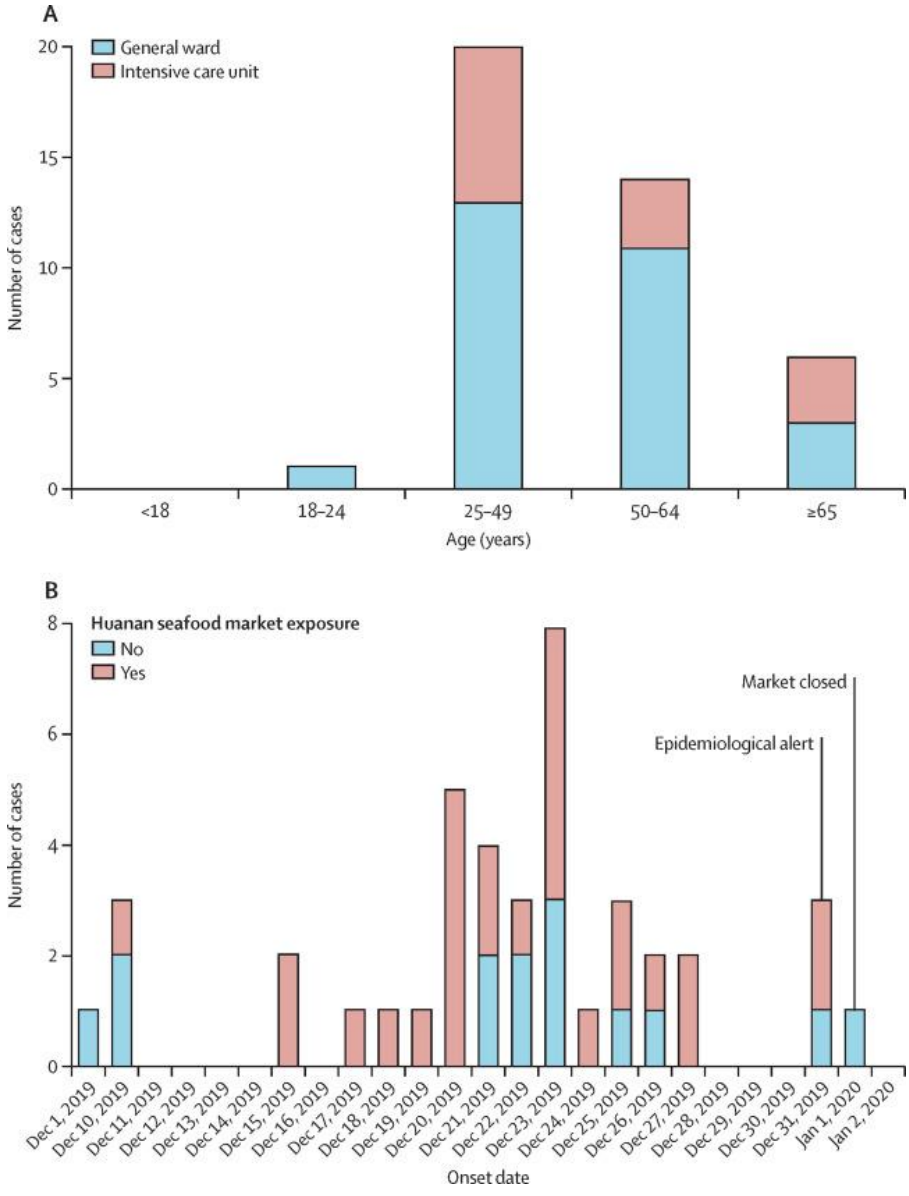

Figure:

Date of illness onset and age distribution of patients with laboratory-confirmed 2019-nCoV infection.

Interessant ist in diesem Zusammenhang auch, dass bei dem ersten bestätigten Patienten in dieser Publikation die Symptome einer COVID-19 Erkrankung bereits am 1. Dezember 2019 festgestellt wurden. Auf Grund der bis zu 14-tägigen Inkubationszeit im Zusammenhang mit der neuartigen Coronavirus-Erkrankung muss man demzufolge davon ausgehen, dass bereits im November 2019 erste Ansteckungen stattgefunden haben. Dies ist u.a. kompatibel mit einem neueren Bericht, wonach bereits im November 2019 ein allererster Fall einer COVID-19 Erkrankung in Frankreich basierend auf einer detaillierten Analyse der Lungenaufnahmen eines Patienten nachträglich festgestellt wurde. In jüngster Zeit wird sogar über die Behandlung von ersten COVID-19 Patienten in verschiedenen Krankenhäusern der Stadt Wuhan bereits im Oktober 2019 berichtet (siehe z.B. [IV.2]). Wir kommen im späteren Verlauf der vorliegenden Studie noch einmal auf diesen zeitlichen Aspekt der Ausbreitung der COVID-19 Erkrankung in der Frühphase der Pandemie zurück.

4. Eine in den Medien häufig zitierte wissenschaftliche Publikation, welche angeblich beweist, dass der Ursprung der derzeitigen Coronavirus-Pandemie eine Zoonose ist, entpuppt sich bei näherer Analyse als ungeeignet, um zwischen den beiden alternativen Theorien zu entscheiden. Unter dem Titel „Forscher widerlegen Verschwörungstheorien“ (siehe beispielsweise [IV.3]) wurde wiederholt auf eine Publikation erschienen im angesehenen Fachjournal „Nature Medicine“ verwiesen, welche angeblich den Beweis liefere, „dass sich der Erreger SARS-CoV-2 auf natürliche Weise entwickelte und nicht mittels Gentechnik in einem Labor entstand“. Geht man dieser Veröffentlichung in der Zeitschrift „Nature Medicine“ nach [III.1], so muss man zunächst erkennen, dass es sich dabei nicht um eine wissenschaftliche Originalpublikation handelt, sondern um einen sogenannten „**Letter to the Editor**“, in dem fünf Virologen ihre persönliche Ansicht über den Ursprung des SARS-CoV-2 Virus darlegen, siehe nachfolgenden Auszug aus der Veröffentlichung:

Nature Medicine 26, pages 450–452 (2020)
Correspondence, Published: 17 March 2020

The proximal origin of SARS-CoV-2

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To the Editor — Since the first reports of novel pneumonia (COVID-19) in Wuhan, Hubei province, China, there has been considerable discussion on the origin of the causative virus, SARS-CoV-2 (also referred to as HCoV-19). Infections with SARS-CoV-2 are now widespread, and as of 11 March 2020, 121,564 cases have been confirmed in more than 110 countries, with 4,373 deaths.

SARS-CoV-2 is the seventh coronavirus known to infect humans; SARS-CoV, MERS-CoV and SARS-CoV-2 can cause severe disease, whereas HKU1, NL63, OC43 and 229E are associated with mild symptoms. Here we review what can be deduced about the origin of SARS-CoV-2 from comparative analysis of genomic data. We offer a perspective on the notable features of the SARS-CoV-2 genome and discuss scenarios by which they could have arisen. Our analyses clearly show that SARS-CoV-2 is not a laboratory construct or a purposefully manipulated virus.

…

In der Einleitung schreiben die Autoren: „Our analyses **clearly show** that SARS-CoV-2 is not a laboratory construct or a purposefully manipulated virus“. Weiter hinten im Text werden dann plötzlich ganz andere Formulierungen verwendet: „It is **improbable** that SARS-CoV-2 emerged through laboratory manipulation of a related SARS-CoV-2-like coronavirus“. „Instead, we **propose** two scenarios that can **plausibly** explain the origin of SARS-CoV-2“. Und schließlich im Schlussteil: „Although the **evidence** shows that SARS-CoV-2 is not a purposefully manipulated virus, **it is currently impossible to prove or disprove the other theories of its origin described here**“. „**More scientific data could swing the balance of evidence to favor one hypothesis over another**“.

Ein wissenschaftlicher „Beweis“, wie ihn die Medien in dieser Publikation gesehen haben, sieht anders aus. Die Fehlinterpretation ist in diesem Falle jedoch eindeutig dem äußerst missverständlichen Eingangsstatement der Autoren zuzuschreiben, welches im klaren Widerspruch zum abschließenden Statement dieses „Letters to the Editor“ steht.

5. Eine weitere wissenschaftliche Originalpublikation [I.4], welche im Kontext der Theorie einer Zoonose in Wissenschaftskreisen immer wieder angeführt wird, stammt federführend von der Forschungsgruppe von Zheng-Li Shi am „Wuhan Institute of Virology“, welche bereits seit vielen Jahren intensive Forschung an Coronaviren von verschiedenen Fledermauspopulationen betrieben hat. Erstaunlich bei dieser Publikation in der berühmten Zeitschrift „NATURE“ ist, dass zwischen dem Einreichungsdatum (20.01.2020) und dem Akzeptanzdatum (29.01.2020) lediglich neun Tage lagen, was in Wissenschaftlerkreisen darauf hindeutet, dass hier keine fundierte kritische Fachbegutachtung dieser Arbeit durch - in der Regel - mehrere Gutachter bzw. Gutachterinnen stattgefunden haben kann. Noch schneller ging es dann mit der eigentlichen Veröffentlichung, welche bereits fünf Tage darauf erfolgte:

***Nature* 579, pages 270–273 (2020)**
Article,
Received: 20 January 2020
Accepted: 29 January 2020
Published: 03 February 2020

A pneumonia outbreak associated with a new coronavirus of probable bat origin

Peng Zhou, Xing-Lou Yang, Xian-Guang Wang, Ben Hu, Lei Zhang, Wei Zhang, Hao-Rui Si, Yan Zhu, Bei Li, Chao-Lin Huang, Hui-Dong Chen, Jing Chen, Yun Luo, Hua Guo, Ren-Di Jiang, Mei-Qin Liu, Ying Chen, Xu-Rui Shen, Xi Wang, Xiao-Shuang Zheng, Kai Zhao, Quan-Jiao Chen, Fei Deng, Lin-Lin Liu, Bing Yan, Fa-Xian Zhan, Yan-Yi Wang, Geng-Fu Xiao and Zheng-Li Shi

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Lin-Lin Liu & Fa-Xian Zhan

Abstract

Since the outbreak of severe acute respiratory syndrome (SARS) 18 years ago, a large number of SARS-related coronaviruses (SARSr-CoVs) have been discovered in their natural reservoir host, bats. Previous studies have shown that some bat SARSr-CoVs have the potential to infect humans. Here we report the identification and characterization of a new coronavirus (2019-nCoV), which caused an epidemic of acute respiratory syndrome in humans in Wuhan, China. The epidemic, which started on 12 December 2019, had caused 2,794 laboratory-confirmed infections including 80 deaths by 26 January 2020. Full-length genome sequences were obtained from five patients at an early stage of the outbreak. The sequences are almost identical and share 79.6% sequence identity to SARS-CoV. Furthermore, we show that 2019-nCoV is 96% identical at the whole-genome level to a bat coronavirus. Pairwise protein sequence analysis of seven conserved non-structural proteins domains show that this virus belongs to the species of SARSr-CoV. In addition, 2019-nCoV virus isolated from the bronchoalveolar lavage fluid of a critically ill patient could be neutralized by sera from several patients. Notably, we confirmed that 2019-nCoV uses the same cell entry receptor—angiotensin converting enzyme II (ACE2)—as SARS-CoV.

Dieser Artikel beinhaltet die wesentliche Aussage, dass der genetische Fingerabdruck des neuartigen Coronavirustyps (damals noch 2019-nCoV genannt), welcher eine COVID-19 Erkrankung hervorruft, zu 96% übereinstimmt mit einem Coronavirustyp „RaTG13“, welcher von Hufeisennasenfledermäusen aus der südchinesischen Provinz Yunnan stammt. Da der genetische Code des neuartigen Coronavirustyps erst am 11. Januar 2020 durch das „China’s National Center for Disease Control and Prevention” veröffentlicht wurde, verblieben demzufolge dem Forscherteam um Zheng-Li Shi lediglich neun Tage um den genetischen Fingerabdruck des neuartigen Coronavirustyps mit demjenigen von sehr vielen anderen Coronavirusarten in Datenbanken abzugleichen und den Virustyp mit der höchsten Ähnlichkeit zu identifizieren. Ferner musste in dieser Zeit noch die Veröffentlichung selbst geschrieben und unter allen Koautoren abgestimmt werden. Interessanterweise wurde das Fledermausvirus mit der Bezeichnung „RaTG13“ bereits im Jahr 2013, also sieben Jahre früher, von der Forschungsgruppe um Zheng-Li Shi aus Hufeisennasenfledermäusen der Provinz Yunnan isoliert, ohne dass dies in früheren Publikationen des Forscherteams um Zheng-Li Shi erwähnt wurde. Das Virus mit der Bezeichnung „RaTG13“ gilt seit der oben erwähnten Veröffentlichung in der Zeitschrift „NATURE“ im Februar 2020 bei vielen Virologen als „natürliche Ursprungsquelle“ der Coronavirus-Pandemie.

Allerdings gibt es in Wissenschaftlerkreisen seit einigen Monaten erhebliche Zweifel bezüglich des Wahrheitsgehalts der Inhalte dieser NATURE-Publikation vom Februar 2020 (siehe beispielsweise [IV.4]). An dieser Stelle sollen drei Beispiele für die geäußerten Vorbehalte wiedergegeben werden (für die vollständigen Versionen sei auf die Quellen [II.1-II.3] verwiesen):

Anomalies in BatCoV/RaTG13 sequencing and provenance

Daoyu Zhang

To this date, the most critical piece of evidence on the purposed "natural origin" theory of SARS-CoV-2, was the sequence known as RaTG13, allegedly collected from a single fecal sample from Rhinolophus Affinis. Understanding the provenance of RaTG13 is critical on the ongoing debate of the Origins of SARS-CoV-2. However, this sample is allegedly "used up" and therefore can no longer be accessed nor sequenced independently, and the only available data was the 3 related Genbank accessions: MN996532.1, SRX7724752 and SRX8357956.

We report these datasets possessed multiple significant anomalies, and the provenence of the promised claims of RaTG13 or it's role in proving a "probable bat origin" of SARS-CoV-2 can not be satisfied nor possibly be confirmed.

…

De-novo Assembly of RaTG13 Genome Reveals Inconsistencies Further Obscuring SARS-CoV-2 Origins

Mohit Singla, Saad Ahmad, Chandan Gupta, Tavpritesh Sethi

Received: 25 August 2020 / Approved: 27 August 2020 / Online: 27 August 2020

Abstract

An intense scientific debate is ongoing as to the origin of SARS-CoV-2. An oft-cited piece of information in this debate is the genome sequence of a bat coronavirus strain referred to as RaTG13 mentioned in a recent Nature paper showing 96.2% genome homology with SARS-CoV-2. This is discussed as a fossil record of a strain whose current existence is unknown. The said strain is conjectured by many to have been part of the ancestral pool from which SARS-CoV-2 may have evolved. Multiple groups have been discussing the features of the genome sequence of the said strain. In this paper, we report that the currently specified level of details are grossly insufficient to draw inferences about the origin of SARS-CoV-2. De-novo assembly, KRONA analysis for metagenomic and re-examining data quality highlights the key issues with the RaTG13 genome and the need for a dispassionate review of this data. This work is a call to action for the scientific community to better collate scientific evidence about the origins of SARS-CoV-2 so that future incidence of such pandemics may be effectively mitigated.

…

All journal articles evaluating the origin or epidemiology of SARS-CoV-2 that utilize the RaTG13 bat strain genomics are potentially flawed and should be retracted

Dean Bengston

Recent SARS-CoV-2 epidemiological origin studies have made their conclusion based-in-part by analyzing a bat coronavirus strain that most closely matches SARS-CoV-2 called RaTG13. However, the origins of this strain are obfuscated and therefore the genomics of the strain cannot be trusted, especially in context of determining the origin of SARS-CoV-2.

…

Zusammenfassend kann festgehalten werden, dass es bis heute keine wissenschaftlich fundierte Grundlage für die Behauptung gibt, dass die gegenwärtige Coronavirus-Pandemie durch eine Zoonose verursacht wurde. Demzufolge ist es aus wissenschaftlichen Gründen nicht angebracht, zum gegenwärtigen Zeitpunkt von einer „Naturkatastrophe" zu sprechen.

2.2 Die Laborunfall-Theorie

Es waren keine „Verschwörungstheoretiker", sondern zwei chinesische Wissenschaftler, Lei und Botao Xiao von der South China University of Technology, die Mitte Februar 2020 eine Studie auf dem internationalen Forschungs-Online-Portal „Research Gate" publizierten, in welcher sie erstmals nach Ausbruch der Epidemie öffentlich mutmaßten, dass das biotechnologische Labor im Zentrum von Wuhan die Quelle für die neuartigen Coronaviren sein könnte. Kurz nach der Veröffentlichung dieser Studie verschwand diese wieder aus der Online-Datenbank des Portals „Research-gate", ist jedoch noch im Web archiviert [II.4].

In der Tat führt der Ausbruch der gegenwärtigen Coronavirus-Pandemie in der Stadt Wuhan auf die berechtigte Frage, warum diese Pandemie gerade in dieser Stadt im Jahre 2019 ihren Anfang genommen hat. Nimmt man eine Zoonose, welche auf einem Wildtiermarkt im Zentrum der Stadt Wuhan stattgefunden hat, als Ursache der gegenwärtigen Pandemie an, so muss man erst einmal festhalten, dass es bereits seit Jahrtausenden Wildtiermärkte in China gab und bis in die jüngste Vergangenheit tausende dieser Märkte in allen Städten Chinas existierten. Man muss sich deshalb fragen, warum gerade im Jahre 2019 eine solche Coronavirus-Pandemie von der Stadt Wuhan ausgegangen ist?

In der Wissenschaft ist die Stadt Wuhan in den vergangenen Jahren in erster Linie durch seine Forschung auf dem Gebiet der Virologie in Erscheinung getreten, nicht zuletzt durch zahlreiche Veröffentlichungen in führenden interdisziplinären wissenschaftlichen Zeitschriften wie „NATURE" und „SCIENCE". Dabei spielte die Forschungsgruppe um Zheng-Li Shi am Wuhan Institut für Virologie seit vielen Jahren eine wichtige Rolle auf dem Gebiet der

Coronaviren-Forschung. Diese begann vor ca. 16 Jahren – noch vor der Errichtung des „Wuhan Institute of Virology“ im Rahmen einer chinesisch-französischen Kooperation – und wurde seit vielen Jahren teilweise in enger Kooperation der chinesischen Forscher mit mehreren amerikanischen und australischen Forschungsgruppen durchgeführt [I.5-I.10]. Die Quelle der Coronaviren für die virologische Forschung waren dabei unterschiedliche Arten von Fledermäusen, welche von dem Wuhan-Forschungsteam in Höhlen verschiedener chinesischer Provinzen im Rahmen zahlreicher Expeditionen eingesammelt wurden. Die Coronaviren wurden dann am Wuhan Institut für Virologie isoliert, vermehrt und deren Wechselwirkung mit tierischen und menschlichen Zellen untersucht (siehe z.B. [I.5, I.6, I.7, I.9]).

Die Forschergruppe um Zheng-Li Shi am „Wuhan Institute of Virology“ hat jedoch nicht nur natürlich vorkommende Coronaviren untersucht, sondern diese gezielt manipuliert mit dem Ziel, diese für den Menschen ansteckender und gefährlicher zu machen. Diese so genannte **„gain-of-function“-Forschung** am „Wuhan Institute of Virology“ ist durch mehrere wissenschaftliche Originalpublikationen in referierten Fachzeitschriften belegt (siehe z.B. [I.5, I.6, I.7, I.8] und wurde bereits seit Jahren von vielen Vertretern der Wissenschaft kritisch beurteilt (siehe z.B. [III.2]). Dieser Vorgeschichte zur derzeitigen Coronavirus-Pandemie sind auf Grund ihrer Bedeutung zwei eigenständige Kapitel im Anschluss an dieses einleitende Kapitel gewidmet. **Insbesondere der Disput in Wissenschaftlerkreisen um das Gefahrenpotential der „gain-of-function“-Forschung, der u.a. in zwei Briefen an den Präsidenten der EU-Kommission im Jahre 2013 zum Ausdruck kommt (siehe Kapitel: „Gain-of-function research”), zeigt auf, wie unterschiedlich die Meinungen unter Wissenschaftlern schon damals war und wie groß der Diskussionsbedarf gerade heute – nach Ausbruch einer weltweiten Pandemie – tatsächlich wäre.**

Obwohl das „Wuhan Institute of Virology“ ein biotechnologisches Labor der höchsten Sicherheitsstufe betreibt, existierten vor Ausbruch der Coronavirus-Pandemie Berichte über erhebliche Sicherheitsmängel im „Wuhan Institute of Virology“ (siehe z. B. [IV.5]):

The Washington Post, April 14, 2020

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

Josh Rogin

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

In January 2018, the U.S. Embassy in Beijing took the unusual step of repeatedly sending U.S. science diplomats to the Wuhan Institute of Virology (WIV), which had in 2015 become China’s first laboratory to achieve the highest level of international bioresearch safety (known

as BSL-4). WIV issued a news release in English about the last of these visits, which occurred on March 27, 2018. The U.S. delegation was led by Jamison Fouss, the consul general in Wuhan, and Rick Switzer, the embassy's counselor of environment, science, technology and health. Last week, WIV erased that statement from its website, though it remains archived on the Internet.

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

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

…

Ein Blick auf die Statistik der dokumentierten Unfälle in biotechnologischen Hochsicherheitslabors zeigt, dass ein ungewollter Austritt hoch infektiöser Viren aus solchen Laboren in der Vergangenheit nicht selten vorkam, sowohl in China als auch etwa in USA. Auch diesem wichtigen Thema ist ein eigenständiges Kapitel im Rahmen dieser Studie gewidmet.

Doch was wissen wir nun eigentlich wirklich über die Frühphase des Ausbruchs der Coronavirus-Pandemie in Wuhan? Aus offiziellen Quellen leider sehr wenig, da China von Anfang an versucht hat, die wahren Begebenheiten zu vertuschen. Darüber wurde bereits intensiv in den Medien berichtet (siehe beispielsweise [IV.6, IV.7, IV.8]). China übte im Verlauf des Jahres 2020 sogar Druck auf die EU und Länder wie Australien aus – bis hin zur Androhung von Sanktionen – falls der chinesische Umgang mit der Pandemie nicht als vorbildlich gelobt oder gar kritische Stellungnahmen über das Verhalten der chinesischen Regierung zu Beginn der Pandemie erfolgen würden.

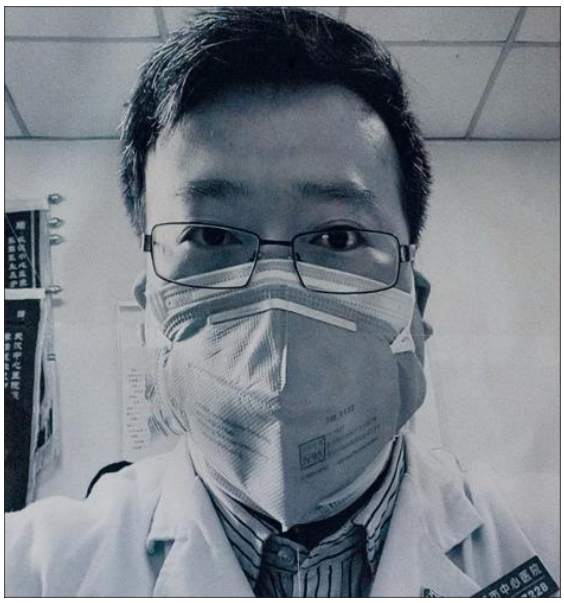
Aus der wissenschaftlichen Fachliteratur (siehe z. B. [III.3]) sowie aus zahlreichen Medienberichten (siehe z.B. [IV.9]) ist bekannt, dass **die chinesischen Ärzte in Wuhan großem Druck ausgesetzt wurden, als sie versucht haben, andere Kollegen oder gar die Öffentlichkeit wahrheitsgemäß über die Vorgänge im Zusammenhang mit der neuen COVID-19 Erkrankung zu informieren**. Ein besonders tragisches Beispiel ist der Arzt Wenliang Li, über dessen Schicksal in der renommierten Zeitschrift „LANCET" wie folgt berichtet wurde:

THE LANCET, VOLUME 395, ISSUE 10225, P682, FEBRUARY 29, 2020

Li Wenliang

Andrew Green

On Dec 30, 2019, Li Wenliang sent a message to a group of fellow doctors warning them about a possible outbreak of an illness that resembled severe acute respiratory syndrome (SARS) in Wuhan, Hubei province, China, where he worked. Meant to be a private message, he encouraged them to protect themselves from infection. Days later, he was summoned to the Public Security Bureau in Wuhan and made to sign a statement in which he was accused of making false statements that disturbed the public order.



Ophthalmologist who warned about the outbreak of COVID-19. Born in Beizhen, China, on Oct 12, 1986, he died after becoming infected with SARS-CoV-2 in Wuhan, China, on Feb 7, 2020, aged 33 years.

In fact, Li was one of the first people to recognise the outbreak of 2019 novel coronavirus disease (COVID-19) in Wuhan that has now spread to 25 countries, killing 1669 people and infecting more than 51 800 people as of Feb 16, 2020. Li returned to work after signing the statement and contracted severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), apparently from a patient. His death sparked outrage in China, where citizens took to message boards to voice their gratitude for Li's dedicated front-line service and to criticise the initial response of Wuhan's security and medical officials to his warning. In the days before his death, Li said “If the officials had disclosed information about the epidemic earlier I think it would have been a lot better”, in an interview with *The New York Times*. “There should be more openness and transparency”, he said.

Der einzige Weg, um an Informationen über die wahren Begebenheiten in der Frühphase der Pandemie zu gelangen – sowohl innerhalb Chinas als auch vom Ausland her – war daher die systematische Analyse der Meldungen in chinesischen sozialen Medien und

Online-Plattformen, wobei viele Informationen nur zeitweise zur Verfügung standen, bevor sie wieder gelöscht wurden.

Dabei fiel beispielsweise die große Diskrepanz zwischen den inoffiziellen und offiziellen Zahlen zu den infizierten Personen und Todesfällen in China in der Frühphase der Pandemie auf. Darüber wurde u.a. auch sehr früh in den Medien benachbarter asiatischer Länder berichtet (siehe z.B. [IV.10], [IV.11]):

TAIWAN NEWS, 05.02.2020

Tencent may have accidentally leaked real data on Wuhan virus deaths

Tencent briefly lists 154,023 infections and 24,589 deaths from Wuhan coronavirus

Keoni Everington

TAIPEI (Taiwan News) — As many experts question the veracity of China's statistics for the Wuhan coronavirus outbreak, Tencent over the weekend appeared to inadvertently release what is potentially the actual number of infections and deaths — which are far higher than official figures, but eerily in line with predictions from a respected scientific journal.

As early as Jan. 26, netizens were reporting that Tencent, on its webpage titled "Epidemic Situation Tracker," briefly showed data on the novel coronavirus (2019-nCoV) in China that was much higher than official estimates, before suddenly switching to lower numbers. Hiroki Lo, a 38-year-old Taiwanese beverage store owner, that day reported that Tencent and NetEase were both posting "unmodified statistics," before switching to official numbers in short order.

Lo told Taiwan News than on Jan. 26 he checked the numbers on both Tencent and NetEase and found them "really scary." He said he did not know whether the numbers were real or not, but did not have much time to think about it as he had a busy day of work ahead at his store.

Lo said he did not check the numbers again until he went home that evening, when he was shocked to see they had dropped dramatically and "something was wrong." He said he noticed individuals on a Hong Kong Facebook group also observed the same bizarre occurrence that day.

On late Saturday evening (Feb. 1), the Tencent webpage showed confirmed cases of the Wuhan virus in China as standing at 154,023, 10 times the official figure at the time. It listed the number of suspected cases as 79,808, four times the official figure.

The number of cured cases was only 269, well below the official number that day of 300. Most ominously, the death toll listed was 24,589, vastly higher than the 300 officially listed that day.

Moments later, Tencent updated the numbers to reflect the government's "official" numbers that day. Netizens noticed that Tencent has on at least three occasions posted extremely high numbers, only to quickly lower them to government-approved statistics.

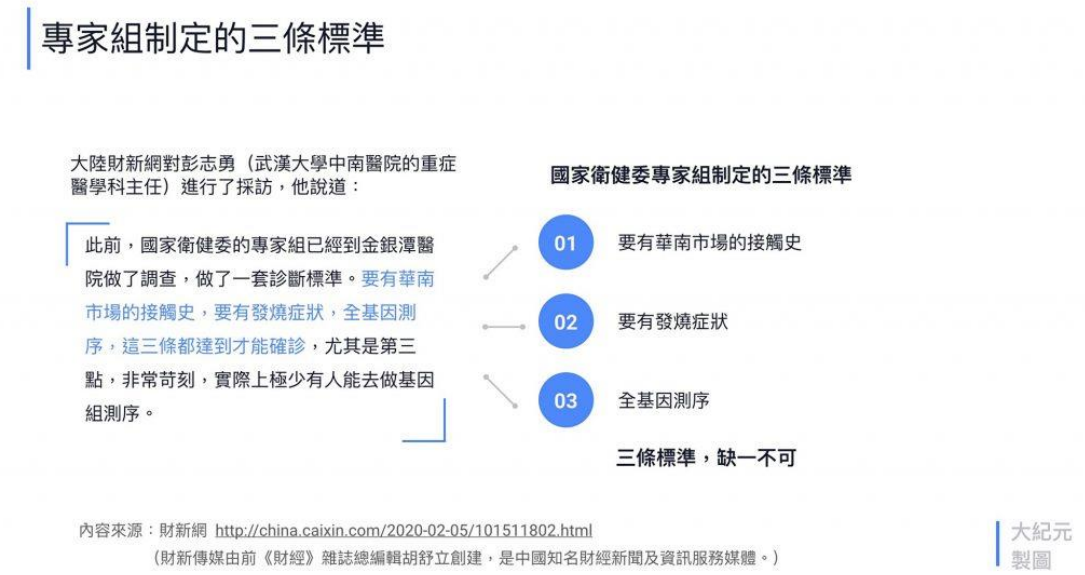
Feb. 1 chart showing higher numbers (left), chart showing "official" numbers (right). (Internet image)

Netizens also noticed that each time the screen with the large numbers appears, a comparison with the previous day's data appears above, which demonstrates a "reasonable" incremental increase, much like the official numbers. This has led some netizens to speculate that Tencent has two sets of data, the real data and "processed" data.

…

Eine der Ursachen, warum die inoffiziellen und offiziellen Zahlen zu den diagnostizierten Coronavirus-Infizierten und -Toten in der Frühphase der Pandemie abwichen, mag u.a. auf die merkwürdige Definition der „offiziellen Corona-Fälle“ zurückzuführen sein. Für eine positive Diagnose mussten drei Voraussetzungen erfüllt sein [IV.12]:

1) **Die betreffende Person musste Kontakt mit dem „Huanan seafood market“ gehabt haben.**
2) Die betreffende Person musste Fiebersymptome zeigen.
3) Die Diagnose einer Coronavirusinfektion musste durch eine Gensequenzierung nachgewiesen werden.



Besonders das erste Kriterium ist im Zusammenhang mit der Frage nach dem Ursprung der Coronavirus-Pandemie relevant: **Die chinesische Regierung hat demnach von Anfang an postuliert, dass der Ursprung der COVID-19 Erkrankung der Wildtiermarkt im Zentrum der Stadt Wuhan sein sollte**, der bekanntlich gleich zu Beginn des Jahres 2020 von der chinesischen Regierung geschlossen wurde. Dafür gab es jedoch weder zum damaligen Zeitpunkt noch bis zum heutigen Tag gesicherte wissenschaftliche Erkenntnisse, so dass das erste der drei oben genannten Kriterien zum Nachweis einer COVID-19 Erkrankung aus medizindiagnostischer Sicht keinen Sinn ergibt, sondern eher als politisch-motivierte Definition zu verstehen ist.

Man muss sich nun natürlich fragen, warum die chinesische Regierung zu diesem frühen Zeitpunkt den Wildtiermarkt als Ursprung der Coronavirus-Pandemie als einzig mögliche Erklärung deklariert hat und seitdem alles unternimmt, die Zoonose-Theorie sowohl innerhalb des eigenen Landes als auch gegenüber dem Ausland zu propagieren.

Der Hintergrund hierzu ist, dass sehr frühzeitig in den chinesischen sozialen Medien zahlreiche Hinweise gegeben und öffentlicht wurden, dass „Patient zero“ der COVID-19 Infektionskette eine junge Wissenschaftlerin des „Wuhan Institute of Virology“ gewesen ist. Ihr Name ist Yanling Huang, geboren am 20. Oktober 1988. Sie war seit 2012 Mitarbeiterin des „Wuhan Institute of Virology“ und hat mindestens sechs wissenschaftliche Arbeiten unter dieser Institutsadresse publiziert. Seit Ende 2019 gilt sie als verschwunden und ihr Foto und ihr Profil wurden auf der Institutswebseite gelöscht (ebenso wie ihre persönliche Webseite):

Der Beweis, dass Yanling Huang Mitarbeiterin des „Wuhan Institute of Virology“ war, kann jedoch noch auf folgender Webseite, welche die Doktoranden des Instituts inkl. Studenten-ID auflistet, gefunden werden (die Originalwebseite ist in chinesischer Sprache verfasst; hier ist eine in die deutsche Sprache übersetzte Version wiedergegeben):

20140923 Der Abschlussstatus des Eröffnungsberichtssystems für Doktoranden 2012
gd.whiov.cas.cn/zxpy/yjsswgg/201409/t20140923_258008.html 1/2

Chinesische Akademie der Wissenschaft
Wuhan Institut für Virologie

Ihre derzeitige Position: Startseite >> Schulausbildung >> Unternehmensmitteilung

20140923 Der Abschlussstatus des Eröffnungsberichtssystems für Doktoranden 2012

Quelle: Veröffentlicht: 23.09.2014

Ordnungsnummer	Studenten ID	Name	Abschlussart	Name des Lehrers	
1	201218012415001	Chai Fan	PhD	Xiao Gengfu	Bestanden die Bewertung
2	201218012415002	Er Xuan	PhD	Yan Huimin	Bestanden die Bewertung
3	201218012415003	Feng Lipeng	PhD	Chen Shiyun	Bestanden die Bewertung
4	201218012415004	Ge Sai	PhD	Yuan Zhiming	Bestanden die Bewertung
5	201218012415005	Xie Jumin	PhD	Guan Wuxiang	Bestanden die Bewertung
6	201218012415006	Kang Zhenyu	PhD	Wang Hualin	Bestanden die Bewertung

7	201218012415007	Kuang Wenhua	PhD	Hu Zhihong	Bestanden die Bewertung
8	201218012415008	Li Xiaojun	PhD	Luo Minhua	Bestanden die Bewertung
9	201218012415009	Li Xiaodan	PhD	Zhang Bo	Bestanden die Bewertung
10	201218012415010	Peng Qin	PhD	Gao Meiying	Bestanden die Bewertung
11	201218012415011	Qiao Jinjuan	PhD	Wei Hongping	Bestanden die Bewertung
12	201218012415012	Shang Yu	PhD	Hu Zhihong	Bestanden die Bewertung
13	201218012415013	Su Lan	PhD	Sun Xiulian	Bestanden die Bewertung
14	201218012415014	Sun Manluan	PhD	Zhang Xianen	Bestanden die Bewertung
15	201218012415015	Tan Bing	PhD	Shi Zhengli	keine Aufzeichnungen
16	201218012415016	Teng Tieshan	PhD	Wei Hongping	Beim Bewertungsteam einreichen
17	201218012415017	Wang Jinpei	PhD	Zhou Ningyi	Beim Bewertungsteam einreichen
18	201218012415018	Yan Liming	PhD	Fang Qin	Bestanden die Bewertung
19	201218012415019	Dichtung	PhD	Zhang Xianen	Bestanden die Bewertung
20	201218012415020	Jae Junjie	PhD	Yuan Zhiming	Beim Bewertungsteam einreichen
21	201218012415021	Zou Jing	PhD	Yuan Zhiming	Bestanden die Bewertung
22	201218012415022	Bi Peng	PhD	Gong Peng	Bestanden die Bewertung
23	201218012415023	Chen Jungang	PhD	Chen Xulin	Bestanden die Bewertung
24	201218012415024	Hao Sujuan	PhD	Guan Wuxiang	Bestanden die Bewertung
25	201218012415025	Li Qian	PhD	Wang Hanzhong	Bestanden die Bewertung
26	201218012415026	Li Xingguang	PhD	Yang Rongge	keine Aufzeichnungen
27	201218012415028	Liu Shuhui	PhD	Chen Xinwen	Bestanden die Bewertung
28	201218012415029	Wu Guiru	PhD	Li Chaoyang	Beim Bewertungsteam einreichen
29	201218012415030	Yan Yan	PhD	Hu Qinxue	Bestanden die Bewertung
30	201218012415031	Yao Yongxuan	PhD	Chen Xinwen	Bestanden die Bewertung
31	201218012415032	Yu Jie	PhD	Yan Huimin	Bestanden die Bewertung
32	201218012415033	Zhang Mudan	PhD	Hu Qinxue	
33	201218012415034	Zheng Caishang	PhD	Wang Hanzhong	Bestanden die Bewertung
34	201218012415035	Zhou Ming	PhD	Hu Kanghong	Bestanden die Bewertung
35	201218012415036	Wang Zhilong	PhD	Tang Hong	Bestanden die Bewertung
36	201228012415001	Chen Xiuxiu	Master-Studium	Zhang Xianen	Bestanden die Bewertung
37	201228012415002	Shi Chenyan	Master-Studium	Yuan Zhiming	Bestanden die Bewertung
38	201228012415003	Wang Mingxiu	Master-Studium	Cui Zongqiang	Bestanden die Bewertung
39	201228012415005	Yan Shicui	Master-Studium	Fang Qin	Bestanden die Bewertung
40	201228012415007	Zhou Yu	Master-Studium	Zhou Ningyi	Bestanden die Bewertung
41	201228012415009	Chen Yajun	Master-Studium	Gao Meiying	Bestanden die Bewertung
42	201228012415010	Feng Lianwei	Master-Studium	Yang Rongge	Bestanden die Bewertung
43	201228012415012	Er Hui	Master-Studium	Zhou Ningyi	Bestanden die Bewertung
44	201228012415013	Huberdan	Master-Studium	Hu Qinxue	Bestanden die Bewertung
45	201228012415014	Huang Yanling	Master-Studium	Wei Hongping	Bestanden die Bewertung
46	201228012415015	Jiang Liangyu	Master-Studium	Chen Xulin	Bestanden die Bewertung
47	201228012415016	Liu Lili	Master-Studium	Wang Yanyi	Bestanden die Bewertung
48	201228012415019	Meng Xiangzheng	Master-Studium	Deng Jiaoyu	Bestanden die Bewertung

49	201228012415021	Shi Jing	Master-Studium	Li Chaoyang	Bestanden die Bewertung
50	201228012415023	Wang Bo	Master-Studium	Shi Zhengli	Bestanden die Bewertung
51	201228012415028	Xu Hao	Master-Studium	Wang Hualin	Bestanden die Bewertung
52	201228012415029	Yang Bo	Master-Studium	Luo Minhua	
53	201228012415031	Zhang Weihong	Master-Studium	Tang Hong	Beim Bewertungsteam einreichen
54	2012E8012461033	Gao Yutao	Master-Studium	Shi Zhengli	Bestanden die Bewertung
55	2012E8012461034	Hou Shoucai	Master-Studium	Sun Xiulian	Bestanden die Bewertung
56	2012E8012461035	Wang Jing	Master-Studium	Wei Hongping	Bestanden die Bewertung
57	2012E8012461036	Wang Yifei	Master-Studium	Chen Shiyun	In Bewertung
58	2012E8012461037	Phasenstern	Master-Studium	Hu Xiaomin	Bestanden die Bewertung
59	2012E8012461038	Xiong Chaochao	Master-Studium	Chen Jianjun	Beim Bewertungsteam einreichen
60	2012E8012461039	Yao Weitong	Master-Studium	Yang Rongge	Bestanden die Bewertung
61	2012E8012461040	Zhao Bali	Master-Studium	Yan Huimin	Bestanden die Bewertung
62	2012E8012461042	Zhu Zheng	Master-Studium	Hu Zhihong	Bestanden die Bewertung
63	2012E8012461043	Wen Lei	Master-Studium	Simon Rayner	Bestanden die Bewertung
64	2012E8012461044	Ma Ruipeng	Master-Studium	Sun Xiulian	Bestanden die Bewertung
65	2012E8012461045	Mei Xiaofen	Master-Studium	Yuan Zhiming	In Bewertung
66	2012E8012461046	Xu Ting	Master-Studium	Gong Rui	Bestanden die Bewertung
67	2012E8012461049	Zhao Kaitao	Master-Studium	Chen Xinwen	Beim Bewertungsteam einreichen

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Auch im Jahr 2018 befand sich Yanling Huang noch am „Wuhan Institute of Virology“, wie ein Gruppenfoto aus jenem Jahr beweist:

Über den folgenden Link [IV.13] können eine umfassende Reportage über das Schicksal von Yanling Huang und die Hintergründe ihres Verschwindens sowie zahlreiche weitere Beweisdokumente abgerufen werden:

https://www.youtube.com/watch?v=bpQFCcSI0pU

Ferner gibt es **eine Webseite z**um Thema „Where is Huang Yan Ling?“, der viele weitere Informationen und Hintergründe zu entnehmen sind:

https://twitter.com/whereisyanling

Trotz der Schwere der Vorwürfe, die wiederholt sowohl in chinesischen als auch internationalen sozialen Medien und Online-Plattformen erhoben wurden, waren bislang weder die verantwortliche Laborleiterin Zheng-Li Shi, noch ein offizieller Vertreter des „Wuhan Institute of Virology“ bereit, über den Verbleib von Yanling Huang Auskunft zu geben. Die chinesische Regierung hat zwar die „Gerüchte“ um Yanling Huang offiziell dementiert, verweigert jedoch andererseits jegliche Auskunft über das Verbleiben der jungen Wissenschaftlerin.

Angesichts der Tatsache, dass in der Frühphase der Pandemie Wissenschaftler, Ärzte, Journalisten sowie Privatpersonen in China von der chinesischen Regierung bedrängt wurden, falsche Angaben zu den Hintergründen der COVID-19 Erkrankung zu machen (siehe z.B. [III.3], [IV.14]) oder gar spurlos verschwunden sind (siehe beispielsweise [IV.6], [IV.15]), ist es für eine Vielzahl von Wissenschaftlern unverständlich, dass einige Virologen im Rahmen eines gemeinsamen Statements [III.4] „die schnelle, offene und transparente“ Informationspolitik von chinesischer Seite gelobt haben. In Wahrheit sind nicht nur Personen wie Yanling Huang [IV.13] und Fang Bin [IV.15] verschwunden, sondern auch wichtige Proben aus der Forschung vorenthalten (siehe z.B. [IV.16], [II.1]) bzw. per Anordnung durch die „Health and Medical Commission of Hubei Province“ Anfang Januar 2020 vernichtet worden.

Das Statement der Gruppe von Virologen lautete wie folgt [III.4]:

THE LANCET 395, ISSUE 10226, E42-E43, MARCH 07, 2020

CORRESPONDENCE

Statement in support of the scientists, public health professionals, and medical professionals of China combatting COVID-19

Charles Calisher, Dennis Carroll, Rita Colwell, Ronald B Corley, Peter Daszak, Christian Drosten, Luis Enjuanes, Jeremy Farrar, Hume Field, Josie Golding, Alexander Gorbalenya, Bart Haagmans, James M Hughes, William B Karesh, Gerald T Keusch, Sai Kit Lam, Juan Lubroth, John S Mackenzie, Larry Madoff, Jonna Mazet, Peter Palese, Stanley Perlman, Leo Poon, Bernard Roizman, Linda Saif, Kanta Subbarao, Mike Turner

We are public health scientists who have closely followed the emergence of 2019 novel coronavirus disease (COVID-19) and are deeply concerned about its impact on global health and wellbeing. We have watched as the scientists, public health professionals, and medical professionals of China, in particular, have worked diligently and effectively to rapidly identify the pathogen behind this outbreak, put in place significant measures to reduce its impact, and share their results transparently with the global health community. This effort has been remarkable.

We sign this statement in solidarity with all scientists and health professionals in China who continue to save lives and protect global health during the challenge of the COVID-19 outbreak. We are all in this together, with our Chinese counterparts in the forefront, against this new viral threat.

The rapid, open, and transparent sharing of data on this outbreak is now being threatened by rumours and misinformation around its origins. We stand together to strongly condemn conspiracy theories suggesting that COVID-19 does not have a natural origin. Scientists from multiple countries have published and analysed genomes of the causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and they overwhelmingly conclude that this coronavirus originated in wildlife,
as have so many other emerging pathogens. This is further supported by a letter from the presidents of the US National Academies of Science, Engineering, and Medicine and by the scientific communities they represent. Conspiracy theories do nothing but create fear, rumours, and prejudice that jeopardise our global collaboration in the fight against this virus. We support the call from the Director-General of WHO to promote scientific evidence and unity over misinformation and conjecture.

We want you, the science and health professionals of China, to know that we stand with you in your fight against this virus.

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

We speak in one voice. To add your support for this statement, sign our letter online. LM is editor of ProMED-mail. We declare no competing interests.

Bereits an dieser Stelle ist anzumerken, dass Personen aus dem Autorenkreis – wie im Falle von Peter Daszak – selbst in „gain-of-function“-Experimente in der Vergangenheit persönlich involviert waren und jahrelang mit der Gruppe um Zheng-Li Shi am „Wuhan Institute of Virology“ gemeinsam geforscht und publiziert haben. Darauf wird in dem späteren Kapitel zu „Gain-of-function research” näher eingegangen.

Ferner ist anzumerken, dass die Aussage: “Scientists from multiple countries have published and analysed genomes of the causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and they overwhelmingly conclude that this coronavirus originated in wildlife, as have so many other emerging pathogens” in dieser Form nicht ohne den Hinweis stehen bleiben kann, dass es mittlerweile mindestens ebenso viele Wissenschaftler aus vielen Ländern, darunter Nobelpreisträger, gibt, die auf Grund von Analysen der genetischen Fingerabdrücke

der neuen SARS-CoV-2 Viren zu gegenteiligen Schlussfolgerunen gekommen sind (siehe beispielsweise: [I.11], [II.5], [II.6], [II.7], [II.8]).

Zusammenfassend kann festgehalten werden, dass es sehr viele Indizien gibt, die einen Laborunfall im „Wuhan Institute of Virology“ als die mit Abstand wahrscheinlichste Ursache für die Corona-Pandemie erscheinen lassen. In diesem Fall würde es sich nicht um eine „Naturkatastrophe“ handeln, sondern um eine von Menschen selbst herbeigeführte Tragödie. Es besteht eine sehr große Gefahr darin, die Frage nach der Ursache für die gegenwärtige Pandemie „als geklärt“ zu deklarieren, wie etwa in dem Statement [III.4] einiger Virologen. Für politische Entscheidungsträger macht es unbestreitbar einen Unterschied, ob sie Wildtiermärkte oder Hochrisikoforschung mit gentechnisch manipulierten Viren weltweit verbieten sollen. Diese Frage muss verstärkt in den Vordergrund rücken, ansonsten könnten Corona- und andere Virenarten noch ein viel größeres Gefahrenpotential entwickeln, nicht nur in der Gegenwart, sondern auch in der Zukunft.

3 Vorgeschichte der Coronavirus-Pandemie: Forschung und gentechnische Manipulation an Coronaviren von Fledermäusen im virologischen Institut in Wuhan, China

Bei früheren Coronavirus-bedingten Krankheiten, wie beispielsweise SARS (2003), haben Mutationen von Coronaviren, die ursprünglich von Fledermäusen stammen, in Zwischenwirtstieren stattgefunden, so dass eine anschließende Übertragung auf den Menschen möglich wurde. Eine direkte Übertragung von Coronaviren von Fledermäusen auf den Menschen war bislang nicht bekannt. Virologen sprechen in diesem Zusammenhang von einer „Anpassungsbarriere". Es war deshalb von hoher Bedeutung, die in Frage kommenden Zwischenwirtstiere für verschiedene Coronavirus-bedingte Erkrankungen jeweils durch intensive Forschung zu identifizieren.

Auffallend bei der gegenwärtigen Pandemie im Vergleich zu früheren Ausbrüchen von Coronavirus-bedingten Erkrankungen ist:

1) Wir haben es in der gegenwärtigen Pandemie mit einem Erreger zu tun, der mit einer **bislang nicht bekannten Effizienz menschliche Zellen angreift**.
2) Dabei werden nicht nur die (oberen) Atemwege, sondern **auch innere Organe angegriffen und in ihrer Funktion teilweise schwer geschädigt**.

Man muss sich daher notwendigerweise die Frage stellen, wie eine solche **nahezu perfekte Adaption von Coronaviren an menschliche Zellrezeptoren** zustande kommen konnte, um zukünftige Pandemie-Gefahrenpotentiale identifizieren zu können.

Im Folgenden wird die Vorgeschichte der Coronavirus-Pandemie näher beleuchtet. Wie durch zahlreiche Publikationen in wissenschaftlichen Fachzeitschriften belegt ist, hat die Forschungsgruppe um Zheng-Li Shi am „Wuhan Institute of Virology" über viele Jahre hinweg Fledermausviren in Höhlen verschiedener südchinesischer Provinzen eingesammelt und nach Wuhan gebracht. Die Forschergruppe hat die natürlich vorkommenden Coronaviren jedoch nicht nur wissenschaftlich studiert, sondern diese gezielt manipuliert mit dem Ziel, die Coronaviren für Menschen ansteckender und gefährlicher zu machen. Diese so genannte „gain-of-function" Forschung am „Wuhan Institute of Virology" ist durch mehrere wissenschaftliche Originalpublikationen in referierten Fachzeitschriften belegt und wurde bereits seit Jahren von vielen Vertretern der Wissenschaft sehr kritisch gesehen.

In einer 2013 in der Zeitschrift „NATURE" erschienenen Veröffentlichung [I.7] berichtet das Forscherteam um **Zheng-Li Shi** und **Peter Daszak** über das erfolgreiche Andocken der Zacken der Coronavirus-Krone an menschliche ACE2-Zellrezeptoren. Dabei wurden sogenannte Hufeisennasenfledermäuse aus der chinesischen Provinz Yunnan als Quelle von SARS-ähnlichen Coronaviren verwendet. Der wesentliche Teil dieser Publikation ist nachfolgend wiedergegeben:

***Nature* 503**, pages 535–538 (2013), Published: 30 October 2013

Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor

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Abstract

The 2002–3 pandemic caused by severe acute respiratory syndrome coronavirus (SARS-CoV) was one of the most significant public health events in recent history. An ongoing outbreak of Middle East respiratory syndrome coronavirus suggests that this group of viruses remains a key threat and that their distribution is wider than previously recognized. Although bats have been suggested to be the natural reservoirs of both viruses, attempts to isolate the progenitor virus of SARS-CoV from bats have been unsuccessful. Diverse SARS-like coronaviruses (SL-CoVs) have now been reported from bats in China, Europe and Africa, but none is considered a direct progenitor of SARS-CoV because of their phylogenetic disparity from this virus and the

inability of their spike proteins to use the SARS-CoV cellular receptor molecule, the human angiotensin converting enzyme II (ACE2). Here we report whole-genome sequences of two novel bat coronaviruses from Chinese horseshoe bats (family: Rhinolophidae) in Yunnan, China: RsSHC014 and Rs3367. These viruses are far more closely related to SARS-CoV than any previously identified bat coronaviruses, particularly in the receptor binding domain of the spike protein. Most importantly, we report the first recorded isolation of a live SL-CoV (bat SL-CoV-WIV1) from bat faecal samples in Vero E6 cells, which has typical coronavirus morphology, 99.9% sequence identity to Rs3367 and uses ACE2 from humans, civets and Chinese horseshoe bats for cell entry. Preliminary *in vitro* testing indicates that WIV1 also has a broad species tropism. Our results provide the strongest evidence to date that Chinese horseshoe bats are natural reservoirs of SARS-CoV, and that intermediate hosts may not be necessary for direct human infection by some bat SL-CoVs. They also highlight the importance of pathogen-discovery programs targeting high-risk wildlife groups in emerging disease hotspots as a strategy for pandemic preparedness.

Main

The 2002–3 pandemic of SARS[1] and the ongoing emergence of the Middle East respiratory syndrome coronavirus (MERS-CoV) demonstrate that CoVs are a significant public health threat. SARS-CoV was shown to use the human ACE2 molecule as its entry receptor, and this is considered a hallmark of its cross-species transmissibility. The receptor binding domain (RBD) located in the amino-terminal region (amino acids 318–510) of the SARS-CoV spike (S) protein is directly involved in binding to ACE2. However, despite phylogenetic evidence that SARS-CoV evolved from bat SL-CoVs, all previously identified SL-CoVs have major sequence differences from SARS-CoV in the RBD of their S proteins, including one or two deletions. Replacing the RBD of one SL-CoV S protein with SARS-CoV S conferred the ability to use human ACE2 and replicate efficiently in mice. However, to date, no SL-CoVs have been isolated from bats, and no wild-type SL-CoV of bat origin has been shown to use ACE2.

We conducted a 12-month longitudinal survey (April 2011–September 2012) of SL-CoVs in a colony of *Rhinolophus sinicus* at a single location in Kunming, Yunnan Province, China. A total of 117 anal swabs or faecal samples were collected from individual bats using a previously published method. A one-step reverse transcription (RT)-nested PCR was conducted to amplify the RNA-dependent RNA polymerase (RdRP) motifs A and C, which are conserved among alphacoronaviruses and betacoronaviruses.

Twenty-seven of the 117 samples (23%) were classed as positive by PCR and subsequently confirmed by sequencing. The species origin of all positive samples was confirmed to be *R. sinicus* by cytochrome b sequence analysis, as described previously[16]. A higher prevalence was observed in samples collected in October (30% in 2011 and 48.7% in 2012) than those in April (7.1% in 2011) or May (7.4% in 2012). Analysis of the S protein RBD sequences indicated the presence of seven different strains of SL-CoVs. In addition to RBD sequences, which closely matched previously described SL-CoVs (Rs672, Rf1 and HKU3), two novel strains (designated SL-CoV RsSHC014 and Rs3367) were discovered. Their full-length genome sequences were determined, and both were found to be 29,787 base pairs in size (excluding the poly(A) tail). The overall nucleotide sequence identity of these two genomes with human SARS-CoV (Tor2 strain) is 95%, higher than that observed previously for bat SL-CoVs in China (88–92%) or Europe (76%). Higher sequence identities were observed at the protein level between these new SL-CoVs and SARS-CoVs. To understand the evolutionary origin of these two novel SL-CoV strains, we conducted recombination analysis with the

Recombination Detection Program 4.0 package using available genome sequences of bat SL-CoV strains (Rf1, Rp3, Rs672, Rm1, HKU3 and BM48-31) and human and civet representative SARS-CoV strains (BJ01, SZ3, Tor2 and GZ02). Three breakpoints were detected with strong *P* values ($<10^{-20}$) and supported by similarity plot and bootscan analysis. Breakpoints were located at nucleotides 20,827, 26,553 and 28,685 in the Rs3367 (and RsSHC014) genome, and generated recombination fragments covering nucleotides 20,827–26,533 (5,727 nucleotides) (including partial open reading frame (ORF) 1b, full-length S, ORF3, E and partial M gene) and nucleotides 26,534–28,685 (2,133 nucleotides) (including partial ORF M, full-length ORF6, ORF7, ORF8 and partial N gene). Phylogenetic analysis using the major and minor parental regions suggested that Rs3367, or RsSHC014, is the descendent of a recombination of lineages that ultimately lead to SARS-CoV and SL-CoV Rs672.

The most notable sequence differences between these two new SL-CoVs and previously identified SL-CoVs is in the RBD regions of their S proteins. First, they have higher amino acid sequence identity to SARS-CoV (85% and 96% for RsSHC014 and Rs3367, respectively). Second, there are no deletions and they have perfect sequence alignment with the SARS-CoV RBD region. Structural and mutagenesis studies have previously identified five key residues (amino acids 442, 472, 479, 487 and 491) in the RBD of the SARS-CoV S protein that have a pivotal role in receptor binding. Although all five residues in the RsSHC014 S protein were found to be different from those of SARS-CoV, two of the five residues in the Rs3367 RBD were conserved.

Despite the rapid accumulation of bat CoV sequences in the last decade, there has been no report of successful virus isolation. We attempted isolation from SL-CoV PCR-positive samples. Using an optimized protocol and Vero E6 cells, we obtained one isolate which caused cytopathic effect during the second blind passage. Purified virions displayed typical coronavirus morphology under electron microscopy. Sequence analysis using a sequence-independent amplification method to avoid PCR-introduced contamination indicated that the isolate was almost identical to Rs3367, with 99.9% nucleotide genome sequence identity and 100% amino acid sequence identity for the S1 region. The new isolate was named SL-CoV-WIV1.

To determine whether WIV1 can use ACE2 as a cellular entry receptor, we conducted virus infectivity studies using HeLa cells expressing or not expressing ACE2 from humans, civets or Chinese horseshoe bats. We found that WIV1 is able to use ACE2 of different origins as an entry receptor and replicated efficiently in the ACE2-expressing cells. This is, to our knowledge, the first identification of a wild-type bat SL-CoV capable of using ACE2 as an entry receptor.

To assess its cross-species transmission potential, we conducted infectivity assays in cell lines from a range of species. Our results indicate that bat SL-CoV-WIV1 can grow in human alveolar basal epithelial (A549), pig kidney 15 (PK-15) and Rhinolophus sinicus kidney (RSKT) cell lines, but not in human cervix (HeLa), Syrian golden hamster kidney (BHK21), Myotis davidii kidney (BK), Myotis chinensis kidney (MCKT), Rousettus leschenaulti kidney (RLK) or Pteropus alecto kidney (PaKi) cell lines. Real-time RT–PCR indicated that WIV1 replicated much less efficiently in A549, PK-15 and RSKT cells than in Vero E6 cells.

To assess the cross-neutralization activity of human SARS-CoV sera against WIV1, we conducted serum-neutralization assays using nine convalescent sera from SARS patients collected in 2003. The results showed that seven of these were able to completely neutralize 100 tissue culture infectious dose 50 (TCID50) WIV1 at dilutions of 1:10 to 1:40, further confirming the close relationship between WIV1 and SARS-CoV.

Our findings have important implications for public health. First, they provide the clearest evidence yet that SARS-CoV originated in bats. Our previous work provided phylogenetic evidence of this, but the lack of an isolate or evidence that bat SL-CoVs can naturally infect human cells, until now, had cast doubt on this hypothesis. Second, the lack of capacity of SL-CoVs to use of ACE2 receptors has previously been considered as the key barrier for their direct spillover into humans, supporting the suggestion that civets were intermediate hosts for SARS-CoV adaptation to human transmission during the SARS outbreak. However, the ability of SL-CoV-WIV1 to use human ACE2 argues against the necessity of this step for SL-CoV-WIV1 and suggests that direct bat-to-human infection is a plausible scenario for some bat SL-CoVs. This has implications for public health control measures in the face of potential spillover of a diverse and growing pool of recently discovered SARS-like CoVs with a wide geographic distribution.

Our findings suggest that the diversity of bat CoVs is substantially higher than that previously reported. In this study we were able to demonstrate the circulation of at least seven different strains of SL-CoVs within a single colony of R. sinicus during a 12-month period. The high genetic diversity of SL-CoVs within this colony was mirrored by high phenotypic diversity in the differential use of ACE2 by different strains. It would therefore not be surprising if further surveillance reveals a broad diversity of bat SL-CoVs that are able to use ACE2, some of which may have even closer homology to SARS-CoV than SL-CoV-WIV1. Our results—in addition to the recent demonstration of MERS-CoV in a Saudi Arabian bat, and of bat CoVs closely related to MERS-CoV in China, Africa, Europe and North America—suggest that bat coronaviruses remain a substantial global threat to public health.

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

Diese Arbeit wurde u.a. durch Kollegen des „Wuhan Institute of Virology“ wie folgt kommentiert [I.12]:

COMMENT on this article in:
Virol. Sin. 28(6), 315 (2013), doi: 10.1007/s12250-013-3402-x.

Bats as animal reservoirs for the SARS coronavirus: hypothesis proved after 10 years of virus hunting

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Abstract

Recently, the team led by Dr. Zhengli Shi from Wuhan Institute of Virology, Chinese Academy of Sciences, and Dr. Peter Daszak from Ecohealth Alliance identified SL-CoVs in Chinese horseshoe bats that were 95% identical to human SARS-CoV and were able to use human angiotensin-converting enzyme 2 (ACE2) receptor for docking and entry. Remarkably, they isolated the first known live bat SL-CoV that replicates in human and related cells. Their findings provide clear evidence that some SL-CoVs circulating in bats are capable of infecting and replicating in human (Ge X Y, et al., 2013). The severe acute respiratory syndrome (SARS) was the first pandemic of the new millennium. It started in November 2002 in Southern China and had spread over 33 countries, causing 8096 infections and 774 dead cases (fatality rate of 9.6%), along with huge economic losses. The etiological agent of SARS was identified as a novel coronavirus (SARS-CoV) (Drosten C, et al., 2003; Ksiazek T G, et al., 2003). However, the origin of SARS-CoV remains elusive. Although it is suggested that bats are the natural reservoirs for SARS-CoV, isolation of a SARS like virus (SL-CoV) from bats have been unsuccessful. To trace the origin of the sudden emerging SARS-CoV, molecular epidemiological studies have been conducted by different research groups. In 2003, Guan et al. isolated SARS-CoVs from Himalayan palm civets and two other species in a live-animal market in Guangdong, China (Guan Y, et al, 2003). The Chinese SARS molecular epidemiology consortium suggested that the early-phase human SARS-CoV strains may have originated from wild animals (The Chinese SARS Molecular Epidemiology Consortium, 2004). These and other evidences suggested that palm civets were the direct source since the isolates from civets were highly related to human isolates from 2002-3 and 2003-4 SARS pandemic (Guan Y, et al, 2013; Song H D, et al., 2005; Wang M, et al, 2005). Since 2004, SL-CoVs have been identified from bats by several research groups including Dr. Shi's lab (Li W, 2005; Lau S K, et al, 2005). These bat isolates are more genetically diverse and share an overall nucleotide identity of 88% to 92% to the SARSCoVs from humans or civets, resulting in the hypothesis that bats may be the natural hosts of SARS-CoV. However, there are still some missing links between previously characterized SL-CoVs from bats and SARS-CoV that precipitated the 2002-3 outbreaks. 1) albeit the overall genome sequence similarity, there are significant differences in spike (S) protein between the previously known SL-CoVs and SARS-CoVs. The sequence identity of S1 fell to 64%, accompanying with insertions and (or) mutations in this region. S1 contains the receptor binding domain (RBD), which plays a key role in receptor recognition and is a major determinant of host range and cross-species infection of SARSCoV. It was suggested that the previously known bat SL-CoV stains cannot jump from bats to civets or humans owing to the significant differences between their RBDs (Li F, 2013); 2) although SL-CoVs have been identified from different bat species, isolation of a live SL-CoVs from bats never succeed; 3) no native SL-CoV from bats could use ACE2 as receptors and infect human cells, only when its RBD is replaced with the counterpart from a human SARS-CoV strain (Li W, et al, 2003; Becker M M, et al, 2008; Ren W, et al, 2008). Therefore, these SL-CoVs seem unlikely to be the immediate precursors of civet or human SARS-CoVs (Li F, 2013).

Zwei Jahre später erschien ein weiterer Artikel der Forschungsgruppe um **Zheng-Li Shi** und **Ralph Baric** in der Zeitschrift „NATURE MEDICINE“, der belegt, dass **gentechnische**

Veränderungen von Coronaviren von Hufeisennasenfledermäusen zu neuen, künstlich erzeugten „Hybridviren“ führen, welche in besonders effizienter Weise an menschliche Atemwegszellen ankoppeln können [I.8]. Die Forscher kreierten dabei ein „chimäres“ Virus, das sich aus dem Oberflächenprotein eines Fledermausvirus namens SHC014 und dem Rückgrat eines SARS-Coronavirus zusammensetzt. Das chimäre Virus infizierte menschliche Atemwegszellen und lieferte den Beweis, dass das Oberflächenprotein von SHC014 die notwendige Struktur hat, um sehr effizient an einen menschlichen Schlüsselrezeptor von Zellen zu binden und diese zu infizieren. Der wesentliche Teil dieser Publikation ist nachfolgend wiedergegeben:

***Nature Medicine* 21**, pages 1508–1513 (2015), Published: 09 November 2015

A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence

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Abstract

The emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS)-CoV underscores the threat of cross-species transmission events leading to outbreaks in humans. Here we examine the disease potential of a SARS-like virus, SHC014-CoV, which is currently circulating in Chinese horseshoe bat populations. Using the SARS-CoV reverse genetics system, we generated and characterized a chimeric virus expressing the spike of bat coronavirus SHC014 in a mouse-adapted SARS-CoV backbone. The results indicate that group 2b viruses encoding the SHC014 spike in a wild-type backbone can efficiently use multiple orthologs of the SARS receptor human angiotensin converting enzyme II (ACE2), replicate efficiently in primary human airway cells and achieve *in vitro* titers equivalent to epidemic strains of SARS-CoV. Additionally, *in vivo* experiments demonstrate replication of the chimeric virus in mouse lung with notable pathogenesis. Evaluation of available SARS-based immune-therapeutic and prophylactic modalities revealed poor efficacy; both monoclonal antibody and vaccine approaches failed to neutralize and protect from infection with CoVs using the novel spike protein. On the basis of these findings, we synthetically re-derived an infectious full-length SHC014 recombinant virus and demonstrate robust viral replication both *in vitro* and *in vivo*. Our work suggests a potential risk of SARS-CoV re-emergence from viruses currently circulating in bat populations.

Diese Experimente bauen auf bereits 2008 und 2010 von der Wuhan-Forschungsgruppe um Zheng-Li Shi im „Journal of Virology“ publizierten Arbeiten auf ([I.5], [I.6]) in denen bereits gezeigt werden konnte, **wie man mit gentechnischen Veränderungen Viren dazu bringen kann, menschliche Zellen gezielt zu infizieren unter Verwendung eines HIV-basierten Pseudovirus.** Die wesentlichen Teile dieser beiden Publikationen sind nachfolgend wiedergegeben:

JOURNAL OF VIROLOGY, Feb. 2008, p. 1899–1907 Vol. 82, No. 4, DOI: 10.1128/JVI.01085-07

Difference in Receptor Usage between Severe Acute Respiratory Syndrome (SARS) Coronavirus and SARS-Like Coronavirus of Bat Origin

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ABSTRACT

Severe acute respiratory syndrome (SARS) is caused by the SARS-associated coronavirus (SARS-CoV), which uses angiotensin-converting enzyme 2 (ACE2) as its receptor for cell entry. A group of SARS-like CoVs (SL-CoVs) has been identified in horseshoe bats. SL-CoVs and SARS-CoVs share identical genome organizations and high sequence identities, with the main exception of the N terminus of the spike protein (S), known to be responsible for receptor binding in CoVs. In this study, we investigated the receptor usage of the SL-CoV S by combining a human immunodeficiency virus-based pseudovirus system with cell lines expressing the ACE2 molecules of human, civet, or horseshoe bat. In addition to full-length S of SL-CoV and SARS-CoV, a series of S chimeras was constructed by inserting different sequences of the SARS-CoV S into the SL-CoV S backbone. Several important observations were made from this study. First, the SL-CoV S was unable to use any of the three ACE2 molecules as its receptor. Second, the SARS-CoV S failed to enter cells expressing the bat ACE2. Third, the chimeric S covering the previously defined receptor-binding domain gained its ability to enter cells via human ACE2, albeit with different efficiencies for different constructs. Fourth, a minimal insert region (amino acids 310 to 518) was found to be sufficient to convert the SL-CoV S from non-ACE2 binding to human ACE2 binding, indicating that the SL-CoV S is largely compatible with SARS-CoV S protein both in structure and in function. The significance of these findings in relation to virus origin, virus recombination, and host switching is discussed.

The outbreaks of severe acute respiratory syndrome (SARS) in 2002-2003, which resulted in over 8,000 infections and close to 800 deaths, was caused by a novel coronavirus (CoV), now known as the SARS-associated CoV (SARS-CoV). The association of SARS-CoV with animals was first revealed by the isolation and identification of very closely related viruses in several Himalayan palm civets (*Paguma larvata*) and a raccoon dog (*Nyctereutes procyonoides*) at a

live-animal market in Guangdong, China. A very high genome sequence identity (more than 99%) exists between the SARS-CoV-like virus from civets and SARS-CoV from humans, supporting the notion that SARS-CoV is of animal origin. However, subsequent studies showed that palm civets on farms and in the field were largely free from SARS-CoV infection. These results suggested that palm civets played a role as an intermediate host rather than as a natural reservoir. Subsequent surveillance studies among different bat populations revealed the presence in several horseshoe bat species (genus *Rhinolophus*) of a diverse group of CoVs, which are very similar to SARS-CoV in genome organization and sequence. These viruses are designated SARS-like CoVs (SL-CoVs) or SARS-CoV-like viruses. Such discoveries raised the possibility that bats are the natural reservoirs of SARS-CoV and triggered a surge in the search for CoVs in different bat species in different geographic locations.
Phylogenetic analysis based on different protein sequences suggested that SL-CoVs found in bats and SARS-CoVs from humans and civets should be placed in a separate subgroup (group b) in CoV group 2 (G2b) to differentiate them from other group 2 CoVs in the genus *Coronavirus*. G2b CoVs display major sequence differences in the N-terminal regions of their S proteins. The S proteins of CoVs play a key role in virus entry into host cells, including binding to host cell receptors and membrane fusion. Angiotensin-converting enzyme 2 (ACE2) has been identified as the functional receptor of SARS-CoV, and the molecular interaction between ACE2 and the SARS-CoV S protein has been well characterized. A 193-residue fragment (amino acids [aa] 318 to 510) in the SARS-CoV S protein was demonstrated to be the minimal receptor-binding domain (RBD) which alone was able to efficiently bind to ACE2. Furthermore, it was shown that minor changes in amino acid residues of the receptor-binding motif (RBM) of SARS-CoV S protein could abolish the entry of SARS-CoV into cells expressing human ACE2 (huACE2). In the corresponding RBD region of the SL-CoV S proteins, there is significant sequence divergence from those of the SARS-CoV S proteins, including two deletions of 5 and 12 or 13 aa. From crystal-structural analysis of the S-ACE2 complex, it was predicted that the S protein of SL-CoV is unlikely to use huACE2 as an entry receptor, although this has never been experimentally proven due to the lack of live SL-CoV isolates. Whether it is possible to construct an ACE2-binding SL-CoV S protein by replacing the RBD with that from SARS-CoV S proteins is also unknown.

In this study, a human immunodeficiency virus (HIV)-based pseudovirus system was employed to address these issues. Our results indicated that the SL-CoV S protein is unable to use ACE2 proteins of different species for cell entry and that SARS-CoV S protein also failed to bind the ACE2 molecule of the horseshoe bat, Rhinolophus pearsonii. However, when the RBD of SL-CoV S was replaced with that from the SARS-CoV S, the hybrid S protein was able to use the huACE2 for cell entry, implying that the SL-CoV S proteins are structurally and functionally very similar to the SARS-CoV S. These results suggest that although the SL-CoVs discovered in bats so far are unlikely to infect humans using ACE2 as a receptor, it remains to be seen whether they are able to use other surface molecules of certain human cell types to gain entry. It is also conceivable that these viruses may become infectious to humans if they undergo N-terminal sequence variation, for example, through recombination with other CoVs, which in turn might lead to a productive interaction with ACE2 or other surface proteins on human cells.

***Archives of Virology* 155(10)**, 1563–1569 (2010)

Published online 2010 Jun 22. doi: 10.1007/s00705-010-0729-6

Angiotensin-converting enzyme 2 (ACE2) proteins of different bat species confer variable susceptibility to SARS-CoV entry

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Abstract

The discovery of SARS-like coronavirus in bats suggests that bats could be the natural reservoir of SARS-CoV. However, previous studies indicated the angiotensin-converting enzyme 2 (ACE2) protein, a known SARS-CoV receptor, from a horseshoe bat was unable to act as a functional receptor for SARS-CoV. Here, we extended our previous study to ACE2 molecules from seven additional bat species and tested their interactions with human SARS-CoV spike protein using both HIV-based pseudotype and live SARS-CoV infection assays. The results show that ACE2s of *Myotis daubentoni* and *Rhinolophus sinicus* support viral entry mediated by the SARS-CoV S protein, albeit with different efficiency in comparison to that of the human ACE2. Further, the alteration of several key residues either decreased or enhanced bat ACE2 receptor efficiency, as predicted from a structural modeling study of the different bat ACE2 molecules. These data suggest that *M. daubentoni* and *R. sinicus* are likely to be susceptible to SARS-CoV and may be candidates as the natural host of the SARS-CoV progenitor viruses. Furthermore, our current study also demonstrates that the genetic diversity of ACE2 among bats is greater than that observed among known SARS-CoV susceptible mammals, highlighting the possibility that there are many more uncharacterized bat species that can act as a reservoir of SARS-CoV or its progenitor viruses. This calls for continuation and expansion of field surveillance studies among different bat populations to eventually identify the true natural reservoir of SARS-CoV.

Introduction

Severe acute respiratory syndrome coronavirus (SARS-CoV) is the aetiological agent responsible for the SARS outbreaks during 2002–2003, which had a huge global impact on public health, travel and the world economy [4, 11]. The host range of SARS-CoV is largely determined by the specific and high-affinity interactions between a defined receptor-binding domain (RBD) on the SARS-CoV spike protein and its host receptor, angiontensin-converting enzyme 2 (ACE2) [6, 7, 9]. It has been hypothesized that SARS-CoV was harbored in its natural reservoir, bats, and was transmitted directly or indirectly from bats to palm civets and then to humans [10]. However, although the genetically related SARS-like coronavirus (SL-CoV) has been identified in horseshoe bats of the genus *Rhinolophus* [5, 8, 12, 18], its spike protein was not able to use the human ACE2 (hACE2) protein as a receptor [13]. Close examination of the crystal structure of human SARS-CoV RBD complexed with hACE2 suggests that truncations in the receptor-binding motif (RBM) region of SL-CoV spike protein abolish its hACE2-

binding ability [7, 10], and hence the SL-CoV found recently in horseshoe bats is unlikely to be the direct ancestor of human SARS-CoV. Also, it has been shown that the human SARS-CoV spike protein and its closely related civet SARS-CoV spike protein were not able to use a horseshoe bat (*R. pearsoni*) ACE2 as a receptor [13], highlighting a critical missing link in the bat-to-civet/human transmission chain of SARS-CoV.

There are at least three plausible scenarios to explain the origin of SARS-CoV. First, some unknown intermediate hosts were responsible for the adaptation and transmission of SARS-CoV from bats to civets or humans. This is the most popular theory of SARS-CoV transmission at the present time [10]. Second, there is an SL-CoV with a very close relationship to the outbreak SARS-CoV strains in a non-bat animal host that is capable of direct transmission from reservoir host to human or civet. Third, ACE2 from yet to be identified bat species may function as an efficient receptor, and these bats could be the direct reservoir of human or civet SARS-CoV. Unraveling which scenario is most likely to have occurred during the 2002–2003 SARS epidemic is critical for our understanding of the dynamics of the outbreak and will play a key role in helping us to prevent future outbreaks. To this end, we have extended our studies to include ACE2 molecules from different bat species and examined their interaction with the human SARS-CoV spike protein. Our results show that there is great genetic diversity among bat ACE2 molecules, especially at the key residues known to be important for interacting with the viral spike protein, and that ACE2s of *Myotis daubentoni* and *Rhinolophus sinicus* from Hubei province can support viral entry.

In der Folgezeit entzündete sich eine **heftige Diskussion unter Wissenschaftlern darüber, ob die aus solchen Experimenten gewonnenen Erkenntnisse das potentielle Risiko einer Pandemie rechtfertigen**. Ein bekannter Virologe des Institut Pasteur in Paris stellte fest, dass die Forscher des Wuhan-Instituts ein neuartiges Virus geschaffen haben, das sich in menschlichen Zellen bemerkenswert gut vermehrt und fügte hinzu: **„Wenn das Virus entweichen würde, könnte niemand die Ausbreitung vorhersagen“**. Ein Molekularbiologe fügte hinzu: **„Die einzige Bedeutung dieser Studie ist die Erzeugung einer Labor-basierten, neuen, nicht-natürlichen Gefahr“**. Die damalige Debatte wurde in zahlreichen Artikeln in Fachzeitschriften und in den Medien aufgegriffen und kommentiert. Zwei Beispiele hierzu sind nachfolgend wiedergegeben ([III.2], [III.5]):

Nature (2015), doi:10.1038/nature.2015.18787

***NATURE* | NEWS**

Engineered bat virus stirs debate over risky research

Lab-made coronavirus related to SARS can infect human cells.

Declan Butler

An experiment that created a hybrid version of a bat coronavirus — one related to the virus that causes SARS (severe acute respiratory syndrome) — has triggered renewed debate over whether engineering lab variants of viruses with possible pandemic potential is worth the risks.

In an article published in *Nature Medicine* on 9 November, scientists investigated a virus called SHC014, which is found in horseshoe bats in China. The researchers created a chimaeric virus, made up of a surface protein of SHC014 and the backbone of a SARS virus that had been adapted to grow in mice and to mimic human disease. The chimaera infected human airway cells — proving that the surface protein of SHC014 has the necessary structure to bind to a key receptor on the cells and to infect them. It also caused disease in mice, but did not kill them.

Although almost all coronaviruses isolated from bats have not been able to bind to the key human receptor, SHC014 is not the first that can do so. In 2013, researchers reported this ability for the first time in a different coronavirus isolated from the same bat population.

The findings reinforce suspicions that bat coronaviruses capable of directly infecting humans (rather than first needing to evolve in an intermediate animal host) may be more common than previously thought, the researchers say.

But other virologists question whether the information gleaned from the experiment justifies the potential risk. Although the extent of any risk is difficult to assess, Simon Wain-Hobson, a virologist at the Pasteur Institute in Paris, points out that the researchers have created a novel virus that "grows remarkably well" in human cells. "If the virus escaped, nobody could predict the trajectory," he says.

Creation of a chimaera

The argument is essentially a rerun of the debate over whether to allow lab research that increases the virulence, ease of spread or host range of dangerous pathogens — what is known as 'gain-of-function' research. In October 2014, the US government imposed a moratorium on federal funding of such research on the viruses that cause SARS, influenza and MERS (Middle East respiratory syndrome, a deadly disease caused by a virus that sporadically jumps from camels to people).

The latest study was already under way before the US moratorium began, and the US National Institutes of Health (NIH) allowed it to proceed while it was under review by the agency, says Ralph Baric, an infectious-disease researcher at the University of North Carolina at Chapel Hill, a co-author of the study. The NIH eventually concluded that the work was not so risky as to fall under the moratorium, he says.

But Wain-Hobson disapproves of the study because, he says, it provides little benefit, and reveals little about the risk that the wild SHC014 virus in bats poses to humans.

Other experiments in the study show that the virus in wild bats would need to evolve to pose any threat to humans — a change that may never happen, although it cannot be ruled out. Baric

and his team reconstructed the wild virus from its genome sequence and found that it grew poorly in human cell cultures and caused no significant disease in mice.

“The only impact of this work is the creation, in a lab, of a new, non-natural risk,” agrees Richard Ebright, a molecular biologist and biodefence expert at Rutgers University in Piscataway, New Jersey. Both Ebright and Wain-Hobson are long-standing critics of gain-of-function research.

In their paper, the study authors also concede that funders may think twice about allowing such experiments in the future. "Scientific review panels may deem similar studies building chimeric viruses based on circulating strains too risky to pursue," they write, adding that discussion is needed as to "whether these types of chimeric virus studies warrant further investigation versus the inherent risks involved”.

But Baric and others say the research did have benefits. The study findings “move this virus from a candidate emerging pathogen to a clear and present danger”, says Peter Daszak, who co-authored the 2013 paper. Daszak is president of the EcoHealth Alliance, an international network of scientists, headquartered in New York City, that samples viruses from animals and people in emerging-diseases hotspots across the globe.

Studies testing hybrid viruses in human cell culture and animal models are limited in what they can say about the threat posed by a wild virus, Daszak agrees. But he argues that they can help indicate which pathogens should be prioritized for further research attention.

Without the experiments, says Baric, the SHC014 virus would still be seen as not a threat. Previously, scientists had believed, on the basis of molecular modelling and other studies, that it should not be able to infect human cells. The latest work shows that the virus has already overcome critical barriers, such as being able to latch onto human receptors and efficiently infect human airway cells, he says. “I don't think you can ignore that.” He plans to do further studies with the virus in non-human primates, which may yield data more relevant to humans.

The Scientist, November 16 (2015)

Lab-Made Coronavirus Triggers Debate

The creation of a chimeric SARS-like virus has scientists discussing the risks of gain-of-function research.

Jef Akst

Ralph Baric, an infectious-disease researcher at the University of North Carolina at Chapel Hill, last week (November 9) published a study on his team’s efforts to engineer a virus with the surface protein of the SHC014 coronavirus, found in horseshoe bats in China, and the backbone of one that causes human-like severe acute respiratory syndrome (SARS) in mice. The hybrid

virus could infect human airway cells and caused disease in mice, according to the team's results, which were published in *Nature Medicine*.

…

Trotz dieser teilweise sehr heftig geführten Debatte und der Warnungen vor einer weltweiten Pandemie durch zahlreiche Vertreter der Wissenschaft setzte die Gruppe um Zheng-Li Shi am „Wuhan Institute of Virology" in Kooperation mit Peter Daszak ihre hoch riskanten Forschungsarbeiten zu gentechnisch veränderten Coronaviren fort, wie die beiden nachfolgenden Arbeiten aus den Jahren 2017 und 2018 belegen ([I.9], [I.10]). Dabei wurden die bereits seit Jahren etablierten Methoden der gentechnischen Manipulationen eingesetzt, wie aus der Arbeit [1.10] ersichtlich ist:

PLoS Pathog 13(11): e1006698. https://doi.org/10.1371/ journal.ppat.1006698

Editor: Christian Drosten, Charité Universitätsmedizin Berlin, GERMANY
Received: February 10, 2017; **Accepted:** October 17, 2017; **Published:** November 30, 2017

RESEARCH ARTICLE

Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus

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Yunnan Institute of Endemic Diseases Control and Prevention, Dali, China;
Dali University, Dali, China;
EcoHealth Alliance, New York, New York, United States of America;
Programme in Emerging Infectious Diseases, Duke-NUS Medical School, Singapore

Abstract

A large number of SARS-related coronaviruses (SARSr-CoV) have been detected in horseshoe bats since 2005 in different areas of China. However, these bat SARSr-CoVs show sequence differences from SARS coronavirus (SARS-CoV) in different genes (S, ORF8, ORF3, *etc*) and are considered unlikely to represent the direct progenitor of SARS-CoV. Herein, we report the findings of our 5-year surveillance of SARSr-CoVs in a cave inhabited by multiple species of

horseshoe bats in Yunnan Province, China. The full-length genomes of 11 newly discovered SARSr-CoV strains, together with our previous findings, reveals that the SARSr-CoVs circulating in this single location are highly diverse in the S gene, ORF3 and ORF8. Importantly, strains with high genetic similarity to SARS-CoV in the hypervariable N-terminal domain (NTD) and receptor-binding domain (RBD) of the S1 gene, the ORF3 and ORF8 region, respectively, were all discovered in this cave. In addition, we report the first discovery of bat SARSr-CoVs highly similar to human SARS-CoV in ORF3b and in the split ORF8a and 8b. Moreover, SARSr-CoV strains from this cave were more closely related to SARS-CoV in the non-structural protein genes ORF1a and 1b compared with those detected elsewhere. Recombination analysis shows evidence of frequent recombination events within the S gene and around the ORF8 between these SARSr-CoVs. We hypothesize that the direct progenitor of SARS-CoV may have originated after sequential recombination events between the precursors of these SARSr-CoVs. Cell entry studies demonstrated that three newly identified SARSr-CoVs with different S protein sequences are all able to use human ACE2 as the receptor, further exhibiting the close relationship between strains in this cave and SARS-CoV. This work provides new insights into the origin and evolution of SARS-CoV and highlights the necessity of preparedness for future emergence of SARS-like diseases.

Author summary

Increasing evidence has been gathered to support the bat origin of SARS coronavirus (SARS-CoV) in the past decade. However, none of the currently known bat SARSr-CoVs is thought to be the direct ancestor of SARS-CoV. Herein, we report the identification of a diverse group of bat SARSr-CoVs in a single cave in Yunnan, China. Importantly, all of the building blocks of SARS-CoV genome, including the highly variable S gene, ORF8 and ORF3, could be found in the genomes of different SARSr-CoV strains from this single location. Based on the analysis of full-length genome sequences of the newly identified bat SARSr-CoVs, we speculate that the direct ancestor of SARS-CoV may have arisen from sequential recombination events between the precursors of these bat SARSr-CoVs prior to spillover to an intermediate host. In addition, we found bat SARSr-CoV strains with different S proteins that can all use the receptor of SARS-CoV in humans (ACE2) for cell entry, suggesting diverse SARSr-CoVs capable of direct transmission to humans are circulating in bats in this cave. Our current study therefore offers a clearer picture on the evolutionary origin of SARS-CoV and highlights the risk of future emergence of SARS-like diseases.

…

***Nature* volume 556**, pages 255–258 (2018)

Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin

Peng Zhou, Hang Fan, Tian Lan, Xing-Lou Yang, Wei-Feng Shi, Wei Zhang, Yan Zhu, Ya-Wei Zhang, Qing-Mei Xie, Shailendra Mani, Xiao-Shuang Zheng, Bei Li, Jin-Man Li, Hua Guo, Guang-Qian Pei, Xiao-Ping An, Jun-Wei Chen, Ling Zhou, Kai-Jie Mai, Zi-Xian Wu, Di Li, Danielle E. Anderson, Li-Biao Zhang, Shi-Yue Li, Zhi-Qiang Mi, Tong-Tong He, Feng Cong, Peng-Ju Guo, Ren Huang, Yun Luo, Xiang-Ling Liu, Jing Chen, Yong Huang, Qiang Sun, Xiang-Li-Lan Zhang, Yuan-Yuan Wang, Shao-Zhen Xing, Yan-Shan Chen, Yuan Sun, Juan Li, Peter Daszak, Lin-Fa Wang, Zheng-Li Shi, Yi-Gang Tong & Jing-Yun Ma

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Abstract

Cross-species transmission of viruses from wildlife animal reservoirs poses a marked threat to human and animal health. Bats have been recognized as one of the most important reservoirs for emerging viruses and the transmission of a coronavirus that originated in bats to humans via intermediate hosts was responsible for the high-impact emerging zoonosis, severe acute respiratory syndrome (SARS). Here we provide virological, epidemiological, evolutionary and experimental evidence that a novel HKU2-related bat coronavirus, swine acute diarrhoea syndrome coronavirus (SADS-CoV), is the aetiological agent that was responsible for a large-scale outbreak of fatal disease in pigs in China that has caused the death of 24,693 piglets across four farms. Notably, the outbreak began in Guangdong province in the vicinity of the origin of the SARS pandemic. Furthermore, we identified SADS-related CoVs with 96–98% sequence identity in 9.8% (58 out of 591) of anal swabs collected from bats in Guangdong province during 2013–2016, predominantly in horseshoe bats (*Rhinolophus* spp.) that are known reservoirs of SARS-related CoVs. We found that there were striking similarities between the SADS and SARS outbreaks in geographical, temporal, ecological and aetiological settings. This study highlights the importance of identifying coronavirus diversity and distribution in bats to mitigate future outbreaks that could threaten livestock, public health and economic growth.

Methods

Sample collection

Bats were captured and sampled in their natural habitat in Guangdong province as described previously. Faecal swab samples were collected in viral transport medium (VTM) composed of Hank's balanced salt solution at pH 7.4 containing BSA (1%), amphotericin (15 μg ml^{-1}), penicillin G (100 units ml^{-1}) and streptomycin (50 μg ml^{-1}). Stool samples from sick pigs were collected in VTM. When appropriate and feasible, intestinal samples were also taken from deceased animals. Samples were aliquoted and stored at –80 °C until use. Blood samples were collected from recovered sows and workers on the farms who had close contact with sick pigs. Serum was separated by centrifugation at 3,000*g* for 15 min within 24 h of collection and preserved at 4 °C. Human serum collection was approved by the Medical Ethics Committee of the Wuhan School of Public Health, Wuhan University and Hummingbird IRB. Human, pigs and bats were sampled without gender or age preference unless indicated (for example, piglets or sows). No statistical methods were used to predetermine sample size.

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Amplification, cloning and expression of human and swine genes

Construction of expression clones for human *ACE2* in pcDNA3.1 has been described previously (Ge, X. Y. et al.: Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 503, 535–538 (2013) and Ren, W. et al.: Difference in receptor usage between severe acute respiratory syndrome (SARS) coronavirus and SARS-like coronavirus of bat origin. J. Virol. 82, 1899–1907 (2008)). Human *DPP4* was amplified from human cell lines. Human *APN* (also known as *ANPEP*) was commercially synthesized. Swine *APN* (also known as *ANPEP*), *DPP4* and *ACE2* were amplified from piglet intestine. Full-length gene fragments were amplified using specific primers (provided upon request). Human *ACE2* was cloned into pCDNA3.1 fused with a His tag. Human *APN* and *DPP4*, swine *APN*, *DPP4* and *ACE2* were cloned into pCAGGS fused with an S tag. Purified plasmids were transfected into HeLa cells. After 24 h, expression human or swine genes in HeLa cells was confirmed by immunofluorescence assay using mouse anti-His tag or mouse anti-S tag monoclonal antibodies (produced in house) followed by Cy3-labelled goat anti-mouse/rabbit IgG (Proteintech Group).

Pseudovirus preparation

The codon-humanized *S* genes of SADS-CoV or MERS-CoV cloned into pcDNA3.1 were used for pseudovirus construction as described previously (Ge, X. Y. et al.: Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 503, 535–538 (2013) and Ren, W. et al.: Difference in receptor usage between severe acute respiratory syndrome (SARS) coronavirus and SARS-like coronavirus of bat origin. J. Virol. 82, 1899–1907 (2008)). In brief, 15 μg of each pHIV-Luc plasmid (pNL4.3.Luc.R-E-Luc) and the S-protein-expressing plasmid (or empty vector control) were co-transfected into 4 × 10^6 HEK293T cells using Lipofectamine 3000 (Thermo Fisher Scientific). After 4 h, the medium was replaced with fresh medium. Supernatants were collected 48 h after transfection and clarified by centrifugation at 3,000*g*, then passed through a 0.45-μm filter (Millipore). The filtered supernatants were stored at −80 °C in aliquots until use. To evaluate the incorporation of S proteins into the core of HIV virions, pseudoviruses in supernatant (20 ml) were concentrated by ultracentrifugation through a 20% sucrose cushion (5 ml) at 80,000*g* for 90 min using a SW41 rotor (Beckman). Pelleted pseudoviruses were dissolved in 50 μl phosphate-buffered saline (PBS) and examined by electron microscopy.

Pseudovirus infection

HeLa cells transiently expressing APN, ACE2 or DPP4 were prepared using Lipofectamine 2000 (Thermo Fisher Scientific). Pseudoviruses prepared above were added to HeLa cells overexpressing APN, ACE2 or DPP4 24 h after transfection. The unabsorbed viruses were removed and replaced with fresh medium at 3 h after infection. The infection was monitored by measuring the luciferase activity conferred by the reporter gene carried by the pseudovirus, using the Luciferase Assay System (Promega) as follows: cells were lysed 48 h after infection, and 20 μl of the lysates was taken for determining luciferase activity after the addition of 50 μl of luciferase substrate.

Reviewer information

Nature thanks C. Drosten, G. Palacios and L. Saif for their contribution to the peer review of this work.

Tatsächlich waren es nicht nur die Forschungsaktivitäten der Gruppe um Zheng-Li Shi am „Wuhan Institute of Virology“ zu Coronaviren, sondern auch Forschungsaktivitäten anderer Gruppen zu anderen Virenarten, welche das Ziel verfolgten, **natürlich vorkommende Viren durch Genmanipulation für den Menschen ansteckender, gefährlicher und tödlicher zu machen.** Diese **„gain-of-function“-Forschung** und die damit verbundene heftige Auseinandersetzung zwischen verschiedenen Vertretern der Wissenschaft soll im nachfolgenden Kapitel näher dargestellt werden.

4 „Gain-of-function research": Internationale Debatte um das Risiko von Forschung zur Manipulation von Viren im Hinblick auf höhere Übertragungsfähigkeit, Gefährlichkeit und Sterblichkeitsraten

Die Debatte um den möglichen Nutzen, aber auch die Gefahren verbunden mit der Forschung zur Manipulation von Viren, um diese für den Menschen ansteckender, gefährlicher und letztlich tödlicher zu machen, startete im Jahr 2011. Ausgelöst wurde diese Debatte in erster Linie durch zwei wissenschaftliche Arbeiten internationaler Forschergruppen, welche zeigten, wie man durch gentechnische Veränderungen H5N1-Viren (Erreger der Vogelgrippe) für Menschen ansteckender machen kann [I.13, I.14]. Diese beiden Arbeiten von den Forschungsgruppen um Yoshihiro Kawaoka und Ron Fouchier, welche im Jahr 2012 in den Zeitschriften „NATURE" und „SCIENCE" publiziert wurden, sollen hier auszugsweise wiedergegeben werden:

***Nature* 486**, 420–428 (2012)

Published: 02 May 2012

Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets

Masaki Imai, Tokiko Watanabe, Masato Hatta, Subash C. Das, Makoto Ozawa, Kyoko Shinya, Gongxun Zhong, Anthony Hanson, Hiroaki Katsura, Shinji Watanabe, Chengjun Li, Eiryo Kawakami, Shinya Yamada, Maki Kiso, Yasuo Suzuki, Eileen A. Maher, Gabriele Neumann and Yoshihiro Kawaoka

Abstract

Highly pathogenic avian H5N1 influenza A viruses occasionally infect humans, but currently do not transmit efficiently among humans. The viral haemagglutinin (HA) protein is a known host-range determinant as it mediates virus binding to host-specific cellular receptors. Here we assess the molecular changes in HA that would allow a virus possessing subtype H5 HA to be transmissible among mammals. We identified a reassortant H5 HA/H1N1 virus—comprising H5 HA (from an H5N1 virus) with four mutations and the remaining seven gene segments from a 2009 pandemic H1N1 virus—that was capable of droplet transmission in a ferret model. The transmissible H5 reassortant virus preferentially recognized human-type receptors, replicated efficiently in ferrets, caused lung lesions and weight loss, but was not highly pathogenic and did not cause mortality. These results indicate that H5 HA can convert to an HA that supports efficient viral transmission in mammals; however, we do not know whether the four mutations in the H5 HA identified here would render a wholly avian H5N1 virus transmissible. The genetic origin of the remaining seven viral gene segments may also critically contribute to transmissibility in mammals. Nevertheless, as H5N1 viruses continue to evolve and infect humans, receptor-binding variants of H5N1 viruses with pandemic potential, including avian–

human reassortant viruses as tested here, may emerge. Our findings emphasize the need to prepare for potential pandemics caused by influenza viruses possessing H5 HA, and will help individuals conducting surveillance in regions with circulating H5N1 viruses to recognize key residues that predict the pandemic potential of isolates, which will inform the development, production and distribution of effective countermeasures.

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Science 336, Issue 6088, pp. 1534-1541, 22 Jun 2012: DOI: 10.1126/science.1213362

SCIENCE REPORT

Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets

Sander Herfst, Eefje J. A. Schrauwen, Martin Linster, Salin Chutinimitkul, Emmie de Wit , Vincent J. Munster , Erin M. Sorrell, Theo M. Bestebroer, David F. Burke, Derek J. Smith , Guus F. Rimmelzwaan, Albert D. M. E. Osterhaus, Ron A. M. Fouchier

Abstract

Highly pathogenic avian influenza A/H5N1 virus can cause morbidity and mortality in humans but thus far has not acquired the ability to be transmitted by aerosol or respiratory droplet ("airborne transmission") between humans. To address the concern that the virus could acquire this ability under natural conditions, we genetically modified A/H5N1 virus by site-directed mutagenesis and subsequent serial passage in ferrets. The genetically modified A/H5N1 virus acquired mutations during passage in ferrets, ultimately becoming airborne transmissible in ferrets. None of the recipient ferrets died after airborne infection with the mutant A/H5N1 viruses. Four amino acid substitutions in the host receptor-binding protein hemagglutinin, and one in the polymerase complex protein basic polymerase 2, were consistently present in airborne-transmitted viruses. The transmissible viruses were sensitive to the antiviral drug oseltamivir and reacted well with antisera raised against H5 influenza vaccine strains. Thus, avian A/H5N1 influenza viruses can acquire the capacity for airborne transmission between mammals without recombination in an intermediate host and therefore constitute a risk for human pandemic influenza.

…

Bereits vor dem offiziellen Erscheinen dieser beiden Veröffentlichungen gab es eine sehr intensive Diskussion und **äußerst kontrovers geführte Debatte unter Wissenschaftlern und Politikern**, ob solche Forschungsergebnisse überhaupt öffentlich und „gain-of-function"-Forschungsaktivitäten zukünftig nicht gänzlich untersagt werden sollten. Es existierten bereits damals Befürchtungen verbunden mit dem **Albtraum einer möglichen Pandemie, verursacht durch das versehentliche Austreten von künstlich erzeugten Viren aus gentechnischen Laboren, mit unüberschaubarem Gefahrenpotential für die Menschheit**.

Einige Beispiele aus wissenschaftlichen Fachzeitschriften [III.6-III.9], welche einen guten Einblick in die damalige Diskussion vermitteln, seien nachfolgend wiedergegeben:

Nature 480, 421–422 (22 December 2011) doi:10.1038/480421a

***NATURE* | NEWS**

Fears grow over lab-bred flu

Scientists call for stricter biosafety measures for dangerous avian-influenza variants.

Declan Butler

It is a nightmare scenario: a human pandemic caused by the accidental release of a man-made form of the lethal avian influenza virus H5N1.

Yet the risk is all too real. Since September, news has been circulating about two groups of scientists who have reportedly created mutant H5N1 variants that can be transmitted between ferrets merely breathing the same air, generally an indicator that the virus could also spread easily among humans.

The work raises the spectre of a disease that spreads as fast as ordinary seasonal flu, but with a fatality rate akin to wild-type H5N1 — an order of magnitude greater than the mortality rate of roughly 2.5% seen during the catastrophic flu pandemic of 1918.

Until now, debate about the new variants has focused on whether the research poses too great a security risk to be published — even if partially redacted — a question currently under consideration by the US National Science Advisory Board for Biosecurity (NSABB).

A number of scientists argue, however, that the NSABB's deliberations have come far too late. Because further research on the new variants now seems inevitable, a far more important question, they say, is whether the labs that hold samples of the virus — and those who will seek to work with them in the future — have sufficient biosafety protection to make sure it cannot escape.

"This horse is out of the barn," says Richard Ebright, a molecular biologist and biodefence expert at Rutgers University in Piscataway, New Jersey. "At this point, it is utterly futile to be discussing restricting the publication of this information," he adds, pointing out that the results have already been seen by many flu scientists, including referees, and are probably spreading through the flu grapevine faster than a speeding neutrino.

Sources say that one of the studies, led by Ron Fouchier of Erasmus Medical Center in Rotterdam, the Netherlands, has been submitted to *Science*, and that the other, led by Yoshihiro Kawaoka of the University of Wisconsin, Madison, has been sent to *Nature*. (*Nature*'s journalists do not have access to submitted manuscripts or the journal's confidential deliberations on them.) Fouchier also presented his results in September at the annual European Scientific Working Group on Influenza conference in Malta.

The mutant strains were not born out of a reckless desire to push the boundaries of high-risk science, but to gain a better understanding of the potential for avian H5N1 to mutate into a form that can spread easily in humans through coughing or sneezing. Some virologists have suggested that any genetic changes that made it more transmissible would probably blunt its deadliness. The new work seems to contradict that comforting idea. The studies should also

help boost surveillance for similar changes in wild-type strains, and to develop diagnostics, drugs and vaccines.

Both experiments were conducted in labs rated at 'biosafety level 3 (BSL-3) enhanced' (see 'Safety by degrees'). Such labs require scientists to shower and change clothes when leaving the lab, and include other safety features such as negative air pressure and passing exhaust air through high-efficiency particulate air filters. This should be quite sufficient to provide protection against an accidental release of the virus, some virologists say.

"Current biosafety rules are adequate for safely doing such transmission experiments with H5N1 viruses or any other influenza virus," says Peter Palese, a virologist at Mount Sinai School of Medicine in New York.

Requiring the more stringent protocols of BSL-4 facilities would hamper the research needed to develop countermeasures against an H5N1 pandemic, says Masato Tashiro, a virologist at the National Institute of Infectious Diseases in Tokyo, because it would limit the number of researchers able to work with the virus. As such, he believes that the work should be done in BSL-3 enhanced facilities.

High security

But others say that to protect not only the researchers working on the viruses, but also society at large, the new H5N1 variants must be restricted to BSL-4 labs. These labs have far tougher safety and security measures, such as requiring workers to wear positive air pressure suits and undergo more rigorous decontamination; some also have additional security measures, such as video surveillance and bomb-proofing. Corralling this research in BSL-4 facilities would also immediately limit the proliferation of the viruses in labs, because only a few dozen such facilities exist worldwide, says Ebright. Indeed, one regulatory official, who requested anonymity, says that he is most concerned about the H5N1 mutants being handled in BSL-3 labs in countries with weak biosafety cultures or competences.

Deborah Middleton, an H5N1 researcher at the high-containment facilities at the Australian Animal Health Laboratory in Geelong, says that the characteristics of the new variants "fulfil the criteria of a BSL-4 pathogen", adding that she believes they would probably be handled as such in her institution. Indeed, the original experiments to create the viruses should also have been conducted in a BSL-4 facility, argues Hervé Raoul, director of the Jean Meriéux-INSERM BSL-4 lab in Lyons, France.

Past experience suggests that the risk of the new variant H5N1 escaping from a lab is far from negligible. Over the past decade, severe acute respiratory syndrome (SARS) has accidentally infected staff at four high-containment labs in mainland China, Taiwan and Singapore, variously rated as BSL-3 and BSL-4. A US National Research Council report released in September detailed 395 biosafety breaches during work with select agents in the United States between 2003 and 2009 — including seven laboratory-acquired infections — that risked accidental release of dangerous pathogens from high-containment labs.

And the rapid spread of an escaped flu virus would make it more dangerous than other deadly pathogens. "When SARS or BSL-4 agents get out, their potential for transmission on a global basis is quite limited," says Michael Osterholm, who heads the University of Minnesota's Center for Infectious Disease Research and Policy in Minneapolis, and is a member of the NSABB. "Influenza presents a very difficult challenge because if it ever were to escape, it is one that would quickly go round the world."

Fouchier declined to comment on these biosafety issues, saying only that his experiments had been reviewed by authorities in the Netherlands and the United States where "H5N1 virus is a

class-3 agent because antivirals and vaccines are available". Kawaoka did not respond to interview requests.

Some scientists say that they are looking to the World Health Organization (WHO) to provide timely leadership in this biosafety debate. But Gregory Hartl, a spokesman for the WHO in Geneva, Switzerland, says the agency is unable to comment, because it has not yet seen the written studies. Meanwhile, the NSABB has not said when it will publish its advice. In a statement to *Nature*, the US Department of Agriculture said that it (and the US Department of Health and Human Services) will conduct any appropriate technical review of the new H5N1 variants.

Ebright laments that important questions of biosafety and biosecurity are largely left to the discretion of individual researchers. "In the United States, there is only voluntary oversight for biosafety, and with the exception of the select agents rule, there is no oversight of biosecurity," he says. Given the choice, says Middleton, flu researchers often resist working in higher biocontainment levels simply because they would no longer have the convenience of doing their research in BSL-3 labs at their own institutes, and because working in a BSL-4 lab is inherently more difficult.

The situation contrasts sharply with the barrage of legislation to regulate research that involves placing human subjects at risk, notes Ebright, where proposed projects are rigorously reviewed before they can start. "What's remarkable," says Ebright, is that for dual-use research of this type on H5N1, "which puts at risk not one individual but potentially hundreds, thousands or millions of individuals, there is no oversight whatsoever".

On 20 December, the US National Science Advisory Board for Biosecurity (NSABB) released a statement outlining its recommendations to the authors of the two flu studies under review, and to the editors of the journals that are considering publishing them. The statement says:

"Due to the importance of the findings to the public health and research communities, the NSABB recommended that the general conclusions highlighting the novel outcome be published, but that the manuscripts not include the methodological and other details that could enable replication of the experiments by those who would seek to do harm. The NSABB also recommended that language be added to the manuscripts to explain better the goals and potential public health benefits of the research, and to detail the extensive safety and security measures taken to protect laboratory workers and the public."

In response, Science's Editor-in-Chief Bruce Alberts said:

"Science editors will be evaluating how best to proceed. Our response will be heavily dependent upon the further steps taken by the US government to set forth a written, transparent plan to ensure that any information that is omitted from the publication will be provided to all those responsible scientists who request it, as part of their legitimate efforts to improve public health and safety."

In response, Nature's Editor-in-Chief Philip Campbell said:

"We have noted the unprecedented NSABB recommendations that would restrict public access to data and methods and recognise the motivation behind them. It is essential for public health that the full details of any scientific analysis of flu viruses be available to researchers. We are discussing with interested parties how, within the scenario recommended by NSABB, appropriate access to the scientific methods and data could be enabled."

Nature 481, 417–418 (26 January 2012), doi:10.1038/481417a
***NATURE* | NEWS**

Caution urged for mutant flu work

Public-health benefits of controversial research questioned.

Declan Butler

Why would scientists deliberately create a form of the H5N1 avian influenza virus that is probably highly transmissible in humans? In the growing debate about research that has done precisely that, a key question is whether the public-health benefits of the work outweigh the risks of a potential pandemic if the virus escaped from the lab.

For the scientists who have created the mutated strains of the H5N1 virus, the justifications are clear. Surveillance of flu viruses could, they argue, allow health organizations to monitor birds and other animals for the mutations that would provide an early warning of a pandemic and enable authorities to act quickly to contain the virus.

That claim is meeting with scepticism, however. More than a dozen flu experts contacted by *Nature* say they believe that the work opens up important vistas in basic research, and that it sends a valuable warning about the potential for the virus to spark a human pandemic. But they caution that virus surveillance systems are ill-equipped to detect such mutations arising in flu viruses. As such, work on the viruses is unlikely to offer significant, immediate public-health benefits, they say.

That tips the balance of risk–benefit assessment in favour of a cautious approach, says Michael Osterholm, who heads the University of Minnesota's Center for Infectious Disease Research and Policy in Minneapolis, and who is a member of the US National Science Advisory Board for Biosecurity (NSABB).

In a paper submitted to *Science*, Ron Fouchier's team at Erasmus Medical Center in Rotterdam, the Netherlands, found that just five mutations allowed avian H5N1 to spread easily among ferrets, which are a good proxy for how flu behaves in other mammals, including humans. All five mutations have been spotted individually — although not together — in wild viruses. Yoshihiro Kawaoka of the University of Wisconsin-Madison and his colleagues have submitted similar work to *Nature*, which is partially described in an online Comment published this week.

Acting on advice from the NSABB, the US government last month asked *Science* and *Nature* to publish only the broad conclusions of the two studies, and not to reveal the scientific details, in order to limit the risk that uncontrolled proliferation of such research might lead to accidental or intentional release of similar mutant viruses. The journals and the authors have agreed to this redaction, provided that a mechanism is established to disseminate the data to flu researchers and public-health officials on a need-to-know basis. The US government, the World Health Organization (WHO) and other bodies are now trying to put this mechanism together, along with a framework for international oversight of such research.

Last week, in a statement jointly published in *Nature* and *Science*, 39 flu researchers declared a 60-day pause in the creation of lab mutant strains of the H5N1 avian flu virus. The hiatus,

they hope, should give scientists and policy-makers time to debate how such research might best proceed, and what safety measures should be required of labs that handle the virus. The signatories to the statement, including the key authors behind the controversial research, plan to bring together some 50 experts at a WHO-hosted meeting in Geneva, Switzerland, next month to discuss these thorny issues.

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Nature 485, 431–434 (24 May 2012), doi:10.1038/485431a
***NATURE* | NEWS FEATURE**

Bird-flu research: The biosecurity oversight

The fight over mutant flu has thrown the spotlight on a little-known government body that oversees dual-use research. Some are asking if it was up to the task.

Brendan Maher

The packages that started arriving by FedEx on 12 October last year came with strict instructions: protect the information within and destroy it after review. Inside were two manuscripts showing how the deadly H5N1 avian influenza virus could be made to transmit between mammals. The recipients of these packages — eight members of the US National Science Advisory Board for Biosecurity (NSABB) — faced the unenviable task of deciding whether the research was safe to publish.

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Nature 493, 460 (24 January 2013) doi:10.1038/493460a
***NATURE* | NEWS**

Work resumes on lethal flu strains

Study of lab-made viruses a 'public-health responsibility'.

Declan Butler

An international group of scientists this week ended a year-long moratorium on controversial work to engineer potentially deadly strains of the H5N1 avian flu virus in the lab.

Researchers agreed to temporarily halt the work in January 2012, after a fierce row erupted over whether it was safe to publish two papers reporting that the introduction of a handful of mutations enabled the H5N1 virus to spread efficiently between ferrets, a model of flu in mammals. Both papers were eventually published, one in *Nature* and one in *Science*.

Now, in a letter simultaneously published on 23 January by *Nature* and *Science*, the 40 scientists involved say that the moratorium has served its purpose: allowing time for authorities to review the conditions under which the research could be safely conducted and for scientists to explain the public-health benefits of the work. Scientists who now have official approval in their countries to conduct such research "have a public-health responsibility to

resume this important work", the letter states, "because the risk exists in nature that an H5N1 virus capable of transmission in mammals may emerge".

The move follows a large international workshop convened on 17–18 December by the US National Institutes of Health in Bethesda, Maryland, to discuss 'gain-of-function research' — that intended to increase the transmissibility, host range or virulence — in H5N1 viruses, and the development of US rules for stricter oversight of research in this area. The proposed rules require an assessment of, for example, whether the scientific aims of such studies could be addressed using alternative, less-risky approaches, and whether biosafety and biosecurity risks can be adequately mitigated. They are expected to enter into force soon, allowing scientists working in the United States or on US-funded grants to restart such research.

The groups that published the original research have outlined a suite of possible follow-up experiments, including a search for other combinations of mutations that would allow H5N1 to transmit between mammals — which could answer basic-science questions and, they argue, aid efforts to watch for dangerous mutations in the wild. The researchers also suggest extending the studies in ferrets to other mammals, such as guinea pigs, because further evidence of transmission within mammalian species would increase confidence that the mutated virus would transmit between humans.

But the scientific community remains divided on whether the practical benefits of the research outweigh the risks of an accidental or deliberate release of a lab-created flu strain. Ian Lipkin, a specialist on emerging infectious diseases at Columbia University in New York, believes that the risks are high and, worse, that such research may end up being done in labs with insufficient biosafety standards.

The World Health Organization (WHO) posted general biosafety guidelines for such work on its website last July, but Lipkin says such guidelines need to be extended and given more teeth before work restarts. He suggests that this could be done by including them in the WHO's international legally binding treaty on global threats to health — the 2005 International Health Regulations. Ron Fouchier at Erasmus Medical Centre in Rotterdam, the Netherlands, who led the research behind last year's *Science* paper, disagrees. He says that national and institutional procedures have long proved adequate. "If we have to wait until all national governments in the world agree on terms and conditions, we can wait for years if not forever," he says. "That is unacceptable."

But even some who support the lifting of the moratorium have misgivings about the future. Ilaria Capua, a flu researcher at the Veterinary Public Health Institute in Legnaro, Italy, who signed the letter, says that she is less concerned about current work, which is limited to a handful of labs with high biosafety standards, than about the risk of proliferation of such research in the longer term. "This is not a decision for scientists," she says, "it's a decision for policy-makers; do we want to continue to invest public funds in this type of work?"

Im Jahr 2012 gab es zahlreiche internationale Workshops, die sich mit den Risiken der „gain-of-function"-Forschung beschäftigten. Ein **Moratorium für diese Art von Forschung** existierte zunächst für ein Jahr (vom Januar 2012 bis Januar 2013). Im Oktober 2014 verhängte dann die amerikanische Regierung unter Barack Obama ein **Verbot für „gain-of-function"-Forschung in den USA** auf Grund von Sicherheitsbedenken [III.10]:

***NATURE* | NEWS**
22 October 2014

US suspends risky disease research

Government to cease funding gain-of-function studies that make viruses more dangerous, pending a safety assessment.

Sara Reardon

The US government surprised many researchers on 17 October when it announced that it will temporarily stop funding new research that makes certain viruses more deadly or transmissible. The White House Office of Science and Technology Policy is also asking researchers who conduct such 'gain-of-function' experiments on influenza, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) to stop their work until a risk assessment is completed — leaving many unsure of how to proceed.

"I think it's really excellent news," says Marc Lipsitch, an epidemiologist at the Harvard School of Public Health in Boston, Massachusetts, who has long called for more oversight for gain-of-function research. "I think it's common sense to deliberate before you act."

Critics of such work argue that it is unnecessarily dangerous and risks accidentally releasing viruses with pandemic potential — such as an engineered H5N1 influenza virus that easily spreads between ferrets breathing the same air. In 2012, such concerns prompted a global group of flu researchers to halt gain-of-function experiments for a year (see *Nature* http://doi.org/wgx; 2012). The debate reignited in July, after a series of lab accidents involving mishandled pathogens at the US Centers for Disease Control and Prevention in Atlanta, Georgia.

The White House's abrupt move seems to be a response to renewed lobbying by gain-of-function critics who wanted such work suspended and others who sought to evaluate its risks and benefits without disrupting existing research.

Arturo Casadevall, a microbiologist at the Albert Einstein College of Medicine in New York City, calls the plan "a knee-jerk reaction". "There is really no evidence that these experiments are in fact such high risk," he says. "A lot of them are being done by very respectable labs, with lots of precautions in place."

Some researchers are confused by the moratorium's wording. Viruses are always mutating, and Casadevall says that it is difficult to determine how much mutation deliberately created by scientists might be "reasonably anticipated" to make a virus more dangerous — the point at

which the White House states research must stop. The government says that this point will be determined for individual grants in discussions between funding officers and researchers.

One of the most prominent laboratories conducting gain-of-function studies is run by Yoshihiro Kawaoka, a flu researcher at the University of Wisconsin–Madison. In 2012, Kawaoka published a controversial paper reporting airborne transmission of engineered H5N1 flu between ferrets. He has since created an H1N1 flu virus using genes similar to those from the 1918 pandemic strain, to show how such a dangerous flu could emerge. The engineered H1N1 was transmissible in mammals and much more harmful than the natural strain.

Kawaoka says that he plans to comply with the White House directive to halt current research once he understands which of his projects it affects. “I hope that the issues can be discussed openly and constructively so that important research will not be delayed indefinitely,” he says.

But it seems that the freeze could be lengthy. The White House says that it will wait for recommendations from the US National Science Advisory Board for Biosecurity (NSABB) and the National Research Council before deciding whether and how to lift the ban. The groups are expected to finish their work within a year. As *Nature* went to press, the NSABB was set to convene on 22 October, its first meeting in two years. Lipsitch, who will speak at the event, says that he will advocate for the development of an objective risk-assessment tool to evaluate individual research projects. In particular, he says, decision-makers should consider whether a gain-of-function study makes a contribution to a public-health goal, such as the prevention and treatment of flu, that could justify both the risk and the use of money that could be spent on safer research.

“There clearly are going to be instances where gain-of-function research is necessary and appropriate, and there are others where the opposite applies,” says Ian Lipkin, a virologist at Columbia University in New York City. The need to understand the ongoing Ebola outbreak in West Africa and control its spread, for instance, emphasizes the importance of infectious-disease research — as well as the regulation of such work, Lipkin says. Although public worry about Ebola being transferred through the air is unfounded, researchers could make a case for the need to determine how the virus could evolve in nature by engineering a more dangerous version in the lab. “I think we should have some sort of guidelines in place before such experiments are even proposed,” says Lipkin. Yet Ebola is not included in the White House’s research-funding ban, and a spokesperson says that there are no plans to include it on the list.

Kurz vor diesem Verbot bewilligte das NIAID (National Institute of Allergy and Infectious Disease) unter dem Direktor Dr. Anthony Fauci gemeinsam mit dem NIH (National Institute of Health) ein 5-Jahres-Projekt in Höhe von 3,7 Millionen USD mit dem Titel „Understanding the Risk of Bat Coronavirus Emergence“ an Peter Daszak (Ecohealth Alliance, Inc.).

Nachfolgend sind hierzu die Informationen von der Webseite des Drittmittelgebers aufgelistet:

Project Information

2R01AI110964-06

Project Number: 2R01AI110964-06 **Contact PI / Project Leader:** DASZAK, PETER

Title: UNDERSTANDING THE RISK OF BAT CORONAVIRUS EMERGENCE **Awardee Organization:** ECOHEALTH ALLIANCE, INC.

Total project funding amount for **6** projects is **$3,748,715***

** Only NIH,CDC,and FDA funding data.*

Page 1 of 1

Project Number	Sub #	Project Title	Contact PI / Project Leader	Organization	FY	Admin IC	Funding IC	FY Cost by IC	Total
2R01AI110964-06		UNDERSTANDING THE RISK OF BAT CORONAVIRUS EMERGENCE	DASZAK, PETER	ECOHEALTH ALLIANCE, INC.	2019	NIAID	NIAID	$661,980	
5R01AI110964-05		UNDERSTANDING THE RISK OF BAT CORONAVIRUS EMERGENCE	DASZAK, PETER	ECOHEALTH ALLIANCE, INC.	2018	NIAID	NIAID	$581,646	
5R01AI110964-04		UNDERSTANDING THE RISK OF BAT CORONAVIRUS EMERGENCE	DASZAK, PETER	ECOHEALTH ALLIANCE, INC.	2017	NIAID	NIAID	$597,112	
5R01AI110964-03		UNDERSTANDING THE RISK OF BAT CORONAVIRUS EMERGENCE	DASZAK, PETER	ECOHEALTH ALLIANCE, INC.	2016	NIAID	NIAID	$611,090	
5R01AI110964-02		UNDERSTANDING THE RISK OF BAT CORONAVIRUS EMERGENCE	DASZAK, PETER	ECOHEALTH ALLIANCE, INC.	2015	NIAID	NIAID	$630,445	
1R01AI110964-01		UNDERSTANDING THE RISK OF BAT CORONAVIRUS EMERGENCE	DASZAK, PETER	ECOHEALTH ALLIANCE, INC.	2014	NIAID	NIAID	$666,442	

Project Information

2R01AI110964-06

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

Abstract Text:

Project Summary: Understanding the Risk of Bat Coronavirus Emergence Novel zoonotic, bat-origin CoVs are a significant threat to global health and food security, as the cause of SARS in China in 2002, the ongoing outbreak of MERS, and of a newly emerged Swine Acute Diarrhea Syndrome in China. In a previous R01 we found that bats in southern China harbor an extraordinary diversity of SARSr-CoVs, some of which can use human ACE2 to enter cells, infect humanized mouse models causing SARS-like illness, and evade available therapies or vaccines. We found that people living close to bat habitats are the primary risk groups for spillover, that at one site diverse SARSr-CoVs exist that contain every genetic element of the SARS-CoV genome, and identified serological evidence of human exposure among people living nearby. These findings have led to 18 published peer-reviewed papers, including two papers in Nature, and a review in Cell. Yet salient questions remain on the origin, diversity, capacity to cause illness, and risk of spillover of these viruses. In this R01 renewal we will address these issues through 3 specific aims: Aim 1. Characterize the diversity and distribution of high spillover-risk SARSr-CoVs in bats in southern China. We will use phylogeographic and viral discovery curve analyses to target additional bat sample collection and molecular CoV screening to fill in gaps in our previous sampling and fully characterize natural SARSr-CoV diversity in southern China. We will sequence receptor binding domains (spike proteins) to identify viruses with the highest potential for spillover which we will include in our experimental investigations (Aim 3). Aim 2. Community, and clinic-based syndromic, surveillance to capture SARSr-CoV spillover, routes of exposure and potential public health consequences. We will conduct biological-behavioral surveillance in high-risk populations, with known bat contact, in community and clinical settings to 1) identify risk factors for serological and PCR evidence of bat SARSr-CoVs; & 2) assess possible health effects of SARSr-CoVs infection in people. We will analyze bat-CoV serology against human-wildlife contact and exposure data to quantify risk factors and health impacts of SARSr-CoV spillover. Aim 3. In vitro and in vivo characterization of SARSr-CoV spillover risk, coupled with spatial and phylogenetic analyses to identify the regions and viruses of public health concern. We will use S protein sequence data, infectious clone technology, in vitro and in vivo infection experiments and analysis of receptor binding to test the hypothesis that % divergence thresholds in S protein sequences predict spillover potential. We will combine these data with bat host distribution, viral diversity and phylogeny, human survey of risk behaviors and illness, and serology to identify SARSr-CoV spillover risk hotspots across southern China. Together these data and analyses will be critical for the future development of public health interventions and enhanced surveillance to prevent the re-emergence of SARS or the emergence of a novel SARSr-CoV.

Public Health Relevance Statement:

Program Director/Principal Investigator: Daszak, Peter Renewal: Understanding the Risk of Bat Coronavirus Emergence Project Narrative Most emerging human viruses come from wildlife, and these represent a significant threat to public health and biosecurity in the US and globally, as was demonstrated by the SARS coronavirus pandemic of 2002-03. This project seeks to understand what factors allow coronaviruses, including close relatives to

SARS, to evolve and jump into the human population by studying viral diversity in their animal reservoirs (bats), surveying people that live in high-risk communities in China for evidence of bat-coronavirus infection, and conducting laboratory experiments to analyze and predict which newly-discovered viruses pose the greatest threat to human health.

NIH Spending Category:

Biodefense; Biotechnology; Clinical Research; Emerging Infectious Diseases; Infectious Diseases; Lung; Pneumonia; Pneumonia & Influenza; Prevention; Rare Diseases

Project Terms:

Acute; Acute Diarrhea; Address; Amino Acid Sequence; Animals; base; Behavior; Behavioral; Biological; biosecurity; Cells; China; Chiroptera; Clinic; Clinic Visits; Clinical; Communities; community clinic; Coronavirus; Coronavirus Infections; Coupled; Data; Data Analyses; Development; Disease Outbreaks; epidemiologic data; Epithelial Cells; experimental study; exposed human population; exposure route; Exposure to; Family suidae; follow-up; food security; Future; genetic element; Genome; Geographic Distribution; Geography; global health; Habitats; Health; high risk; high risk population; Human; human population study; humanized mouse; In Vitro; in vivo; Individual; Infection; Influenza; Investigation; laboratory experiment; Lead; Maps; Middle East Respiratory Syndrome Coronavirus; Modeling; Molecular; Monoclonal Antibodies; mouse model; Nature; novel; pandemic disease; Paper; Patients; Phylogenetic Analysis; Phylogeny; Prevalence; prevent; Principal Investigator; programs; Proteins; Public Health; public health intervention; Publishing Peer Reviews; Questionnaires; Readiness; Reagent; receptor binding; recombinant virus; respiratory; Risk; Risk Behaviors; Risk Factors; sample collection; Sampling; SARS coronavirus; screening; Serologic tests; Serological; seropositive; Severe Acute Respiratory Syndrome; Site; Surveys; Syndrome; syndromic surveillance; Technology; Testing; Therapeutic Intervention; Therapeutic Monoclonal Antibodies; therapeutic vaccine; Time; trait; Transgenic Organisms; Vaccines; Viral; virology; Virus; Work; Zoonoses

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Diese Forschungsaktivitäten von Peter Daszak wurden in der Zeit des Verbots der „gain-of-function"-Forschung durch die Barack-Regierung nicht eingestellt, sondern weitgehend durch die Kooperation mit der Forschergruppe um Zheng-Li Shi an das „Wuhan Institute of Virology" ausgelagert [IV.17]. Dies geschah im Wissen und im Einvernehmen mit dem NIAID-Direktor Dr. Anthony Fauci.

Tatsächlich sind wohl sehr viel mehr Gelder für „gain-of-function" Experimente an Peter Daszak und seine „EcoHealth Alliance" geflossen, wie jüngst öffentlich wurde [IV.18]:

Independent Science News
FOR FOOD AND AGRICULTURE

BIOTECHNOLOGY, HEALTH, NEWS DECEMBER 16, 2020

Peter Daszak's EcoHealth Alliance Has Hidden Almost $40 Million In Pentagon Funding And Militarized Pandemic Science

Sam Husseini

"Pandemics are like terrorist attacks: We know roughly where they originate and what's responsible for them, but we don't know exactly when the next one will happen. They need to be handled the same way — by identifying all possible sources and dismantling those before the next pandemic strikes."

This statement was written in the *New York Times* earlier this year by Peter Daszak. Daszak is the longtime president of the EcoHealth Alliance, a New York-based non-profit whose claimed focus is pandemic prevention. But the EcoHealth Alliance, it turns out, is at the very centre of the COVID-19 pandemic in many ways.

To depict the pandemic in such militarized terms is, for Daszak, a commonplace. In an Oct. 7 online talk organized by Columbia University's School of International and Public Affairs, Daszak presented a slide titled "Donald Rumsfeld's Prescient Speech":
"There are known knowns; there are things we know that we know. There are known unknowns; that is to say, there are things that we know we don't know. But there are also unknown unknowns — there are things we don't know we don't know." (This Rumsfeld quote is in fact from a news conference).

In the subsequent online discussion, Daszak emphasized the parallels between his own crusade and Rumsfeld's, since, according to Daszak, the "potential for unknown attacks" is "the same for viruses".

Daszak then proceeded with a not terribly subtle pitch for over a billion dollars. This money would support a fledgling virus hunting and surveillance project of his, the Global Virome Project — a "doable project" he assured watchers — given the cost of the pandemic to governments and various industries.

Also on the video was Columbia University professor Jeffrey Sachs. Sachs is a former special advisor to the UN, the former head of the Millennium Villages Project, and was recently appointed Chair of the newly-formed EAT Lancet Commission on the pandemic. In September, Sachs' commission named Daszak to head up its committee on the pandemic's origins. Daszak is also on the WHO's committee to investigate the pandemic's origin. He is the only individual on both committees.

These leadership positions are not the only reason why Peter Daszak is such a central figure in the COVID-19 pandemic, however. His appointment dismayed many of those who are aware that Daszak's EcoHealth Alliance funded bat coronavirus research, including virus collection, at the Wuhan Institute for Virology (WIV) and thus could themselves be directly implicated in the outbreak.

For his part, Daszak has repeatedly dismissed the notion that the pandemic could have a lab origin. In fact, a recent FOIA by the transparency group U.S. Right To Know revealed that Peter Daszak drafted an influential multi-author letter published on February 18 in the Lancet. That letter dismissed lab origin hypothesese as "conspiracy theory." Daszak was revealed to have orchestrated the letter such as to "avoid the appearance of a political statement."

…

Wie aus dem oben ausschnittsweise wiedergegebenen Artikel zu entnehmen ist, wurde **Peter Daszak zum Mitglied der von der WHO eingesetzten Untersuchungskommission zur Klärung der Frage nach dem Ursprung der Coronavirus-Pandemie ernannt**. Dies hat in Wissenschaftlerkreisen für Unverständnis gesorgt, da hier ein **eindeutiger Interessenkonflikt** vorliegt, zumal Peter Daszak selbst über Jahre in die „gain-of-function"-Forschung am „Wuhan Institute of Virology" involviert war (siehe z. B. [III.11]).

In Europa gab es ebenfalls eine intensive Auseinandersetzung zwischen Wissenschaftlern, welche „gain-of-function" Experimente befürworteten und weiter betreiben wollten und solchen, die darin ein zu hohes Gefahrenpotential hinsichtlich der Möglichkeit einer weltweiten Pandemie sahen. Die beiden folgenden Artikel vermitteln beispielhaft einen Eindruck von der damaligen Diskussion in Europa ([III.12], [III.13]):

Nature 503, 19 (07 November 2013), doi:10.1038/503019a

***NATURE* | NEWS**

Pathogen-research laws queried

Scientists fear EU biosafety rules could complicate publication of work on infectious diseases.

Declan Butler

Leading virologists have written to the president of the European Commission to urge him to clarify how laws designed to curb the proliferation of biological weapons apply to the publication of research on dangerous pathogens. The move by the European Society for Virology (ESV) comes after a Dutch court in September upheld a government order that scientists who engineered forms of H5N1 avian influenza to make them transmissible between mammals needed to seek an export permit before publishing such work.

The ESV's five-page letter to José Manuel Barroso, dated 16 October, warns that the court ruling sets an unwelcome precedent. H5N1 is just one of more than 100 dangerous human, animal and plant pathogens and toxins that fall under European Union (EU) export-control legislation from 2009. This means, say the virologists, that any EU scientist who works on one of the listed pathogens could be forced to apply for an export permit before publishing their research.

They write that to better inform courts and policy-makers on scientific issues related to biosecurity laws, the European Commission should consider creating an equivalent of the US National Science Advisory Board for Biosecurity — an independent committee in Bethesda, Maryland, that advises on issues of biosecurity and dual-use research (findings that could be adapted for harmful purposes). …

***NATURE* | NEWS**

Nature doi:10.1038/nature.2013.14429, 20 December 2013

Scientists call for urgent talks on mutant-flu research in Europe

Benefits and risks of 'gain-of-function' work must be evaluated, they say.

Heidi Ledford

A group of over 50 researchers has called on the European Commission to hold a scientific briefing on research that involves engineering microbes to make them more deadly.

In an 18 December letter to European Commission president José Manuel Barroso, the scientists — including representatives from the non-profit Foundation for Vaccine Research in Washington DC — urged the commission to organize the briefing, and to formally evaluate the risks and benefits of such 'gain-of-function' research.

"Gain-of-function research into highly pathogenic microbes with pandemic potential has global implications for public health," says Ian Lipkin, an infectious disease researcher at Columbia University in New York, who is one of the signatories of the letter. "We are not seeking to shut down all gain-of-function research, but asking that stakeholders meet to establish guidelines for doing it."

The recent controversy over gain-of-function studies began in 2011 when Ron Fouchier, a virologist at the Erasmus Medical Center in Rotterdam, the Netherlands, sought to publish a study detailing how his team had engineered H5N1 avian influenza strains that could infect ferrets in seperate cages through the air. Avian flu infections can be deadly for humans, but presently circulating strains of the virus are specific to birds and rarely infect mammals.

Proponents of the work say that it provides insight into how avian flu strains could naturally evolve to become more dangerous — results that could inform flu surveillance as well as vaccine and drug development. Opponents say that the work is too risky, because it involves engineering a deadly form of flu that could escape from research facilities or, in the wrong hands, could be intentionally released to cause a pandemic.

In October, the European Society for Virology (ESV) wrote its own letter to the European Commission, voicing concern that the Dutch government had used European export regulations to regulate the dissemination of Fouchier's research results, pushing him to apply

for an export licence to publish his study in the journal *Science*. This approach to regulating sensitive research is inappropriate, argued ESV president Giorgio Palù, a virologist at the University of Padua in Italy, on behalf of the society. The letter urged the commission to evaluate alternative means of overseeing such work.

Although the 18 December statement from scientists and the Foundation for Vaccine Research is framed as a response to the ESV's October letter, it explicitly does not tackle the issue of export controls; instead, it argues against some of the purported benefits of Fouchier's research. The work does not aid vaccine or drug development, says virologist Simon Wain-Hobson of the Pasteur Institute in Paris, who is chair of the foundation and a co-author of the letter, in part because flu outbreaks are impossible to predict. He also disputes claims that viruses similar to those engineered by Fouchier's laboratory are already appearing in the field.

Palù says that the letter from Wain-Hobson and signatories misses the crux of the ESV's concerns. "We don't want to enter into the scientific quarrel," says Palù. "Our intent was just to say that the export legislation is not the proper way to deal with this research."

But Wain-Hobson says that it is important for regulators to be informed about the scientific debate. "We're not against the science, and we're not against working on deadly pathogens," he explains. "But this is different — this research is making something new."

And although most of the discussion so far has centred on flu, Wain-Hobson argues that it is time for regulators to think ahead to similar studies of other pathogens. "Flu was just the match that set off the barrel of gunpowder," he says. "This research has been going on for more than ten years — the technology is powerful now."

…

Wie aus dem oben wiedergegebenen Bericht hervorgeht, hatte sich am 18. Dezember 2013 eine Gruppe von 56 Wissenschaftlern an den damaligen Präsidenten der Europäischen Kommission, José Manuel Barroso, gewandt mit der Bitte, die Gefahren verbunden mit gentechnisch veränderten Viren, welche für den Menschen tödlicher sein können als natürlich vorkommende Viren, zu evaluieren. **Auf Grund der Bedeutung dieses Schreibens für die politische Diskussion um „gain-of-function"-Forschung in Europa soll dieser Brief im Folgenden in voller Länge wiedergegeben werden:**

The FOUNDATION for VACCINE RESEARCH

WORKING TO SECURE OUR CHILDREN'S FUTURE

December 18, 2013

Mr. José Manuel Barroso
President of the European Commission
Berlaymont Building
200 Rue de la Loi, 13th Floor
1049 Brussels, Belgium

cc:
Mrs. Viviane Reding, Vice President of the European Commission
Mrs. Máire Geoghegan-Quinn, Commissioner for Research, Innovation and Science
Mr. Tonio Borg, Commissioner for Health and Consumer Policy
Mr. Neven Mimica, Commissioner for Consumer Protection

RESPONSE TO LETTER BY THE EUROPEAN SOCIETY FOR VIROLOGY
ON "GAIN-OF-FUNCTION" INFLUENZA RESEARCH
AND
PROPOSAL TO ORGANIZE A SCIENTIFIC BRIEFING
FOR THE EUROPEAN COMMISSION &
CONDUCT A COMPREHENSIVE RISK-BENEFIT ASSESSMENT

Dear President Barroso,

We are writing to you on behalf of the Foundation for Vaccine Research and the 56 undersigned scientists to express our concern about a recent letter sent to you by the European Society for Virology (ESV). Several members of our group and the undersigned are members of the ESV.

We would like to correct some of the scientific misstatements in that letter. We would also like to propose: (1) a scientific briefing for the European Commission on so-called "gain-of-function" research, more properly defined as research to increase the pathogenicity, transmissibility, or alter the host range of highly pathogenic microbes with pandemic potential, including, but not limited to, influenza A viruses such as H5N1 and H7N9, and (2) consideration of a comprehensive risk-benefit assessment of this type of research. It is overdue that the risks associated with gain-of-function research be rigorously assessed and quantified. Researchers stand poised to conduct gain-of-function experiments with the SARS coronavirus and a host of other microbes with pandemic potential.

Misstatements
We would like to rebut some of the misleading scientific statements contained in ESV's letter of October 16 about EU laws, rules, and regulations governing the submission of manuscripts to international scientific journals, especially the need for export licenses for papers describing the results of so-called "gain-of-function" transmission experiments with highly pathogenic avian influenza H5N1 viruses conducted by Dr. Ron Fouchier at the Erasmus Medical Center in Rotterdam (*1*).

We do not take a position on the issue of export licenses, although we do understand the Dutch government's concern.

Regarding the scientific misstatements in ESV's letter, we take particular exception to the following sentence:

It's time. *Campaign for an HIV, TB and Malaria Vaccine*
601 Pennsylvania Avenue NW, Suite 900, South Building, Washington, DC 20004
Tel +1 202 220 3008 • Fax +1 202 639 8238 • www.vaccinefoundation.org • www.itstimecampaign.org
THE IT'S TIME CAMPAIGN IS A PROGRAM OF THE FOUNDATION *for* VACCINE RESEARCH

"However, it has to be mentioned that, in this specific case, **the "gain of function" was used to reproduce what nature already selected** (as demonstrated by sequencing of field mutants) with the variation that the aim of the study was to predict/anticipate biological evolution and to provide us with critical information to specify preventive and therapeutic measures, e.g., the improved surveillance and proper evaluation of candidate vaccines and drugs."

First, the statement that gain-of-function was used "to reproduce what nature already selected" is incorrect. Nature has *not* already selected an H5N1 virus that is readily transmissible between mammals. Highly pathogenic avian influenza H5N1 viruses are primarily transmitted between birds, not between mammals, and are only inefficiently transmitted between humans, if at all.

Fouchier *et al.* created novel mutant strains of H5N1 viruses that are genetically different from *any* known H5N1 virus strain found in nature, and that, importantly, have a specific property that makes them more dangerous than *any* known natural H5N1 virus, i.e., they are efficiently transmitted between mammals via respiratory droplets. Using ferrets, the preferred animal model for research with influenza A viruses, Fouchier and colleagues employed laboratory techniques that do *not* exist in nature, notably laboratory-directed, so-called "forced evolution," to see "what it would take" for H5N1 viruses to become transmissible via the aerosol route. Naturally occurring H5N1 viruses are highly virulent for humans – killing as many as 60% of those with known infections – but are not readily transmissible between mammals, including between humans. The sole purpose of the experiments in question was to generate H5N1 viruses that could be transmitted between mammals as readily as seasonal flu via respiratory droplets, i.e., by coughing or sneezing.

Despite intensive field surveillance conducted by national health authorities, government agencies, local and regional disease surveillance networks in Southeast Asia and elsewhere over a period of 16 years, *there is no evidence that efficiently mammalian-transmissible H5N1 viruses have ever emerged naturally in the wild*. Whereas it is correct that some individual mutations and some subsets of mutations identified by Fouchier *et al*., after repeated passage of H5N1 viruses between ferrets, have been found in nature, these mutations in different genetic backgrounds do *not suffice* to confer efficient binding to mammalian receptors. Additional mutations are necessary (*2*). The only unambiguous way to find out whether a field isolate is capable of aerosol transmission between ferrets is to perform a transmission experiment. Furthermore, whether the results of such experiments could extend to humans is unknown. Mapping mutations is *not* a surrogate marker for transmission. In summary, the statement that "gain-of-function" was used to reproduce "what nature already selected (as demonstrated by sequencing of field mutants)" is simply untrue.

Second, there is no compelling evidence or scientific basis for the assertion that gain-of-function research conducted by Fouchier *et al.* – or, indeed, by any other group (*3,4*) – can help us "predict or anticipate biological evolution and provide us with critical information to specify preventive and therapeutic measures, e.g., the improved surveillance and proper evaluation of candidate vaccines and drugs."

Given the highly unpredictable nature of influenza viruses, it is not possible to predict or anticipate biological evolution with any certainty and thereby to predict or anticipate the next influenza outbreak (*5-13*). Indeed, the track record in this domain is extremely poor. Evolutionary pressures result in multiple reassortment and mutational events that follow no clear pathway and are impossible to predict or associate with a specific outcome in any population (*11,14*). The experimental design of these influenza gain-of-function experiments is such that the outcome is strongly influenced by the experimenter. Hence, the probability of anticipating nature is very low indeed.

Third, there is no scientific basis for the claim that gain-of-function research may lead to the development of more effective vaccines, a major argument advanced by proponents of gain-of-function research, by providing "critical information for the proper evaluation of candidate vaccines."

Such a claim fails to appreciate the complexities of how influenza vaccines are developed (*14*). Gain-of-function studies on highly pathogenic avian influenza H5N1 viruses conducted to date in Europe, North America and Asia have contributed nothing so far to the development of new vaccines or prophylactic measures. The choice of H5N1 virus with which to make a vaccine is based on immunogenicity, not on virulence. Vaccine developers will need the actual H5N1 pandemic strain that is spreading in order to make that selection, rather than one obtained via gain-of-function experiments. Influenza vaccines have been manufactured for many decades based on the isolation of a virus with a specific pandemic potential or seasonal prevalence. It has so far been necessary to produce a new vaccine to protect against every influenza virus suspected of pandemic or seasonal threat, irrespective of the structure of the viral hemagglutinin or detected mutations in its amino acid sequence. Moreover, it is unlikely that any manufacturer would start epidemic vaccine production without knowing with certainty which strain to use. In this context, it is difficult to see how gain-of-function research can lead to more effective vaccines, at least in the near future.

Fourth, there is little evidence for the claim that gain-of-function research can provide "critical information for the proper evaluation of candidate drugs." Our 25 years of experience with HIV-1, another virus with a high propensity to mutate, has taught us that the only way to evaluate the efficacy of candidate antiviral drugs for RNA viruses is to conduct clinical trials. If ever H5N1 influenza went pandemic, we could only hope that the strain would be sensitive to some of the existing anti-influenza drugs. It would take several years to evaluate and get a new antiviral drug to market.

Taken together, these bold yet misleading claims made by the European Society for Virology are claims that have been repeatedly refuted (*14,15*). These misstatements weaken their case and should be corrected.

The power of synthetic biology has received considerable attention in recent years. Synthetic biologists do not deliberately try to increase the danger level of pathogens, toxins or the environment in which we live. It would be of the utmost concern if they did. By contrast, the influenza gain-of-function transmission experiments conducted by Fouchier *et al.* are notable for their *deliberate intent* to make a pathogen more dangerous for humanity. To justify such experiments, there must be extraordinary practical benefits that outweigh the risk of accidental release.

Despite significant improvements in safety conditions in research laboratories during the last decade, there is no such thing as "zero" risk. In this context, the potential for accidental release of a hazardous pathogen is real, not hypothetical, as demonstrated by an alarming increase in the number of potential and actual release events in laboratories working with high-threat pathogens (*16*). The number of potential and actual release events in Europe has not been recorded. However, between 2003 and 2009 the United States Centers for Disease Control and Prevention (CDC) recorded 395 domestic potential release events in laboratories working with high-threat pathogens (*17*). In Asia, three cases of laboratory-acquired SARS infections were reported in 2003, one in Singapore, one in Taiwan, and one in Beijing (*18-20*). These laboratory-acquired infections occurred after the WHO declared the end of the SARS outbreak. Moreover, the Beijing SARS infections spread beyond the laboratory into the community before the infections were detected and stopped.

Accidents do happen even in high-containment laboratories. The accidental release of even an attenuated virus strain can have global consequences. We need look no further than the re-emergence of the H1N1 influenza virus in 1977, after a 20-year hiatus. Most scientists who have investigated the 1977 outbreak concluded that the re-emergence was the result of an accidental release from a laboratory source (*21*), most likely from a laboratory in the former Soviet Union that was working on a live-attenuated H1N1 virus vaccine. Although the virus was an attenuated strain, it was nevertheless highly transmissible and went global, causing an epidemic, albeit a mild one.

For this reason, we are primarily concerned about the safety of gain-of-function research and the consequences of an accidental release. We are in a situation where the probabilities of a laboratory accident that leads to global spread of an escaped mutated virus are small but finite, while the impact of global spread could be catastrophic. Many other types of research on the biology of influenza viruses are possible that could provide crucial scientific information without creating a virus capable of transmission in mammals – that is, without the risk entailed by the experiments of Fouchier *et al*. In contrast to the substantial risks of gain-of-function research, the benefits of such research are hypothetical at best. There is little to no pre-existing immunity in the general population to the H5N1 virus, and none to the H7N9 virus discovered earlier this year in China. Moreover, there are only limited quantities of H5N1 vaccines readily available and stockpiled (vaccines which may not be a good match), and there is no licensed H7N9 vaccine. As a result, the accidental or deliberate release of an artificial, laboratory-generated, human-transmissible H5N1 or H7N9 virus into the community could be difficult or impossible to contain. There are few situations where a small but finite risk could, in the event of an accidental release, have such far-reaching consequences.

Proposals

1. A scientific briefing for the European Commission
Since the controversy surrounding H5N1 – and now H7N9 (*22*) – gain-of-function research is a complex scientific issue, and since the consequences of an accidental release affect the entire population of the European Union, we would like to propose that a scientific briefing be organized for the European Commission.

Such a briefing could be prepared at relatively short notice. The purpose of the briefing would be to inform Commissioners and their staff – and Members of the European Parliament, if desired – about gain-of-function research, presenting arguments in favour of and against the research. Given this information, Commissioners and MEPs would be in a better position to determine whether the risks are outweighed by the potential benefits, e.g., in predicting a pandemic or developing more effective vaccines. The National Academy of Sciences in Washington will shortly be debating these topics in a symposium. It is vitally important that European voices be heard and that Europeans participate in this debate. Indeed, there is an opportunity for Europe to take the lead on this issue.

The Foundation for Vaccine Research has the experience and the expertise to organize such a briefing, as one of the organizers and the moving force behind a 2-day international symposium, "H5N1 Research: Biosafety, Biosecurity and Bioethics," held at the Royal Society in London on April 3-4, 2012. The symposium was open to the public and webcast live. It was the first and remains the largest meeting organized to date on this topic. We would be happy to follow up with a detailed proposal regarding how such a scientific briefing could be organized for the European Commission.

2. A comprehensive risk-benefit assessment of gain-of-function research

Despite two years of controversy surrounding gain-of-function research and the lack of a scientific consensus, we still do not have a comprehensive risk-benefit analysis, as we would have hoped for on such an important topic. Many organizations, groups and individuals in Europe and the United States, including the journal *Nature*, have called for an independent risk-benefit assessment, but so far without success (*9,23*). A rigorous, comprehensive risk-benefit assessment could help determine whether the unique risks to human life posed by these sorts of experiments are balanced by unique public health benefits which could not be achieved by alternative, safe scientific approaches. Since scientists do not agree on the scientific merits of gain-of-function research, it will be hard to quantify the benefits. However, the risks *can* be quantified, as has been suggested in several preliminary studies (*24-28*). A comprehensive risk assessment would be able to quantify the risks of a release of a mutated virus into the community in terms of the loss of human life, the cost to health care systems, the financial and socio-economic costs, and the liability costs. These are man-made viruses and so liability becomes a novel issue, absent in the case of a naturally occurring epidemic.

Given your position as President of the European Commission, the combined experience and expertise of Commissioners and their staff, and the resources at your command, the Commission could make an important and immediate contribution by calling for a rigorous, comprehensive risk-benefit assessment of gain-of-function research to inform decision makers in Europe and worldwide. We have explored the feasibility of conducting such an assessment and would be happy to follow up with your staff with a detailed proposal regarding how an assessment could be undertaken.

Next steps

We would be honoured to follow up directly with Science Commissioner, Máire Geoghegan-Quinn, and her staff, on how a scientific briefing for the European Commission could be organized at short notice, as well as how a comprehensive risk-benefit analysis could be conducted.

We look forward to hearing from you,

Sincerely,

Professor Simon Wain-Hobson, D.Phil.
Chief, Molecular Retrovirology Unit
Department of Virology
Institut Pasteur, Paris
FVR Board Chair

Dieses Schreiben zeigt eindrücklich auf, wie unterschiedlich selbst unter Virologen die Einschätzung des Gefahrenpotentials von „gain-of-function"-Forschung bereits damals war. Unter den 56 Unterzeichnern des Schreibens waren u.a. die **drei Nobelpreisträger Harald zur Hausen, Richard Ernst und Sir Richard Roberts.**

Festzuhalten bleibt – unabhängig von dem jeweiligen Standpunkt – dass das Coronaviren-Forschungsprogramm die gegenwärtige Pandemie NICHT verhindert hat. Man muss sich also berechtigterweise fragen, welchen Sinn diese Hochrisikoforschung tatsächlich hat neben der Tatsache, dass diese Forschung selbst ein sehr großes Gefahrenpotential für die Weltbevölkerung darstellt.

Wie berechtigt die Bedenken der Unterzeichner dieses Schreiben waren, wird eindrücklich belegt durch die hohe Zahl an Unfällen in biotechnologischen Laboren selbst der höchsten Sicherheitsstufe. Dies soll Gegenstand des nachfolgenden Kapitels sein.

5 Wie sicher sind Hochsicherheitslabore zur Forschung an gefährlichen Krankheitserregern?

Tatsächlich ist die Gefahr, welche durch biotechnologische Labore selbst der höchsten Sicherheitsstufe ausgehen, nicht zu unterschätzen, was zahlreiche Berichte der Vergangenheit und der jüngsten Gegenwart in verschiedenen Ländern belegen. Zwei Beispiele von solchen Berichten sind nachfolgend wiedergegeben ([III.14], [IV.19]):

Nature 510, 443 (26 June 2014), doi:10.1038/510443a

***NATURE* | EDITORIAL**

Biosafety in the balance

An accident with anthrax demonstrates that pathogen research always carries a risk of release — and highlights the need for rigorous scrutiny of gain-of-function flu studies.

The news last week of an accident involving live anthrax bacteria at the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, is troubling. Some 84 workers were potentially exposed to the deadly Ames strain at three CDC labs. But the incident will cause much wider ripples: it highlights the risks of the current proliferation of biocontainment labs and work on dangerous pathogens. If an accident can happen at the CDC, then it can happen anywhere.

Details are sparse, but it seems that the anthrax was being inactivated in a biosafety-level-3 (BSL-3) high-containment lab so that it could be studied at the three BSL-2 labs. But live bacteria survived the inactivation step, and were not detected before samples were sent out. The CDC considers the risk that the exposed workers have been infected to be low, and all have been offered protective antibiotics.

Such lab accidents are fortunately not commonplace. A CDC analysis in 2012 reported, for example, that there were 727 incidents of theft, loss or release of Select Agents and Toxins in the United States between 2004 and 2010, resulting in 11 laboratory-acquired infections and no secondary transmission (R. D. Henkel *et al*. *Appl. Biosafety* **17,** 171–180; 2012). Anthrax is contracted by direct exposure to spores, and does not spread between people. Much more potentially dangerous are lab accidents involving agents that do. It is impossible to read about the CDC incident and not breathe a large sigh of relief that it did not involve a novel engineered pandemic influenza strain.

Groups led by Ron Fouchier of the Erasmus Medical Center in Rotterdam, the Netherlands, and Yoshihiro Kawaoka of the University of Wisconsin–Madison created a storm in late 2011 when they artificially engineered potentially pandemic forms of the H5N1 avian flu virus. In January last year, researchers ended a voluntary 12-month moratorium on such gain-of-function flu research, which can increase the host range, transmissibility or virulence of viruses (see *Nature* **493,** 460; 2013), and work resumed.

This month, Kawaoka's group reported that it had engineered a *de novo* flu virus from wild-avian-flu-strain genes that coded for proteins similar to those in the 1918 pandemic virus (T. Watanabe *Cell Host Microbe* **15,** 692–705; 2014). The researchers were able to make a virulent version that could transmit between ferrets, and they concluded that a 1918-like virus could therefore emerge from wild avian flu viruses.

In the century since the 1918 flu hit, no similar pandemic variant has emerged despite wild animal flu viruses mutating and reassorting incessantly. The 1918 H1N1 virus was reconstructed in 2005, but human immunity to it became widespread following the 2009 H1N1 pandemic. There are no mammalian-transmissible 1918-like avian flus in the wild; the only ones that exist are Kawaoka's team's engineered strains.

"The idea of an accidental release of a potentially pandemic flu virus cannot be completely written off."

Researchers such as Kawaoka and Fouchier argue that by engineering mutant viruses in the lab, they can identify mutations and traits that allow the pathogens to spread between mammals. This in turn, they argue, allows assessment of the pandemic potential of animal-flu viruses. In the long term, such experiments could help to elucidate the mechanisms of virus transmissibility and pathogenicity. But their shorter-term public-health benefits have been overstated. The risks and benefits must therefore be carefully weighed, and rigorous oversight is needed to ensure that such work is done only at facilities with the highest standards of biosafety.

Other scientists argue that the concept of predicting the pandemic potential of flu viruses from mutations, although appealing, is simplistic. They say that the identified mutations are but a handful out of millions of possible combinations, many of which might also allow mammalian transmission. They argue that mutations in specific proteins cannot reliably predict traits, and that outcomes depend on interactions between various other background genetic changes throughout the virus.

These points were highlighted in a paper in *PLoS Medicine* last month (M. Lipsitch and A. P. Galvani *PLoS Med.* **11,** e1001646; 2014), and in a letter by 56 leading virologists, infectious-disease specialists and public-health experts to European Commission president José Manuel Barroso last December (see *Nature* http://doi.org/tdb; 2013). They also question the claimed public-health benefits of such research, and argue that similar information could be obtained through safer experiments. Opponents of gain-of-function flu research call, in particular, for more rigorous risk–benefit assessments. The CDC accident shows that, should such research proliferate, the idea of an accidental release of a potentially pandemic flu virus cannot be completely written off. This demands that such research proposals receive the utmost scrutiny.

A US Government Accountability Office report released in February last year expressed concern that the proliferation of US high-containment labs following the terrorist attacks of 11 September 2001 and the anthrax-letter attacks the same year was proceeding without a rigorous assessment of the nation's real needs across all government agencies, universities and private companies. "Increasing the number of laboratories also increases the aggregate national risk," it noted. No one keeps track, for example, of how many BSL-3 labs there are in the United

States alone, although their number is thought to be in the thousands. The number of such labs is increasing in China and elsewhere.

After smallpox was eradicated in 1980, there was a concerted international effort to reduce the number of labs holding stocks to just two: one at the CDC and one at the Russian State Research Center of Virology and Biotechnology in Koltsovo. All research at these centres must be approved by the World Health Organization. The fewer the labs that perform experiments, the smaller is the risk of an accidental release. But as the CDC accident reminds us, should gain-of-function flu research proliferate, in particular at facilities with less than exemplary biosafety standards, the risks of an accidental release of a potentially pandemic flu virus will be multiplied.

The New York Times, August 5th (2019)

Deadly Germ Research Is Shut Down at Army Lab Over Safety Concerns

Problems with disposal of dangerous materials led the government to suspend research at the military's leading biodefense center.

By Denise Grady

Safety concerns at a prominent military germ lab have led the government to shut down research involving dangerous microbes like the Ebola virus.

"Research is currently on hold," the United States Army Medical Research Institute of Infectious Diseases, in Fort Detrick, Md., said in a statement on Friday. The shutdown is likely to last months, Caree Vander Linden, a spokeswoman, said in an interview.

The statement said the Centers for Disease Control and Prevention decided to issue a "cease and desist order" last month to halt the research at Fort Detrick because the center did not have "sufficient systems in place to decontaminate wastewater" from its highest-security labs.

But there has been no threat to public health, no injuries to employees and no leaks of dangerous material outside the laboratory, Ms. Vander Linden said.

In the statement, the C.D.C. cited "national security reasons" as the rationale for not releasing information about its decision.

The institute is a biodefense center that studies germs and toxins that could be used to threaten the military or public health, and also investigates disease outbreaks. It carries out research projects for government agencies, universities and drug companies, which pay for the work. It has about 900 employees.

The shutdown affects a significant portion of the research normally conducted there, Ms. Vander Linden said.

The suspended research involves certain toxins, along with germs called select agents, which the government has determined have "the potential to pose a severe threat to public, animal or plant health or to animal or plant products." There are 67 select agents and toxins; examples include the organisms that cause Ebola, smallpox, anthrax and plague, and the poison ricin.

In theory, terrorists could use select agents as weapons, so the government requires any organization that wants to handle them to pass a background check, register, follow safety and security procedures, and undergo inspections through a program run by the C.D.C. and the United States Department of Agriculture. As of 2017, 263 laboratories — government, academic, commercial or private — had registered with the program.

The institute at Fort Detrick was part of the select agent program until its registration was suspended last month, after the C.D.C. ordered it to stop conducting the research.

The problems date back to May 2018, when storms flooded and ruined a decades-old steam sterilization plant that the institute had been using to treat wastewater from its labs, Ms. Vander Linden said. The damage halted research for months, until the institute developed a new decontamination system using chemicals.

Bereits zwei Jahre vor Ausbruch der Corona-Pandemie wurde auch vor Sicherheitsrisiken im „Wuhan Institute of Virology" gewarnt, wie aus Berichten von US-Diplomaten in China hervorgeht. Ein entsprechender Kommentar hierzu ist nachfolgend wiedergegeben [IV.5]:

THE WASHINGTON POST, April 14, 2020

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

Josh Rogin

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

In January 2018, the U.S. Embassy in Beijing took the unusual step of repeatedly sending U.S. science diplomats to the Wuhan Institute of Virology (WIV), which had in 2015 become China's first laboratory to achieve the highest level of international bioresearch safety (known as BSL-4). WIV issued a news release in English about the last of these visits, which occurred on March 27, 2018. The U.S. delegation was led by Jamison Fouss, the consul general in

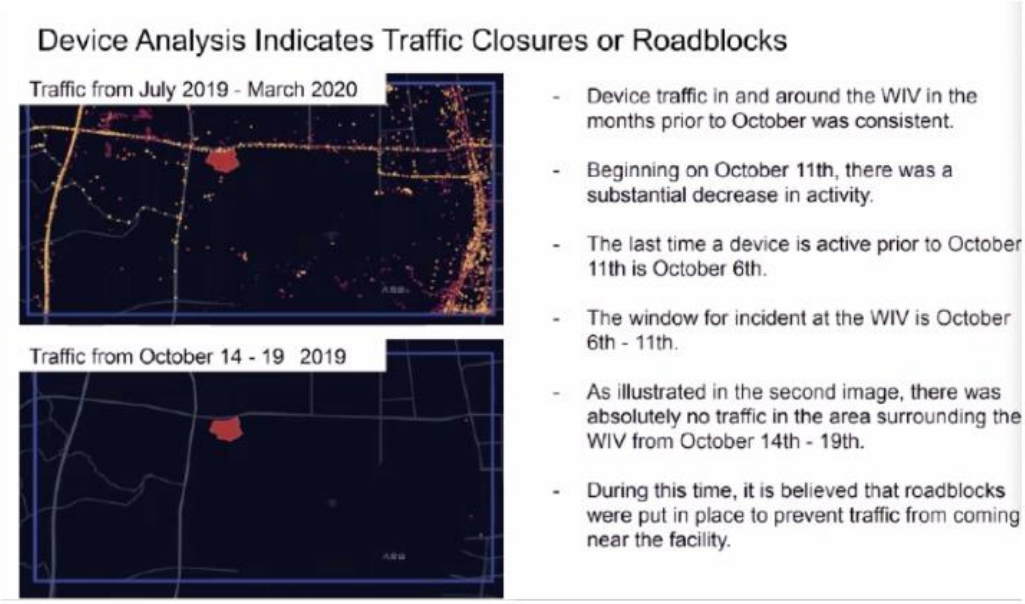
Wuhan, and Rick Switzer, the embassy's counselor of environment, science, technology and health. Last week, WIV erased that statement from its website, though it remains archived on the Internet.

Auch nach Ausbruch der Corona-Pandemie sind Belege für gravierende Sicherheitsmängel am „Wuhan Institute of Virology" öffentlich geworden. So haben beispielsweise chinesische Journalisten Filmaufnahmen vom Institutsgelände gedreht und ins Netz gestellt, welche die unsachgerechte Entsorgung von Laborabfällen belegen (siehe beispielsweise [IV.20], insbesondere den Filmabschnitt ab Zeitpunkt 8:15):

https://www.youtube.com/watch?v=qbUgF_mQy90

Ferner sind Fotos und Videoaufnahmen von Forschern des „Wuhan Institute of Virology" öffentlich geworden, die zeigen, dass diese **keine oder unzureichende Schutzkleidung** beim Einsammeln von Fledermausproben sowie bei deren Untersuchung im Labor getragen haben (siehe beispielsweise [IV.21]).

Eine Analyse der Handynutzungsaktivitäten im und um das „Wuhan Institute of Virology" in der zweiten Hälfte des Jahres 2019 gibt Hinweise darauf, dass es in der ersten Oktoberhälfte 2019 zu einer **zeitweisen Unterbrechung des Laborbetriebs sowie zu Absperrungen rund um das Institutsgelände** kam [IV.22], siehe nachfolgende Grafik:



Gleichzeitig gab es erste bestätigte Fälle von COVID-19 Erkrankungen mit Todesfolge in verschiedenen Krankenhäusern der Stadt Wuhan bereits im Oktober 2019 [IV.2]. Es liegt daher die Vermutung nahe, dass die Absperrungen rund um das „Wuhan Institute of Virology" mit

Untersuchungen zum Ursprung dieser Krankheitsfälle standen, zumal bereits zu diesem Zeitpunkt Hinweise in den chinesischen sozialen Medien kursierten, dass die erste COVID-19 Erkrankte eine Mitarbeiterin dieses Instituts war (siehe Kapitel: „Zentrale Frage nach dem Ursprung der Coronavirus-Pandemie: Naturkatastrophe oder Laborunfall?).

Die Frage stellt sich natürlich, warum das „Wuhan Institute of Virology" als wahrscheinlichster Ursprungsort der Coronavirus-Pandemie unter allen Umständen von der chinesischen Regierung aus dem Verdacht gebracht werden sollte. Es gibt mittlerweile viele Vertreter aus Wissenschaft und Politik (siehe beispielsweise [II.9], [IV.23]), die eine **Verbindung zwischen wissenschaftlicher Hochrisikoforschung mit Fledermausviren und militärischen Interessen** sehen. Tatsächlich ist die **„dual use"-Möglichkeit der „gain-of-function"-Forschung** bereits seit Jahren im wissenschaftlichen und politischen Raum diskutiert worden. Dass es enge Verbindungen zwischen dieser Art wissenschaftlicher Forschung und militärischen Interessen gibt, ist keine „Verschwörungstheorie", sondern durch eine Vielzahl von Koautorenschaften in der wissenschaftlichen Fachliteratur belegt. Zwei Beispiele hierfür sind nachfolgend wiedergegeben [I.15], [I.16]:

Journal of Virology, Volume 88, Number 12, p. 7070 –7082, June 2014

Identification of Diverse Alphacoronaviruses and Genomic Characterization of a Novel Severe Acute Respiratory Syndrome-Like Coronavirus from Bats in China

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Yunnan Institute of Endemic Diseases Control and Prevention, Dali, Yunnan Province, China;
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DOI: 10.1128/JVI.00631-14

ABSTRACT

Although many severe acute respiratory syndrome-like coronaviruses (SARS-like CoVs) have been identified in bats in China, Europe, and Africa, most have a genetic organization significantly distinct from human/civet SARS CoVs in the receptor-binding domain (RBD),

which mediates receptor binding and determines the host spectrum, resulting in their failure to cause human infections and making them unlikely progenitors of human/civet SARS CoVs. Here, a viral metagenomic analysis of 268 bat rectal swabs collected from four counties in Yunnan Province has identified hundreds of sequences relating to alpha- and betacoronaviruses. Phylogenetic analysis based on a conserved region of the RNA-dependent RNA polymerase gene revealed that alphacoronaviruses had diversities with some obvious differences from those reported previously. Full genomic analysis of a new SARS-like CoV from Baoshan (LYRa11) showed that it was 29,805 nucleotides (nt) in length with 13 open reading frames (ORFs), sharing 91% nucleotide identity with human/civet SARS CoVs and the most recently reported SARS-like CoV Rs3367, while sharing 89% with other bat SARS-like CoVs. Notably, it showed the highest sequence identity with the S gene of SARS CoVs and Rs3367, especially in the RBD region. Antigenic analysis showed that the S1 domain of LYRa11 could be efficiently recognized by SARS-convalescent human serum, indicating that LYRa11 is a novel virus antigenically close to SARS CoV. Recombination analyses indicate that LYRa11 is likely a recombinant descended from parental lineages that had evolved into a number of bat SARS-like CoVs.

IMPORTANCE

Although many severe acute respiratory syndrome-like coronaviruses (SARS-like CoVs) have been discovered in bats worldwide, there are significant different genic structures, particularly in the S1 domain, which are responsible for host tropism determination, between bat SARS-like CoVs and human SARS CoVs, indicating that most reported bat SARS-like CoVs are not the progenitors of human SARS CoV. We have identified diverse alphacoronaviruses and a close relative (LYRa11) to SARS CoV in bats collected in Yunnan, China. Further analysis showed that alpha- and betacoronaviruses have different circulation and transmission dynamics in bat populations. Notably, full genomic sequencing and antigenic study demonstrated that LYRa11 is phylogenetically and antigenically closely related to SARS CoV. Recombination analyses indicate that LYRa11 is a recombinant from certain bat SARS-like CoVs circulating in Yunnan Province.

…

Emerging Microbes & Infections 7(1), 154 (2018).
doi: 10.1038/s41426-018-0155-5.

Genomic characterization and infectivity of a novel SARS-like coronavirus in Chinese bats

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Abstract

SARS coronavirus (SARS-CoV), the causative agent of the large SARS outbreak in 2003, originated in bats. Many SARS-like coronaviruses (SL-CoVs) have been detected in bats, particularly those that reside in China, Europe, and Africa. To further understand the evolutionary relationship between SARS-CoV and its reservoirs, 334 bats were collected from Zhoushan city, Zhejiang province, China, between 2015 and 2017. PCR amplification of the conserved coronaviral protein RdRp detected coronaviruses in 26.65% of bats belonging to this region, and this number was influenced by seasonal changes. Full genomic analyses of the two new SL-CoVs from Zhoushan (ZXC21 and ZC45) showed that their genomes were 29,732 nucleotides (nt) and 29,802 nt in length, respectively, with 13 open reading frames (ORFs). These results revealed 81% shared nucleotide identity with human/civet SARS CoVs, which was more distant than that observed previously for bat SL-CoVs in China. Importantly, using pathogenic tests, we found that the virus can reproduce and cause disease in suckling rats, and further studies showed that the virus-like particles can be observed in the brains of suckling rats by electron microscopy. Thus, this study increased our understanding of the genetic diversity of the SL-CoVs carried by bats and also provided a new perspective to study the possibility of cross-species transmission of SL-CoVs using suckling rats as an animal model.

…

Das Thema **„Biosecurity“** hat in den vergangenen Jahren steigende Bedeutung erlangt, insbesondere auf Grund der Tatsache, dass Hochrisikoforschung und die Entwicklung von Biowaffen oftmals Hand in Hand gehen und eine **substantielle Gefahr für die Gesundheit der Weltbevölkerung** darstellen (siehe beispielsweise [II.10]):

Biosecurity and the Risk to Global Health

Christian Enemark

The Oxford Handbook of Global Health Politics

Edited by Colin McInnes, Kelley Lee, and Jeremy Youde
Online Publication Date: Jan 2018
Print Publication Date: Mar 2020
DOI: 10.1093/oxfordhb/9780190456818.013.12

Global health is potentially diminished by practices of biosecurity aimed at safeguarding the health of human populations against selected infectious disease risks. Some diseases inspire so much government concern that they are accorded the status of security issues, and adopting a security-based rationale for prevention and response efforts can garner extra resources and stronger powers for risk-reduction purposes. However, such an approach can result in practices that are counterproductive from a health perspective. This chapter shows that biosecurity can endanger global health in at least four areas of policy concern: the development of defences against biological weapons, the management of security risks arising from laboratory research on pathogenic microorganisms, the prioritization of disease risks and response mechanisms as part of an agenda of global health security, and the use of national borders to contain transnational contagion.

So verheerend die Auswirkungen von Atombombenabwürfen, von Atomreaktorunfällen oder von Einsätzen chemischer Kampfstoffe in der Vergangenheit waren, so sind die Auswirkungen davon letztlich regional eingegrenzt gewesen. Die gegenwärtige Coronavirus-Pandemie zeigt uns jedoch, welche Gefahren durch freigesetzte gefährliche Krankheitserreger global für die gesamte Weltbevölkerung tatsächlich existieren. Zukünftige internationale Abkommen müssen sich daher verstärkt auf B- (neben A- und C-) Gefährdungspotentialen konzentrieren.

6 Rolle der Wissenschaft im Zusammenhang mit der Frage nach dem Ursprung der Coronavirus-Pandemie

Wissenschaftliche Erkenntnisse, Analysen und Vorhersagen spielen in der Coronavirus-Pandemie eine zentrale Rolle. Die hohe Bedeutung der Wissenschaft für die Gesellschaft in Zeiten der Corona-Krise wird u.a. auch in Stellungnahmen zahlreicher wissenschaftlicher Fachgesellschaften betont [IV.24].

In der gegenwärtigen Pandemie ist die seriöse Vermittlung von wissenschaftlichen Erkenntnissen essentiell für die Akzeptanz notwendiger Maßnahmen zur Eindämmung der Virusausbreitung sowie für den Schutz von Risikogruppen. Dabei kommt es bei der Wissenschaftskommunikation insbesondere darauf an, die Komplexität wissenschaftlicher Sachverhalte in der Weise zu reduzieren, dass deren wesentliche Inhalte nicht verloren gehen und von der Bevölkerung nachvollziehbar sind.

Verschiedene Wege der Verbreitung von Informationen für die breite Öffentlichkeit wurden seit Beginn der Pandemie seitens der Wissenschaft genutzt. Hierzu gehören Wissenschaftssendungen im Fernsehen, Radio-Podcasts, Talkshows, aber auch Artikel in Zeitungen und Zeitschriften sowie in Online-Medien. Die Erfolge dieser umfangreichen Bemühungen der Wissenschaftskommunikation in den vergangenen Monaten lässt sich u.a. aus Ergebnissen von Umfragen in der Bevölkerung ablesen [IV.25]: 77 Prozent der Befragten in Deutschland geben an sich gut über die Coronavirus-Pandemie informiert zu fühlen, und 73 Prozent der Befragten akzeptieren die staatlich verordneten Maßnahmen zur Eindämmung der Coronavirus-Pandemie.

Das generelle Vertrauen der deutschen Bevölkerung in Wissenschaft und Forschung ist in der Zeit der Coronavirus-Pandemie deutlich gestiegen: von ca. 50 Prozent vor der Pandemie auf 73 Prozent im Mai 2020 [IV.25]. Fast 90 Prozent der Befragten sind der Meinung, dass wissenschaftliche Erkenntnisse wichtig sind, um die Ausbreitung der Coronavirus-Pandemie in Deutschland zu verlangsamen. Und schließlich sind 81 Prozent der Befragten der Ansicht, dass politische Entscheidungen im Umgang mit der Coronavirus-Pandemie auf wissenschaftlichen Erkenntnissen beruhen sollten [IV.25].

Jeder Vertreter bzw. jede Vertreterin des Wissenschaftssystems zeigt sich derzeit über diese Entwicklung hoch erfreut und nutzt die Gelegenheit der Stunde, auf die Notwendigkeit des weiteren Ausbaus der wissenschaftlichen Bildung und Forschung hinzuweisen [IV.24].

Die Frage, die sich in diesem Zusammenhang jedoch stellt, ist, inwieweit diese positive Entwicklung aus Sicht der Wissenschaft gefährdet sein könnte, wenn der Ursprung der Coronavirus-Pandemie keine Zoonose (und damit vergleichbar einer Naturkatastrophe), sondern ein biotechnologisches Labor eines wissenschaftlichen Instituts für Virologie der Stadt Wuhan in China wäre, wie in dieser vorliegenden Studie als wahrscheinlichstes Szenario dargelegt und begründet wurde. Wie würde sich die Stimmungslage in der Bevölkerung in Deutschland, aber auch weltweit, verändern, wenn die gegenwärtige weltweite Krise nicht die Folge eines Zufalls der Natur – einer zufälligen Mutation eines Coronavirus einer Fledermaus unter Mitwirkung eines Zwischenwirtstieres – wäre, sondern das Resultat einer Unachtsamkeit eines Wissenschaftlers bzw. einer Wissenschaftlerin bei der Durchführung hoch risikoreicher Forschung mit weltweitem Pandemie-Potential [IV.26]? Würden nicht verstärkt Fragen nach der Verantwortung der Wissenschaft angesichts der Dimension der gegenwärtigen weltweiten

Katastrophe aufkommen? Würden nicht Forderungen nach einer sofortigen Einstellung solcher Art von Forschung erhoben werden? Wie viele wissenschaftliche Labore weltweit müssten befürchten, in Folge des gewaltigen öffentlichen und politischen Drucks geschlossen zu werden? Wäre dies ein Szenario, welches ggf. von der Wissenschaft selbst ausgeschlossen werden müsste? **Welchen Einfluss hätte dies auf die erforderliche Klärung der wichtigen Frage nach dem Ursprung der Coronavirus-Pandemie? Kann die Wissenschaft selbst in dieser Frage ergebnisoffen bleiben? Gibt es Anzeichen dafür, dass sie dies schon seit geraumer Zeit nicht mehr ist?**

Es ist zweifellos erstaunlich, inwieweit sich einige namhafte Virologen sehr frühzeitig in öffentlichen Stellungnahmen (siehe u.a. [IV.1], [IV.3]) auf den Tiermarkt in Wuhan als Quelle des SARS-CoV-2 Erregers festgelegt haben, wobei immer wieder neue Vermutungen über das mögliche Zwischenwirtstier (u.a. Schlangen, Schleichkatzen, Schuppentiere, Marderhunde) geäußert wurden. Bislang konnte jedoch wissenschaftlich nicht bewiesen werden, dass tatsächlich eine Zoonose stattgefunden hat. Dass das Labor des Wuhan Instituts für Virologie, an dem nachweislich - d.h. durch die existierende wissenschaftliche Literatur belegt - über viele Jahre hinweg hoch risikoreiche Forschung an Coronaviren einschließlich gentechnisch veränderter Varianten durchgeführt wurde, ebenfalls als Quelle des SARS-CoV-2 Erregers in Frage käme, wurde von einigen Virologen von Anfang an ausgeschlossen, ohne dass es hierfür bis zum heutigen Tag einen wissenschaftlich nachvollziehbaren Grund gibt. Ohne einen Beweis für die eine oder andere Theorie vorliegen zu haben, wäre es ein Gebot der Wissenschaft, in dieser Frage eine neutrale, d.h. ergebnisoffene Position zu beziehen. Dies ist erstaunlicherweise jedoch nicht der Fall.

In den Medien wurde sehr frühzeitig im Zusammenhang mit der These des Laborursprungs der Coronavirus-Pandemie von einer „Verschwörungstheorie“ gesprochen, ohne allerdings zu begründen, warum die wissenschaftlich durchaus plausible Annahme bezüglich des Ursprungs der Pandemie den Charakter einer „Verschwörung“ hat.

Seltsam klingt ebenso das Statement von 27 Wissenschaftlern und Wissenschaftlerinnen [III.4], publiziert in der Fachzeitschrift „The Lancet“, in welchem die Unterzeichner Folgendes erklären: „We have watched as the scientists, public health professionals, and medical professionals of China, in particular, have worked diligently and effectively to rapidly identify the pathogen behind this outbreak, put in place **significant measures to reduce its impact**, and **share their results transparently with the global health community**“. „The **rapid, open, transparent sharing of data on this outbreak** is now being threatened by rumours and misinformation around its origin“. „**We stand together to strongly condemn conspiracy theories suggesting that COVID-19 does not have a natural origin**“. Abgesehen davon, dass auch in dieser Veröffentlichung kein wissenschaftlicher Beweis dafür erbracht wird, dass der SARS-CoV-2 Erreger seinen Ursprung nicht in dem Wuhan Labor für Virologie hat, ist die Bestätigung einer „transparenten“ Informationspolitik von chinesischer Seite in offensichtlichem Widerspruch zur Faktenlage (siehe u.a. [III.3], [IV.6]-[IV.12], [IV.14], [IV.15]).

Noch seltsamer ist, dass wissenschaftliche Publikationen der Forschergruppe um Zheng-Li Shi vom „Wuhan Institute of Virology“, welche in Zeitschriften der „**NATURE**“-Gruppe erschienen sind und die gezielte Genmanipulation von Coronaviren im Hinblick auf höhere Ansteckungsraten und Gefährlichkeit für den Menschen belegen, sowie Kommentarartikel, die

hierauf Bezug nehmen, vom SpringerNature-Verlag mit folgendem Hinweis nachträglich versehen wurden:

30 March 2020 *Editors' note, March 2020: We are aware that this article is being used as the basis for unverified theories that the novel coronavirus causing COVID-19 was engineered. There is no evidence that this is true; scientists believe that an animal is the most likely source of the coronavirus.*

Dieses Statement der bislang hoch angesehenen wissenschaftlichen Verlagsgruppe **SpringerNature** hat gleich in mehrfacher Weise für Unverständnis in Wissenschaftlerkreisen gesorgt:

- Der Satz „scientists believe…" ist in dieser Form unhaltbar, da es eine nachgewiesene und durch viele Publikationen belegte **Pluralität der Meinungen unter Wissenschaftlern** gibt, was den Ursprung der Coronavirus-Pandemie anbelangt. Der Satz hätte allenfalls lauten dürfen „some scientists believe…".
- Ferner ist die Formulierung „scientists believe…" schon aus dem Grund für ein wissenschaftliches Journal unangemessen, da **Wissenschaft auf verifizierbaren Fakten aufbaut und nicht auf dem, was eine Untermenge von Wissenschaftlern glaubt**.

Leider ist dies nicht das erste Mal, dass der SpringerNature-Verlag dem Druck der chinesischen Regierung nachgibt, wie beispielsweise der nachfolgende Artikel [IV.27] belegt:

***The New York Times*, Nov. 1, 2017**

Leading Western Publisher Bows to Chinese Censorship

Javier C. Hernández

BEIJING — One of the world's largest academic publishers was criticized on Wednesday for bowing to pressure from the Chinese government to block access to hundreds of articles on its Chinese website.

Springer Nature, whose publications include Nature and Scientific American, acknowledged that at the government's request, it had removed articles from its mainland site that touch on topics the ruling Communist Party considers sensitive, including Taiwan, Tibet, human rights and elite politics.

The publisher defended its decision, saying that only 1 percent of its content was inaccessible in mainland China.

Under President Xi Jinping, China has grown increasingly confident in using its vast market as a bargaining chip, forcing foreign firms to acquiesce to strict demands on free speech.

Academic publishers have become a popular target, part of Mr. Xi's efforts to restrict the flow of ideas at universities.

…

In dem Wissenschaftsmagazin „**Scientific American**", welches ebenfalls vom SpringerNature-Verlag herausgegeben wird, wird die Leiterin des Coronavirenforschungsprogramms am „Wuhan Institute of Virology", Zheng-Li Shi, von der chinesischen Autorin als wissenschaftliche Pionierin und Heldin vorgestellt [IV.28]. Es findet sich darin keinerlei Hinweis auf die Vorgeschichte der kritischen Diskussion um das Risiko und die Gefahren, welche mit der am Wuhan-Institut durchgeführten „gain-of-function"-Forschung einhergehen. Der Artikel endet mit dem Statement: The „team has estimated that there are as many as 5.000 coronavirus strains waiting to be discovered in bats globally". The team „is planning a national project to systematically sample viruses in bat caves – with much greater scope and intensity than the team's previous attempts". Die Frage bleibt allerdings offen, ob die Weltgemeinschaft eine 5.000-fache Gefahr für weitere Coronavirus-bedingte Pandemien akzeptieren möchte, unabhängig vom Ursprung des SARS-CoV-2 Virus.

Während in der wissenschaftlichen Literatur seit Monaten nur die Version des Tiermarktes als Quelle der SARS-CoV-2 Viren propagiert wird, werden gleichzeitig anderslautende Ergebnisse von wissenschaftlichen Studien mit unterschiedlichen Strategien unterdrückt. Ein Forschungsteam aus New Delhi berichtete im Rahmen eines Vorabdrucks einer Publikation [II.8], dass die Wissenschaftler HIV-RNA-Sequenzen bei der genetischen Analyse des SARS-CoV-2 Virus gefunden hätten, was auf einen künstlichen Ursprung dieses neuartigen Coronavirus-Typs hindeutet. Die Autoren wurden daraufhin von namhaften Virologen vehement kritisiert und aufgefordert, die Veröffentlichung zurückzuziehen.

Interessanterweise fand auch der französische Nobelpreisträger und Entdecker der HIV-Viren, Luc Montagnier, gemeinsam mit einem Kollegen bei der gentechnischen Untersuchung von SARS-CoV-2 Viren RNA-Sequenzen von HIV-Viren, die nicht auf natürliche Weise zum Bestandteil dieser neuartigen Coronaviren geworden sein könnten [II.7]. In einem Interview des französischen Fernsehens sagte Montagnier: „Um eine HIV-Sequenz in das Genom einzubringen, sind molekulare Werkzeuge nötig, und das kann nur in einem Labor gemacht werden". Die Reaktion auf diese Äußerung des französischen Nobelpreisträgers waren keine wissenschaftlichen Argumente der Gegenseite, sondern ausschließlich diffamierende Kommentare, die sich entweder auf das Alter von Montagnier bezogen [IV.29] oder in die Richtung zielten, dass der Nobelpreisträger mittlerweile „umstritten" wäre [IV.30]. Tatsächlich wurden HIV-basierte Pseudoviren für Genmanipulationsexperimente von der Wuhan Forschungsgruppe um Zheng-Li Shi eingesetzt, wie mehrere Publikationen in der wissenschaftlichen Fachliteratur belegen (siehe z.B. [I.6], [I.10]).

Auch die chinesische Virologin Li-Meng Yan hat basierend auf detaillierten Analysen der Gensequenz von SARS-CoV-2-Viren, welche die COVID-19 Erkrankung hervorrufen, eindeutige Hinweise auf einen nicht-natürlichen Ursprung dieser neuartigen Viren gefunden [II.5]. Nach Veröffentlichung ihrer Arbeit auf dem Online-Portal Zenodo im September 2020 wurde sie von mehreren Virologen heftig kritisiert. Dabei fand sie heraus, dass das SARS-CoV-2-Virus ein Laborprodukt unter Verwendung von Fledermausviren mit den Namen ZC45 und

ZXC21 als Templat bzw. Rückgrat darstellt. Genau diese Coronavirentypen wurden jedoch auch von der Gruppe chinesischer Wissenschaftler und Ärzte bei der Analyse der Gensequenzen von Erregern der allerersten COVID-19 Patienten in Wuhan identifiziert. Diese Arbeit erschien im Februar 2020 in der hoch angesehenen Fachzeitschrift „THE LANCET“ [I.3]. Beide Arbeiten sind nachfolgend ausschnittsweise wiedergegeben:

Unusual Features of the SARS-CoV-2 Genome Suggesting Sophisticated Laboratory Modification Rather Than Natural Evolution and Delineation of Its Probable Synthetic Route

Yan, Li-Meng; Kang, Shu; Guan, Jie; Hu, Shanchang

The COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 has led to over 910,000 deaths worldwide and unprecedented decimation of the global economy. Despite its tremendous impact, the origin of SARS-CoV-2 has remained mysterious and controversial. The natural origin theory, although widely accepted, lacks substantial support. The alternative theory that the virus may have come from a research laboratory is, however, strictly censored on peer-reviewed scientific journals. Nonetheless, SARS-CoV-2 shows biological characteristics that are inconsistent with a naturally occurring, zoonotic virus. In this report, we describe the genomic, structural, medical, and literature evidence, which, when considered together, strongly contradicts the natural origin theory. The evidence shows that SARS-CoV-2 should be a laboratory product created by using bat coronaviruses ZC45 and/or ZXC21 as a template and/or backbone. Building upon the evidence, we further postulate a synthetic route for SARS-CoV-2, demonstrating that the laboratory-creation of this coronavirus is convenient and can be accomplished in approximately six months. Our work emphasizes the need for an independent investigation into the relevant research laboratories. It also argues for a critical look into certain recently published data, which, albeit problematic, was used to support and claim a natural origin of SARS-CoV-2. From a public health perspective, these actions are necessary as knowledge of the origin of SARS-CoV-2 and of how the virus entered the human population are of pivotal importance in the fundamental control of the COVID-19 pandemic as well as in preventing similar, future pandemics.

…

LANCET VOLUME 395, ISSUE 10224, P565-574, FEBRUARY 22, 2020

Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding

Roujian Lu, Xiang Zhao, Juan Li, Peihua Niu, Bo Yang, Honglong Wu, Wenling Wang, Hao Song, Baoying Huang, Na Zhu, Yuhai Bi, Xuejun Ma, Faxian Zhan, Liang Wang, Tao Hu, Hong Zhou, Zhenhong Hu, Weimin Zhou, Li Zhao, Jing Chen, Yao Meng, Ji Wang, Yang Lin, Jianying Yuan,

Zhihao Xie, Jinmin Ma, William J Liu, Dayan Wang, Wenbo Xu, Edward C Holmes, George F Gao, Guizhen Wu, Weijun Chen, Weifeng Shi, and Wenjie Tan

Summary

Background

In late December, 2019, patients presenting with viral pneumonia due to an unidentified microbial agent were reported in Wuhan, China. A novel coronavirus was subsequently identified as the causative pathogen, provisionally named 2019 novel coronavirus (2019-nCoV). As of Jan 26, 2020, more than 2000 cases of 2019-nCoV infection have been confirmed, most of which involved people living in or visiting Wuhan, and human-to-human transmission has been confirmed.

Methods

We did next-generation sequencing of samples from bronchoalveolar lavage fluid and cultured isolates from nine inpatients, eight of whom had visited the Huanan seafood market in Wuhan. Complete and partial 2019-nCoV genome sequences were obtained from these individuals. Viral contigs were connected using Sanger sequencing to obtain the full-length genomes, with the terminal regions determined by rapid amplification of cDNA ends. Phylogenetic analysis of these 2019-nCoV genomes and those of other coronaviruses was used to determine the evolutionary history of the virus and help infer its likely origin. Homology modelling was done to explore the likely receptor-binding properties of the virus.

Findings

The ten genome sequences of 2019-nCoV obtained from the nine patients were extremely similar, exhibiting more than 99·98% sequence identity. Notably, 2019-nCoV was closely related (with 88% identity) to two bat-derived severe acute respiratory syndrome (SARS)-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21, collected in 2018 in Zhoushan, eastern China, but were more distant from SARS-CoV (about 79%) and MERS-CoV (about 50%). Phylogenetic analysis revealed that 2019-nCoV fell within the subgenus Sarbecovirus of the genus Betacoronavirus, with a relatively long branch length to its closest relatives bat-SL-CoVZC45 and bat-SL-CoVZXC21, and was genetically distinct from SARS-CoV. Notably, homology modelling revealed that 2019-nCoV had a similar receptor-binding domain structure to that of SARS-CoV, despite amino acid variation at some key residues.

Der Streit um die Deutungshoheit bei der Frage nach dem Ursprung der Coronavirus-Pandemie gipfelte im Verlauf des Jahres 2020 in der Aussage eines namhaften Virologen in Deutschland, dass Wissenschaftler und Wissenschaftlerinnen, die nicht auf dem Gebiet der Virologie, ja sogar auf dem speziellen Gebiet der Coronaviren arbeiten, sich besser nicht zu den Themen im Zusammenhang mit der Coronavirus-Pandemie äußern sollten [IV.29]. Dieses Statement ist offensichtlich eng mit der Frage des heutigen Verständnisses von Wissenschaft verknüpft: **Soll Wissenschaft nur noch als Gesamtheit der spezifischen Fachwissenschaften begriffen werden mit klaren Abgrenzungen der „Zuständigkeiten“ einzelner wissenschaftlicher Disziplinen oder gibt es nicht auch übergeordnete Fragen der Wissenschaft, zu denen man nicht zuletzt die kritische, selbstreflektierende Betrachtung von Vorgängen in der**

Wissenschaft, aber auch Fragen nach der Verantwortung der Wissenschaft für das Wohlergehen der Menschheit zählen müsste?

Es gibt nicht wenige Wissenschaftler, die gegenwärtig von dem schlimmsten Fall einer koordinierten Irreführung der breiten Öffentlichkeit bei der Frage nach dem Ursprung der Coronavirus-Pandemie sprechen (siehe z.B. [II.9]).

Eine Gruppe von „Concerned People of the World“ hat mittlerweile einen offenen Brief an die Mitglieder der WHO-Untersuchungskommission zum Ursprung der Coronavirus-Pandemie geschrieben [IV.31], in dem es einleitend heißt:

“Every human being is entitled to know the truth of the origins of the COVID-19 pandemic".

Dem wäre eigentlich nichts mehr hinzuzufügen, mit Ausnahme des Verweises auf die Inhalte der Fragen, welche durch eine Gruppe von Wissenschaftler formuliert wurden und aus denen hervorgeht, welche Aufgaben bei der Untersuchung der Vorgänge in Wuhan, insbesondere im letzten Quartal des Jahres 2019, zu erfüllen sind [IV.31]:

Open Letter to the WHO COVID-19 International Investigation Team

Prof. Dr. Thea Fisher, MD, DMSc(PhD) (Nordsjællands Hospital, Denmark)
Prof. John Watson (Public Health England, United Kingdom)
Prof. Dr. Marion Koopmans, DVM PhD (Erasmus MC, Netherlands)
Prof. Dr. Dominic Dwyer, MD (Westmead Hospital, Australia)
Vladimir Dedkov, Ph.D (Institut Pasteur, Russia)
Dr. Hung Nguyen, PhD (International Livestock Research Institute (ILRI), Vietnam)
PD. Dr. med vet. Fabian Lendertz (Robert Koch-Institute, Germany)
Dr. Peter Daszak, Ph.D (EcoHealth Alliance, USA)
Dr. Farag El Moubasher, Ph.D (Ministry of Public Health, Qatar)
Prof. Dr. Ken Maeda, PhD, DVM (National Institute of Infectious Diseases, Japan)
Copy to: Peter K. Ben Embarek Scientist - Programme Manager at World Health Organization.

Dear Fellow Scientists,

The COVID-19 pandemic has been ravaging the world for over a year now and it is showing no sign of easing in many countries, with infection cases and death tolls continuing to climb. Millions of our brothers and sisters have lost their loved ones, their jobs, businesses, livelihoods and education opportunities. The economies of many nations have been severely compromised, resulting in great tribulation for many sectors, with many closed or bankrupt businesses and millions of unemployed.

Sadly today, we are all still as clueless as to the origins of COVID-19 as we were 10 months ago, despite numerous scientific studies and research conducted around the world since then.

We are glad that the WHO is able to form an investigation team of 10 international experts sitting in the East to undertake the task of unravelling these mysteries and take us from darkness to light.

We, the concerned people around the world, on behalf of all those who have died, widowers, widows, distressed sons, daughters and orphans, therefore call on you to conduct the investigation with transparency, impartiality and bravery without bowing to any pressure or national interest.

Such an investigation, to be both credible and successful must take into consideration all scenarios in a scientific way without giving preference to any default hypothesis, however disturbing this may be.

In support of this investigation, a dedicated group of researchers in various parts of the world have spent months unearthing documents, web pages, papers, and reports to compile a list of relevant and as yet unanswered questions about the origins of COVID-19.

We therefore call on the WHO investigation team to answer the following questions which we feel are of paramount importance to a successful investigation into the origins of SARS-COV-2.

We wish you success and thank you sincerely for your endeavours in search of the truth!

From Concerned People of the World

"Every human being is entitled to know the truth of the origins of the COVID-19 pandemic"

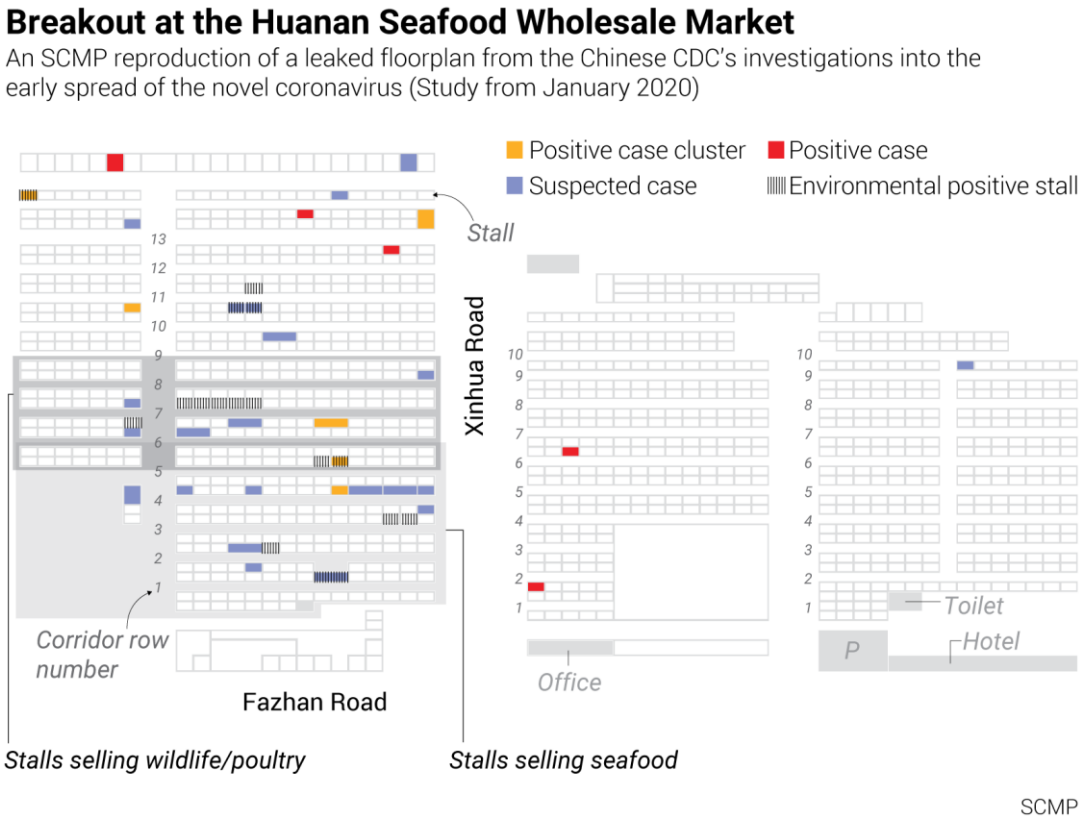
Questions for the WHO January 2021 mission

A. Questions about the positive samples from the market

1. What animals in the Wuhan Huanan Seafood Market were tested, what types of specimens were obtained (apart from frozen animal carcasses), and what were all the results?

2. Were samples gathered from the Huanan market prior to it being sanitized? If so, have these samples been shared with the WHO and what do they reveal?

3. Recently, a floor plan map of the Huanan Seafood Market was "leaked" to the public.



Why did it take 10 months for this map to be published and then only via a "leak"?

4. What does this "One Health" blueprint map of the market reveal in terms of

   a. the 33 positive & 552 negative "environmental samples"

   b. the 27 + persons epidemiologically linked to the Market

   c. all the negative & any positive specimens from specific animals

   d. the role of sewage and drainage in the Market outbreak.

5. Why were a further 70 environmental samples obtained on Jan 12 from the market, after the 515 samples obtained on Jan 1st, and what did these later samples reveal?

6. How many of the samples collected on Jan 12th tested positive for SARS-CoV-2?

7. What are the results of testing in other markets in Wuhan such as the North Hankou Seafood Market, and those outside Wuhan in Hubei province, and outside Hubei province?

8. What animal species were tested? For example, those species now known to be susceptible to the virus, such as: ferrets, cats, mink, tigers, dogs and others?

9. What animals were sold on the 22 stalls in the Western Section of the Wuhan Seafood Market where 14 of the 31 positive samples came from?

10. What were the sources and types of wildlife species sold at this Market and why has China still not disclosed this information nearly one year after the events?

11. What information on the investigation of the purported animal source of the virus at the Wuhan Seafood Market was provided in the WHO mission report?

12. Why have antibody tests (IgM & IgG) used to identify infected humans & animals in Wuhan between Sep-Dec 2019 not been made public?

13. What was the destination of the animals after the market was closed?

14. Why has China not published results of their investigation into the 4 key data streams identified by Dr. Alyward in Annex D of the WHO-China Joint Mission on Coronavirus Disease 2019 Report (28-02- 2020)?

1. Vendor records of animal sales
2. Samples kept from swabbing including gutters where urine & faeces collect.
3. Freezers full of animal parts.
4. Tracking of earliest patients

B. Questions about the alleged November 17th Patient

15. In light of the confirmed report of the November 17th Covid-19 patient published in the SCMP, why is that patient not officially acknowledged?

16. What has been ascertained from the CCDC regarding contact tracing of that patient?

C. Questions about February 20th data collection of suspected early Covid-19 cases in Wuhan

Reference material: https://gillesdemaneuf.medium.com/early-cases-of-suspected-covid-19-in-wuhan-feb-20-data-collection-b7740ed1436f

17. Was the WHO actually shown this data?

18. Was the WHO team directed to hospitals with early cases during their one-day visit to Wuhan in February?

19. Given that the very rushed request for medical and admission data still returned some candidates for early Covid-19 cases (going back to the very beginning of October or earlier), did China take the time to do a more thorough and coherent data collection exercise? If not, why not ? If yes, where are the results?

20. Were these early cases followed up to refine their diagnostics, especially in the cases of deaths (for instance by testing any available sample for antibodies), and were early patients' work unit, location, and residence all recorded? If not, why not? If yes, where are the results?

21. Was that data collection exercise eventually extended to suspected cases prior to the 1st October 2019?

22. How should we interpret the cluster of imaging cases with similarities to Covid-19 pathology at Wuhan Puren Riverside Hospital with admission dates of 1st and 2nd October 2019, in that same collected data?

23. Will the WHO team have access to patient details and files and be able to interview selected cases?

D. Questions about the official national database of Covid-19 managed by Pr. Yu Chanhua

24. Did the official national database of actual and suspected cases managed by Pr. Yu Chanhua (宇传华) and his team contain any suspected October or November cases prior to the Wuhan data collection exercise in February?

25. Were the results of the above data collection added to that national database managed by Pr. Yu Chuanhua, even if starting first as suspected cases (especially for Form 2 and Form 3 cases) before further checks?

26. Were the suspected pre-December cases - such as the 29th Sep CT-imaging case and some November cases he mentioned as being present in the national database - confirmed?

27. Were these conclusions of that verification work eventually shared with the WHO?

E. Questions about the NUDT ‘‘War Epidemic Resumption Big Data” platform and related data

28. Were the ‘‘War Epidemic Resumption Big Data” platform (战疫复工大数据) developed at the NUDT (National University of Defense Science and Technology) and its corresponding epidemic data shown to the WHO mission?

29. Was Pr. Yu Chuanhua’s data work fed into the “War Epidemic Resumption Big Data platform”?

30. Why was a version of the “War Epidemic Resumption Big Data platform” with limited data resolution available only for a while at the web portal of the NUDTy (https://nudtdata.com.cn), before being taken offline?

F. Questions about the proceedings of the WHO February 2020 mission

31. Did the WHO consider the implications on public trust of the inclusion of Pr. Dong Xioaping (董小平) in a prominent role on the Chinese side of the February 2020 WHO mission,

given that he had been sanctioned for his role in the multiple SARS leaks at the Beijing CDC P3 lab in 2004??

32. Why was the WHO visit of Wuhan delayed until after the rushed completion of the Data Collection (point C above)?

G. Questions about deleted Wuhan Institute of Virology Viral pathogen databases

33. Why are all the Wuhan Institute of Virology databases (including the 61.5 Mb SQL version) still offline? Pr. Zhengli Shi claimed they were offline for cybersecurity issues and would be made available "when they felt safe". This was 5 months ago. There are at least 100 unpublished sequences of bat betacoronaviruses on these databases which need to be sequenced by international scientists.

a. WIV Database 1: http://batvirus.whiov.ac.cn/ (Archive seems to be unavailable)

b. WIV SQL online Database 2: http://csdata.org/p/308/

Archived:https://web.archive.org/web/20200507214518/http://csdata.org/p/308/

and: http://archive.is/HLuio

c. WIV Database 3: http://www.viruses.nsdc.cn/vri.jsp

- Archived: https://web.archive.org/web/20200125203943/http://www.viruses.nsdc.cn/vri.jsp
- Discussion of significance here:

Guoke Faji 2019/236 and the SARS-CoV-2 Outbreak http://archive.is/uHqSw#selection-29.0-29.47

d. WIV Database 4: http://www.viruses.nsdc.cn/chinavpi

Archived: https://web.archive.org/web/20200404100024/http:/www.viruses.nsdc.cn/chinavpi

Referenced in a paper by Zhiming Yuan of the Key Laboratory of Special Pathogens and Biosafety, Wuhan Institute of Virology, (+86-27-87197242, Email: yzm@wh.iov.cn)

"Investigation of Viral Pathogen Profiles in Some Natural Hosts and Vectors in China", https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6178075/

e. WIV Database 5: http://www.wfcc.info/ccinfo/collection/col_by_country/c/86/

- Archived: https://web.archive.org/web/20200515223251/http://www.wfcc.info/ccinfo/collection/col_by_country/c/86/ which in turn links to: http://wfcc.info/ccinfo/collection/by_id/613
- Archived: https://web.archive.org/web/20200108181714/http://wfcc.info/ccinfo/collection/by_id/613 links to: http://www.virus.org.cn/ (404 for the database in question)
- Archived: https://web.archive.org/web/20191230091754/http://www.virus.org.cn/

- And an archived description of the WIV database: https://web.archive.org/web/20200117011358/http://www.whiov.ac.cn/xwdt_105286/zhxw/201804/t20180423_5000795.html

In order to clarify the deletion of these databases, please note that these are under the management of:

Prof. Fei Deng and Prof. Zhihong Hu:

address: Xiaohongshan NO. 44, Wuhan, Hubei, 430071

tel: (86) 27-87168465 Fax: (86) 27-87168465

e-mails: Prof. Fei Deng: df@wh.iov.cn and Prof. Zhihong Hu huzh@wh.iov.cn

34. Why were the description and many keywords in the online SQL version of the WIV database altered by Professor Zhengli Shi on Dec 30th while she was returning from Shanghai to Wuhan on the night train?

- Version 1 of the SQL database description: "Wildlife-borne Viral Pathogen Database"

(Release time: July 17th, 2019) Originally available here: http://csdata.org/p/308/2/

Can be seen here: https://web.archive.org/web/20200507214437/http://csdata.org/p/308/2/

- Version 2 of the same SQL database: "Bat and rodent-borne viral pathogen database"

(Updated on December 30th 2019 from Shanghai to Wuhan night train by Pr. Shi)

Originally available here: http://csdata.org/p/308/4/

Can be seen here:https://web.archive.org/web/20200507214519/http://csdata.org/p/308/4/

H. Question about Chinese BatCoV vaccine development programs

35. Can China provide details about any specific strategy followed to prepare for Disease X (a combination of pre-emergent BatCoV features which would represent the most threatening evolutionary front)?

I. Questions about RaTG13 and the 8 SARSr of the Ra7896 Clade

36. Was RaTG13 a consensus sequence as recently claimed by Peter Daszak in an interview (TWiV 623) with Vincent Racaniello?

37. Some RaTG13 amplicons include a "7896" label. So, was Ra7896 in fact used for sequencing RaTG13?

38. Why did WIV not fully sequence the 8 SARSr of the 7896-clade further than their RdRp when they were the second closest viruses to SARS-CoV-2?

39. Were these 8 remaining SARSr from the 7896 clade collected from the same Tongguan mine as RaTG13?

40. Will Ecohealth publish the initial draft of Latinne et al. (2020)

41. There is a correlative series of isolates from WIV but two are missing from the series. Specifically, why were the WIV6 and WIV15 isolates never disclosed? See numbered series.

J. Mojiang Miners Pneumonia Cases

42. Can WIV clarify the full details of the 2012 pneumonia outbreak among the Mojiang miners, especially regarding the subsequent samplings and all blood and BALF results?

43. Can WIV clarify what happened to the samples collected from the Mojiang miners between 2012 and 2019 and whether they are still available for independent analysis?

44. Did WIV culture any virus from the Tongguan mineshaft pneumonia cases in animals or cell lines? If so, were the sequences used as "backbones" for creating other viruses?

K. Laboratory Questions

45. Professor Zhengli Shi recently stated that she would welcome any kind of visit to her Laboratory in order to clarify the origins of SARS-COV-2 (BBC 2020). In light of this declaration, will the WHO investigation team therefore inspect or organise inspections of the following laboratories in Wuhan:

a. WCDC Pathogen BSL-2 at 288 Machang Road

b. Wuhan University Institute of Model Animal ABSL-3 at 115 Donghu Road

c. Huazhong Agricultural University ABSL-3

d. Hubei CDC BSL-3 and Hubei Animal CDC ABSL-3 (in Wuhan)

e. Wuhan Institute of Virology BSL-2 and BSL-3 in Xiaohongshan park

f. Wuhan Institute of Virology BSL-2, BSL-3, ABSL-3, BSL-4 at Zhengdian park

g. Wuhan Institute of Biological Products (vaccine development & production platform) Zhengdian park and its former location (see map)

46. Will the WHO have access to the laboratory records which are supposed to be exhaustive and kept for 20 years at least? Specifically:

1. Lab notebooks
2. Safety procedures, safety audit reports and safety incident reports,
3. Project proposals, status updates and project reports,
4. Environmental audit reports and environmental incident reports
5. Facility improvement projects and monthly reports
6. Purchasing records by department for supplies and new equipment
7. Facility and equipment maintenance logs and records

L. Miscellaneous Questions

47. Are any of the 10 members of the WHO investigation team fluent in Mandarin?

48. Has the CCDC shared primary isolates of SARS-CoV-2 with the WHO and the international community? If not, why not?

49. Why was the WIV unable to transfer samples to the University of Texas Medical Laboratory in Galveston in line with their request? (House Foreign Affairs Committee Report on the Origins of the COVID-19)

50. In light of the "leak" of hospital data which revealed an investigation by the Chinese health authorities into early cases of covid-19 in Wuhan & Hubel province, will the WHO team query the patient details & files to further clarify the putative cases of covid-19 in October at Wuhan Hospitals.

7 Quellenangaben

I) Wissenschaftliche Literatur basierend auf wissenschaftlicher Begutachtung („Peer review“):

[I.1] Fan Wu, Su Zhao, Bin Yu, Yan-Mei Chen, Wen Wang, Zhi-Gang Song, Yi Hu, Zhao-Wu Tao, Jun-Hua Tian, Yuan-Yuan Pei, Ming-Li Yuan, Yu-Ling Zhang, Fa-Hui Dai, Yi Liu, Qi-Min Wang, Jiao-Jiao Zheng, Lin Xu, Edward C. Holmes and Yong-Zhen Zhang, Nature 579, 265–269 (2020): „A new coronavirus associated with human respiratory disease in China“.

[I.2] Chaolin Huang, Yeming Wang, Xingwang Li, Lili Ren, Jianping Zhao, Yi Hu, Li Zhang, Guohui Fan, Jiuyang Xu, Xiaoying Gu, Zhenshun Cheng, Ting Yu, Jiaan Xia, Yuan Wei, Wenjuan Wu, Xuelei Xie, Wen Yin, Hui Li, Min Liu, Yan Xiao, Hong Gao, Li Guo, Jungang Xie, Guangfa Wang, Rongmeng Jiang, Zhancheng Gao, Qi Jin, Jianwei Wang and Bin Cao, Lancet 395, 497–506 (2020): „Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China“.

[I.3] Roujian Lu, Xiang Zhao, Juan Li, Peihua Niu, Bo Yang, Honglong Wu, Wenling Wang, Hao Song, Baoying Huang, Na Zhu, Yuhai Bi, Xuejun Ma, Faxian Zhan, Liang Wang, Tao Hu, Hong Zhou, Zhenhong Hu, Weimin Zhou, Li Zhao, Jing Chen, Yao Meng, Ji Wang, Yang Lin, Jianying Yuan, Zhihao Xie, Jinmin Ma, William J Liu, Dayan Wang, Wenbo Xu, Edward C Holmes, George F Gao, Guizhen Wu, Weijun Chen, Weifeng Shi and Wenjie Tan, Lancet 395, 565–74 (2020): „Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding“.

[I.4] Peng Zhou, Xing-Lou Yang, Xian-Guang Wang, Ben Hu, Lei Zhang, Wei Zhang, Hao-Rui Si, Yan Zhu, Bei Li, Chao-Lin Huang, Hui-Dong Chen, Jing Chen, Yun Luo, Hua Guo, Ren-Di Jiang, Mei-Qin Liu, Ying Chen, Xu-Rui Shen, Xi Wang, Xiao-Shuang Zheng, Kai Zhao, Quan-Jiao Chen, Fei Deng, Lin-Lin Liu, Bing Yan, Fa-Xian Zhan, Yan-Yi Wang, Geng-Fu Xiao and Zheng-Li Shi, Nature 579, 270-273 (2020): „A pneumonia outbreak associated with a new coronavirus of probable bat origin“.

[I.5] Wuze Ren, Xiuxia Qu, Wendong Li, Zhenggang Han, Meng Yu, Peng Zhou, Shu-Yi Zhang, Lin-Fa Wang, Hongkui Deng, and Zhengli Shi, Journal of Virology 82, 1899-1907 (2008): „Difference in Receptor Usage between Severe Acute Respiratory Syndrome (SARS) Coronavirus and SARS-Like Coronavirus of Bat Origin”.

[I.6] Yuxuan Hou, Cheng Peng, Meng Yu, Yan Li, Zhenggang Han, Fang Li, Lin-Fa Wang, and Zhengli Shi, Arch.Virol. 155, 1563-1569 (2010): „Angiotensin-converting enzyme 2 (ACE2) proteins of different bat species confer variable susceptibility to SARS-CoV entry”.

[I.7] Xing-Yi Ge, Jia-Lu Li, Xing-Lou Yang, Aleksei A. Chmura, Guangjian Zhu, Jonathan H. Epstein, Jonna K. Mazet, Ben Hu, Wei Zhang, Cheng Peng, Yu-Ji Zhang, Chu-Ming Luo, Bing Tan, Ning Wang, Yan Zhu, Gary Crameri, Shu-Yi Zhang, Lin-Fa Wang, Peter

Daszak and Zheng-Li Shi, Nature 503, 535-538 (2013): „Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor".

[I.8] Vineet D Menachery, Boyd L Yount Jr, Kari Debbink, Sudhakar Agnihothram, Lisa E Gralinski, Jessica A Plante, Rachel L Graham, Trevor Scobey, Xing-Yi Ge, Eric F Donaldson, Scott H Randell, Antonio Lanzavecchia, Wayne A Marasco, Zhengli-Li Shi and Ralph S Baric, Nature Medicine 21, 1508-1513 (2015): "A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence".

[I.9] Ben Hu , Lei-Ping Zeng , Xing-Lou Yang , Xing-Yi Ge, Wei Zhang,Bei Li, Jia-Zheng Xie, Xu-Rui Shen, Yun-Zhi Zhang, Ning Wang, Dong-Sheng Luo, Xiao-Shuang Zheng, Mei-Niang Wang, Peter Daszak, Lin-Fa Wang, Jie Cui and Zheng-Li Shi, PLoS Pathogens 13(11), e1006698 (2017): "Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus".

[I.10] Peng Zhou, Hang Fan, Tian Lan, Xing-Lou Yang, Wei-Feng Shi, Wei Zhang, Yan Zhu, Ya-Wei Zhang, Qing-Mei Xie, Shailendra Mani, Xiao-Shuang Zheng, Bei Li, Jin-Man Li, Hua Guo, Guang-Qian Pei, Xiao-Ping An, Jun-Wei Chen, Ling Zhou, Kai-Jie Mai, Zi-Xian Wu, Di Li, Danielle E. Anderson, Li-Biao Zhang, Shi-Yue Li, Zhi-Qiang Mi, Tong-Tong He, Feng Cong, Peng-Ju Guo, Ren Huang, Yun Luo, Xiang-Ling Liu, Jing Chen, Yong Huang, Qiang Sun, Xiang-Li-Lan Zhang, Yuan-Yuan Wang, Shao-Zhen Xing, Yan-Shan Chen, Yuan Sun, Juan Li, Peter Daszak, Lin-Fa Wang, Zheng-Li Shi, Yi-Gang Tong and Jing-Yun Ma, Nature 556, 255-258 (2018): "Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin".

[I.11] D. Paraskevis, E. G. Kostaki, G. Magiorkinis, G. Panayiotakopoulos, G. Sourvinos, S. Tsiodras, Infect. Genet. Evol. 79, 104212 (2020). doi: 10.1016/j.meegid.2020.104212. Epub 2020 Jan 27: https://www.biorxiv.org/content/10.1101/2020.01.26.920249v1: "Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event".

[I.12] Manli Wang and Zhihong Hu, Virol. Sin. 28(6), 315-317 (2013): "Bats as animal reservoirs for the SARS coronavirus: Hypothesis proved after 10 years of virus hunting".

[I.13] Masaki Imai, Tokiko Watanabe, Masato Hatta, Subash C. Das, Makoto Ozawa, Kyoko Shinya, Gongxun Zhong, Anthony Hanson, Hiroaki Katsura, Shinji Watanabe, Chengjun Li, Eiryo Kawakami, Shinya Yamada, Maki Kiso, Yasuo Suzuki, Eileen A. Maher, Gabriele Neumann and Yoshihiro Kawaoka, Nature 486, 420-428 (2012): "Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets".

[I.14] Sander Herfst, Eefje J. A. Schrauwen, Martin Linster, Salin Chutinimitkul, Emmie de Wit, Vincent J. Munster, Erin M. Sorrell, Theo M. Bestebroer, David F. Burke, Derek J. Smith, Guus F. Rimmelzwaan, Albert D. M. E. Osterhaus, Ron A. M. Fouchier, Science 336, 1534-1541 (2012): "Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets".

[I.15] Biao He, Yuzhen Zhang, Lin Xu, Weihong Yang, Fanli Yang, Yun Feng, Lele Xia, Jihua Zhou, Weibin Zhen, Ye Feng, Huancheng Guo, Hailin Zhang, Changchun Tua, Journal of Virology 88, 7070-7082 (2014): "Identification of Diverse Alphacoronaviruses and Genomic Characterization of a Novel Severe Acute Respiratory Syndrome-Like Coronavirus from Bats in China".

[I.16] Dan Hu, Changqiang Zhu, Lele Ai, Ting He, Yi Wang, Fuqiang Ye, Lu Yang, Chenxi Ding, Xuhui Zhu, Ruicheng Lv, Jin Zhu, Bachar Hassan, Youjun Feng, Weilong Tan, Changjun Wang, Emerging Microbes & Infections 7, 154 (2018): "Genomic characterization and infectivity of a novel SARS-like coronavirus in Chinese bats".

II) Wissenschaftliche Literatur ohne „Peer review" („Preprints"):

[II.1] Daoyu Zhang: "Anomalies in BatCoV/RaTG13 sequencing and provenance". In Web: https://zenodo.org/record/3987503#.Xz9GzC-z3GI (2020).

[II.2] M. Singla, S. Ahmad, C. Gupta, and T. Sethi: "De-novo Assembly of RaTG13 Genome Reveals Inconsistencies Further Obscuring SARS-CoV-2 Origins". In Web: https://doi.org/10.20944/preprints202008.0595.v1 (2020).

[II.3] Dean Bengston: "All journal articles evaluating the origin or epidemiology of SARS-CoV-2 that utilize the RaTG13 bat strain genomics are potentially flawed and should be retracted". In Web: https://doi.org/10.31219/osf.io/wy89d (2020).

[II.4] Botao Xiao und Lei Xiao: "The possible origins of 2019-nCoV coronavirus". In: Web. https://web.archive.org/web/20200214144447/https:/www.researchgate.net/publication/339070128_The_possible_origins_of_2019-nCoV_coronavirus (February 2020)

[II.5] Li-Meng Yan, Shu Kang, Jie Guan and Shanchang Hu: "Unusual Features of the SARS-CoV-2 Genome Suggesting Sophisticated Laboratory Modification Rather Than Natural Evolution and Delineation of Its Probable Synthetic Route". In Web: https://zenodo.org/record/4028830#.X_BoYNhKh3j (14.09.2020).

[II.6] Sakshi Piplani, Puneet Kumar Singh, David A. Winkler, Nikolai Petrovsky: "In silico comparison of spike protein-ACE2 binding affinities across species; significance for the possible origin of the SARS-CoV-2 virus". In: Web. (13.05.2020). arXiv:2005.06199v1

[II.7] Jean Claude Perez and Luc Montagnier: "COVID-19, SARS and Bats Coronaviruses Genomes Unexpected Exogeneous RNA Sequences". In: Web. https://osf.io/d9e5g/

[II.8] P. Pradhan, A. K. Pandey, A. Mishra, P. Gupta, P. K. Tripathi, M. B. Menon, J. Gomes, P. Vivekanandan, and B. Kundu: Uncanny similarity of unique inserts in the 2019-nCoV spike protein to HIV-1 gp120 and Gag., bioRxiv preprint. In Web: https://doi.org/10.1101/2020.01.30.927871 (2020, later withdrawn by the authors)

[II.9] Li-Meng Yan, Shu Kang, Jie Guan, Shanchang Hu: „SARS-CoV-2 Is an Unrestricted Bioweapon: A Truth Revealed through Uncovering a Large-Scale, Organized

Scientific Fraud". In: Web: https://zenodo.org/record/4073131#.X_DBm9hKh3g (08.10.2020).

[II.10] Christian Enemark: "Biosecurity and the Risk to Global Health", The Oxford Handbook of Global Health Politics, edited by Colin McInnes, Kelley Lee, and Jeremy Youde. Online Publication Date: Jan 2018. DOI: 10.1093/oxfordhb/9780190456818.013.12

III) Briefe, Korrespondenz und Kommentare publiziert in der wissenschaftlichen Literatur:

[III.1] Kristian G. Andersen, Andrew Rambaut, W. Ian Lipkin, Edward C. Holmes and Robert F. Garry, Nature Medicine 26, 450-452 (2020): "The proximal origin of SARS-CoV-2".

[III.2] Declan Butler, Nature (2015), doi:10.1038/nature.2015.18787: "Engineered bat virus stirs debate over risky research". In Web: https://www.nature.com/news/engineered-bat-virus-stirs-debate-over-riskyresearch-1.18787

[III.3] Andrew Green, Lancet 395, p. 682, February 29, 2020: "Li Wenliang".

[III.4] Charles Calisher, Dennis Carroll, Rita Colwell, Ronald B Corley, Peter Daszak, Christian Drosten, Luis Enjuanes, Jeremy Farrar, Hume Field, Josie Golding, Alexander Gorbalenya, Bart Haagmans, James M Hughes, William B Karesh, Gerald T Keusch, Sai Kit Lam, Juan Lubroth, John S Mackenzie, Larry Madoff, Jonna Mazet, Peter Palese, Stanley Perlman, Leo Poon, Bernard Roizman, Linda Saif, Kanta Subbarao, Mike Turner, Lancet 395, Issue 10226, PE42-E43 (2020): "Statement in support of the scientists, public health professionals, and medical professionals of China combatting COVID-19". In Web: https://doi.org/10.1016/S0140-6736(20)30418-9

[III.5] Jef Akst, The Scientist (16. November 2015): „Lab-Made Coronavirus Triggers Debate".

[III.6] Declan Butler, Nature 480, 421-422 (2011): "Fears grow over lab-bred flu".

[III.7] Declan Butler, Nature 481, 417-418 (2012): "Caution urged for mutant flu work".

[III.8] Brendan Maher, Nature 485, 431-434 (2012): "Bird-flu research: The biosecurity oversight".

[III.9] Declan Butler, Nature 493, 460 (2013): "Work resumes on lethal flu strains".

[III.10] Sara Reardon, Nature 514, 411-412 (2014): "US suspends risky disease research".

[III.11] Smriti Mallapaty, Nature 588, 208 (2020): „The Scientists Investigating The Pandemic's Origins".

[III.12] Declan Butler, Nature 503, 19 (2013): "Pathogen-research laws queried".

[III.13] Heidi Ledford, Nature (2013), „Scientists call for urgent talks on mutant-flu research in Europe". In: Web. (20.12.2013). https://doi.org/10.1038/nature.2013.14429.

[III.14] Editorial, Nature 510, 443 (2014): “Biosafety in the balance”. In: Web. (25.06.2014). https://www.nature.com/news/biosafety-in-the-balance-1.15447

IV) Artikel in Print- und Online-Medien:

[IV.1] FOCUS Online Redaktion: „Woher kommt das Virus? Drosten bringt neuen Ansatz zum Corona-Ursprung ins Spiel“. In: Web. (08.05.2020). https://www.focus.de/gesundheit/news/woher-kommt-das-coronavirus-drosten-bringt-neuen-ansatz-zu-ursprung-ins-spiel_id_11924915.html

[IV.2] Eva Fu, THE EPOCH TIMES, Singapore Edition: “Exclusive: China Had COVID-Like Patients Months Before Official Timeline”. In: Web. https://epochtimes.today/exclusive-china-had-covid-like-patients-months-before-official-timeline/

[IV.3] FOCUS Online Redaktion: „Wie ist das Wuhan-Virus entstanden? Forscher widerlegen Verschwörungstheorien“. In: Web. (24.03.2020). https://www.focus.de/gesundheit/news/verschwoerungstheorie-endgueltig-widerlegt-nicht-aus-dem-labor-forscher-beweisen-dass-sars-cov-2-natuerlich-entstanden-ist_id_11801624.html

[IV.4] Lawrence Sellin, GMWATCH: “Explained: Scientific indications that show COVID-19 is man-made”. In: Web. (15.05.2020). https://www.gmwatch.org/en/news/latest-news/19406

[IV.5] Josh Rogin, THE WASHINGTON POST, 14. April (2020): „State Department cables warned of safety issues at Wuhan lab studying bat coronaviruses”.

[IV.6] TAGESSPIEGEL: „Kritiker verschwinden, die EU wird vorgeführt: So dreist vertuscht China die Ursprünge von Corona“. In: Web. (07.05.2020). https://www.tagesspiegel.de/politik/kritiker-verschwinden-die-eu-wird-vorgefuehrt-so-dreist-vertuscht-china-die-urspruenge-von-corona/25809708.html

[IV.7] ZEIT Online: „Ursprung der Pandemie: Behörden in China informierten WHO nicht proaktiv über Coronavirus“. In: Web. (04.07.2020). https://www.zeit.de/wissen/gesundheit/2020-07/who-chronologie-coronavirus-pandemie-covid-19-ausbruch

[IV.8] Lukas Rogalla, FRANKFURTER RUNDSCHAU: „Fehlverhalten offengelegt - ‚Wuhan Files‘: Dokumente aus China offenbaren Chaos zu Beginn der Corona-Pandemie“. In: Web. (03.12.2020). https://www.fr.de/politik/corona-coronavirus-china-wuhan-leaks-virus-ursprung-kekule-virologe-italien-90119716.html

[IV.9] MERKUR: Coronavirus-Held ist nun selber tot – er ließ nicht zu, dass alles vertuscht wird. In: Web. (01.03.2020). https://www.merkur.de/welt/coronavirus-china-vertuschung-wuhan-li-wenliang-arzt-zr-13529620.html

[IV.10] Keoni Everington, TAIWAN NEWS: “Tencent may have accidentally leaked real data on Wuhan virus deaths. In: Web. (05.02.2020). https://www.taiwannews.com.tw/en/news/3871594

[IV.11] Christina Zhao, NEWSWEEK: “Wuhan COVID-19 death toll may be in tens of thousands”. In: Web. (29.03.2020). https://www.newsweek.com/wuhan-covid-19-death-toll-may-tens-thousands-data-cremations-shipments-urns-suggest-1494914

[IV.12] GREATGAMEINDIA: “COVID19 Files – Scientific Investigation on Mysterious Origin of Coronavirus”. In: Web. (21.02.2020). https://greatgameindia.com/covid19-files-scientific-investigation-on-mysterious-origin-of-coronavirus/

[IV.13] https://www.youtube.com/watch?v=bpQFCcSI0pU

[IV.14] Matthew Strong, TAIWAN NEWS: “China asked WHO to cover up coronavirus outbreak: German intelligence service”. In: Web. (09.05.2020). https://www.taiwannews.com.tw/en/news/3931126

[IV.15] Wikipedia: Fang Bin. In: Web. (28.01.2020). https://en.wikipedia.org/wiki/Fang_Bin

[IV.16] Sharri Markson, DAILY TELEGRAPH: “Coronavirus NSW: Dossier lays out case against China bat virus program”. In: Web. (04.05.2020). https://www.dailytelegraph.com.au/coronavirus/bombshell-dossier-lays-out-case-against-chinese-bat-virus-program/news-story/55add857058731c9c71c0e96ad17da60

[IV.17] Christina Lin: “Why US outsourced bat virus research to Wuhan”. In: Web. (April 2020). https://www.ispsw.com/wp-content/uploads/2020/04/689_Lin.pdf

[IV.18] Sam Husseini, INDEPENDENT SCIENCE NEWS: “Peter Daszak’s EcoHealth Alliance Has Hidden Almost $40 Million In Pentagon Funding And Militarized Pandemic Science”. In: Web. (16.12.2020). https://www.independentsciencenews.org/news/peter-daszaks-ecohealth-alliance-has-hidden-almost-40-million-in-pentagon-funding/

[IV.19] Denise Grady, THE NEW YORK TIMES, 5. August (2019): „Deadly Germ Research Is Shut Down at Army Lab Over Safety Concerns”.

[IV.20] https://www.youtube.com/watch?v=qbUgF_mQy90&feature=youtu.be

[IV.21] Steve Watson, SUMMIT NEWS: “Video From 2018 Shows Chinese Scientists Working On Coronavirus In Wuhan Lab”. In: Web. (30.04.2020). https://summit.news/2020/04/30/video-from-2018-shows-chinese-scientists-working-on-coronavirus-in-wuhan-lab

[IV.22] https://www.documentcloud.org/documents/6884792-MACE-E-PAI-COVID-19-ANALYSIS-Redacted.html

[IV.23] GREATGAMEINDIA: “Transcript: Bioweapons Expert Dr. Francis Boyle on Coronavirus”. In: Web. (05.02.2020). https://greatgameindia.com/transcript-bioweapons-expert-dr-francis-boyle-on-coronavirus/

[IV.24] Positionspapier der mathematisch-naturwissenschaftlichen Fachgesellschaften zur COVID-19-Pandemie vom 06.05.2020. In Web: http://www.wissenschaft-verbindet.de/pdf/Stellungnahme_der_Fachgesellschaften_zu_Corona.pdf

[IV.25] Wissenschaft im Dialog, Wissenschaftsbarometer Corona Spezial. In Web: https://www.wissenschaft-im-dialog.de/projekte/wissenschaftsbarometer/wissenschaftsbarometer-corona-spezial/

[IV.26] Sara Dorn, NEW YORK POST: "'Growing body of evidence' shows COVID-19 leaked from Chinese lab: US official". In: Web. (02.01.2021). https://nypost.com/2021/01/02/growing-body-of-evidence-shows-covid-19-leaked-from-chinese-lab-us-official/?utm_medium=SocialFlow&utm_campaign=SocialFlow&utm_source=NYPTwitter

[IV.27] Javier C. Hernández, THE NEW YORK TIMES: "Leading Western Publisher Bows to Chinese Censorship". In: Web. (01.11.2017). https://www.nytimes.com/2017/11/01/world/asia/china-springer-nature-censorship.html

[IV.28] Jane Qiu, Scientific American: "How China's 'Bat Woman' Hunted Down Viruses from SARS to the New Coronavirus". In: Web. (01.06.2020). https://www.scientificamerican.com/article/how-chinas-bat-woman-hunted-down-viruses-from-sars-to-the-new-coronavirus1/
NOTE: This article was originally published with the title "**Chasing Plagues**" in Scientific American 322, 6, 24-32 (June 2020).

[IV.29] 40. NDR Info Podcast: „Das Coronavirus-Update mit Christian Drosten" vom 12.05.2020. In Web: https://www.ndr.de/nachrichten/info/podcast4684.html

[IV.30] Mathias Bröckers: „pLai3ΔenvLuc2 - Wurde mit HIV-Pseudovirus das Coronavirus für den Menschen gefährlich?" In: Web. (20.04.2020). https://www.heise.de/tp/features/pLai3-envLuc2-Wurde-mit-HIV-Pseudovirus-das-Coronavirus-fuer-den-Menschen-gefaehrlich-4705632.html

[IV.31] Open Letter to the WHO COVID-19 International Investigation Team. In: Web. https://www.ipetitions.com/petition/open-letter-to-the-who-covid-19-international

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