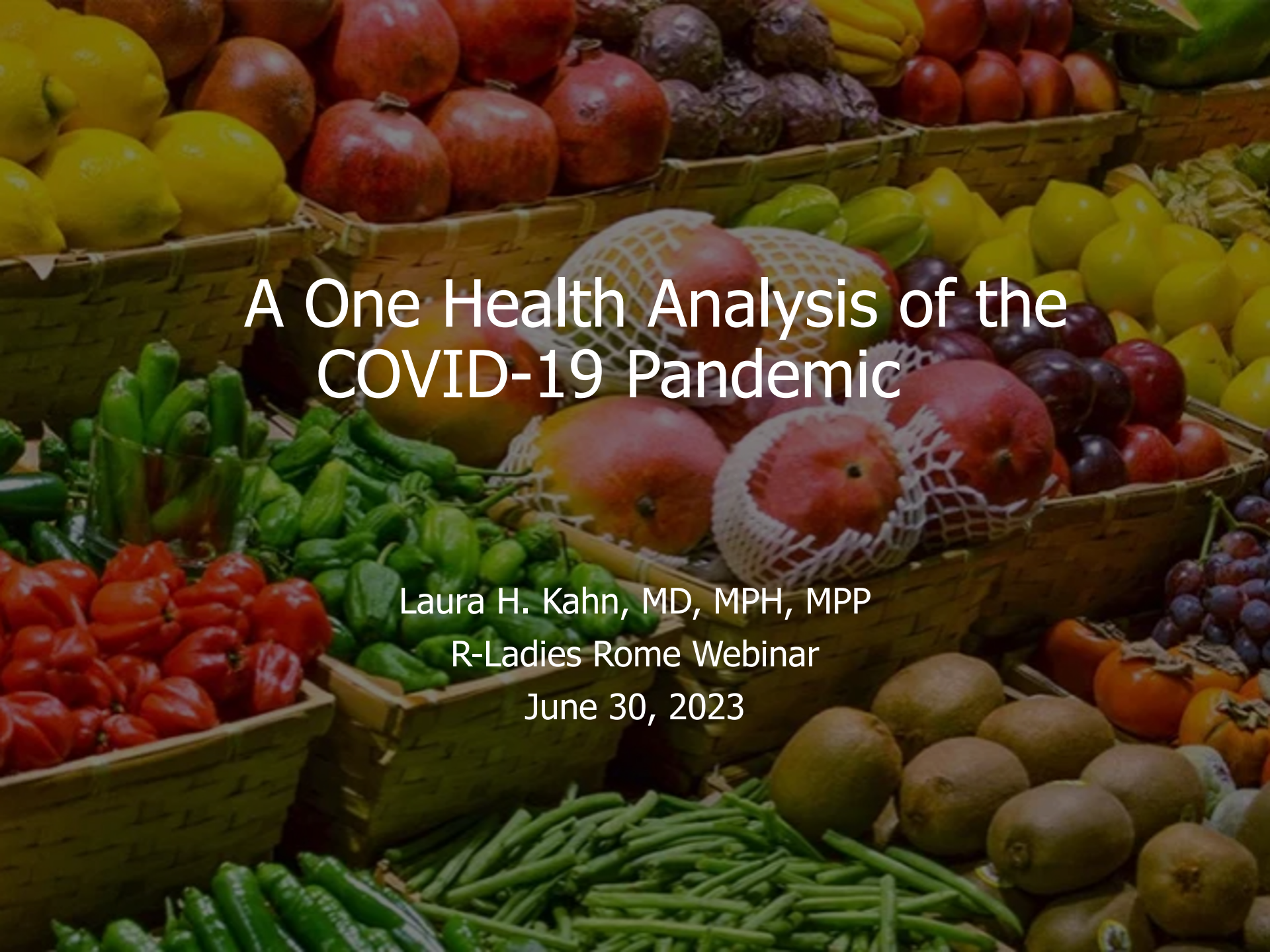


A One Health Analysis of the COVID-19 Pandemic

Laura H. Kahn, MD, MPH, MPP

R-Ladies Rome Webinar

June 30, 2023

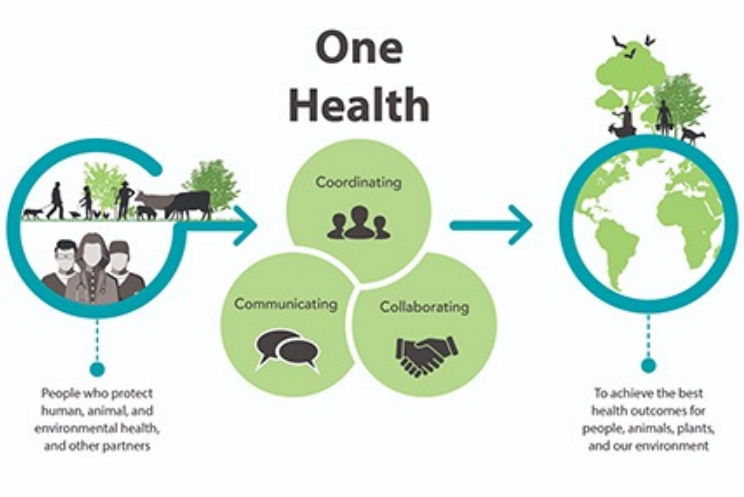
The One Health concept: human, animal, plant, environmental & ecosystem health are linked.

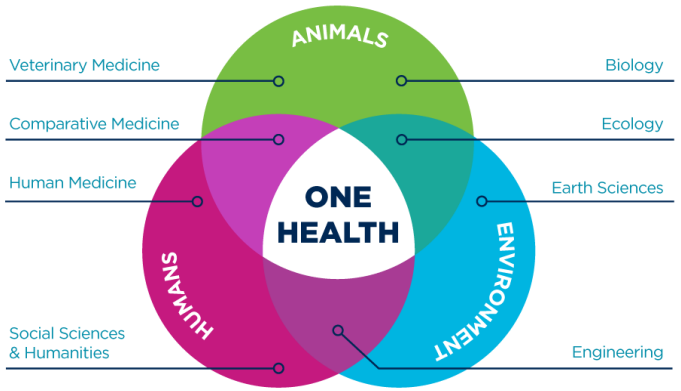
This concept provides a useful framework for examining complex issues such as pandemics.

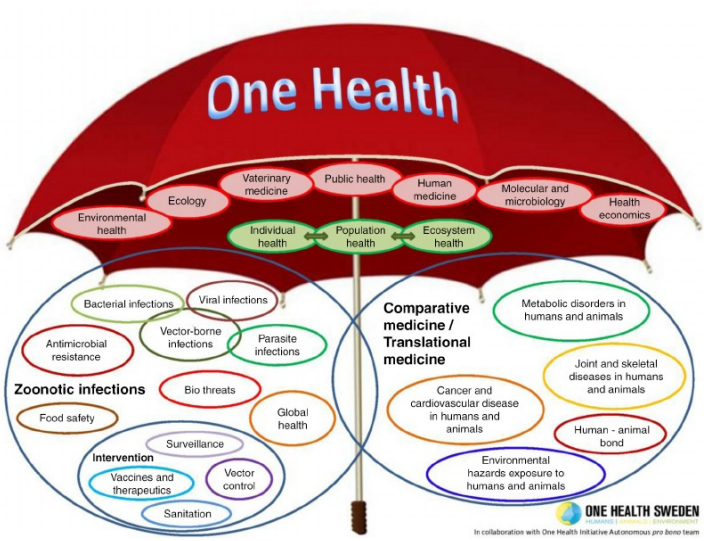
We must examine the root causes of pandemics if we are to develop effective policies to mitigate and prevent them.

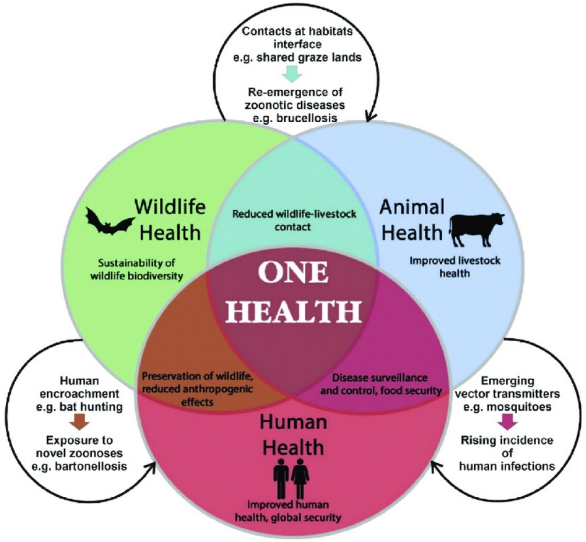
People interact with their environment every day by inhaling air, drinking water, and ingesting plants and animals (i.e. food).

http://www.onehealthinitiative.com


One Health
Coordinating
Communicating
Collaborating
People who protect human, animal, and environmental health, and other partners
To achieve the best health outcomes for people, animals, plants, and our environment


ANIMALS
HUMANS
ENVIRONMENT
ONE HEALTH
Veterinary Medicine
Comparative Medicine
Human Medicine
Biology
Ecology
Earth Sciences
Social Sciences & Humanities
Engineering


One Health
Ecology
Vaterinary medicine
Public health
Human medicine
Molecular and microbiology
Health economics
Environmental health
Individual health
Population health
Ecosystem health
Bacterial infections
Viral infections
Vector-borne infections
Parasite infections
Antimicrobial resistance
Zoonotic infections
Bio threats
Food safety
Global health
Surveillance
Intervention
Vaccines and therapeutics
Vector control
Sanitation
Comparative medicine / Translational medicine
Metabolic disorders in humans and animals
Joint and skeletal diseases in humans and animals
Cancer and cardiovascular disease in humans and animals
Human - animal bond
Environmental hazards exposure to humans and animals
ONE HEALTH SWEDEN


Contacts at habitats interface
e.g. shared graze lands
Re-emergence of zoonotic diseases
e.g. brucellosis
Wildlife Health
Sustainability of wildlife biodiversity
Reduced wildlife-livestock contact
Animal Health
Improved livestock health
ONE HEALTH
Human encroachment
e.g. bat hunting
Exposure to novel zoonoses
e.g. bartonellosis
Preservation of wildlife, reduced anthropogenic effects
Disease surveillance and control, food security
Emerging vector transmitters
e.g. mosquitoes
Rising incidence of human infections
Human Health
Improved human health, global security

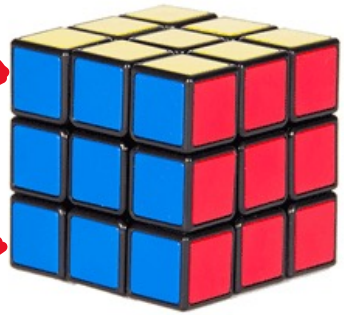
Multi-Dimensional One Health Matrix: A Cube

One Health Factors

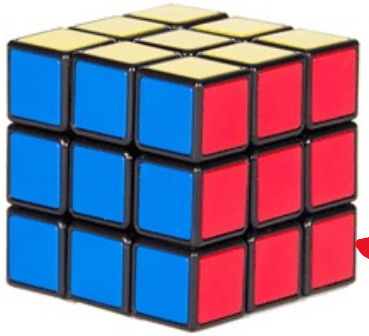
Humans & Animals

Plants

Environments & Ecosystems



Complexity Factors

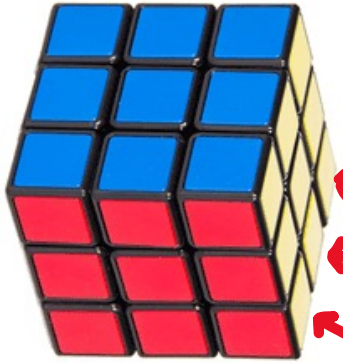


Microbial/Cellular

Individual

Population

Political, Social, Economic Factors



Local/Regional

National

International/Global

One Health Framework in 2 Dimensions

One Health and Complexity Factors	Microbial	Individual	Population
Humans			
Animals			
Plants			
Environments & Ecosystems			
Political, Social, Economic Factors	**Local & Regional**	**National**	**International & Global**

Environments: abiotic (e.g. soil, water, air) aspects of defined geographic areas.
Ecosystems: biotic interactions (e.g. microbial, flora, fauna) within defined geographic areas.

Adapted by L. Kahn for policy development from Rabinowitz, et al. BMC Med Educ. 2017. 17(1): 45. https://doi.org/10.1186/s12909-017-0883-6.

4 One Health Mini Analyses

One Health Factors:

Animals
(Domestic & Wild)

Humans

Environments

Biosafety/Biosecurity/Bioethics

Complexity Factors:

Population

Individual

Microbial/Cellular

Political/Social/Economic Factors

Time Factor: Years

1st One Health Analysis

Animals
(Domestic & Wild)

Populations

Coronavirus epidemics have been occurring in domesticated food animals since the 1930s.
Most transmission has been fecal-oral, but aerosolization possible.
Natural spillover data (animal antibodies and antibodies from occupational exposures) exists for SARS-CoV-1 and MERS-CoV, but not for SARS-CoV-2.

Avian Infectious Bronchitis Virus
First Recognized Coronavirus Outbreak

First identified in **US Midwest 1931**.
Since then, global distribution.
High mortality in young chicks.
Respiratory secretions, fecal-oral, possibly aerosol transmission.

Porcine Epidemic Diarrhea Virus

Emerged in **UK in 1971**.
90-95% mortality in piglets.
Explosive **fecal-oral** transmission.
A 2010 outbreak in China affected
>10 provinces and > 1 million piglets died.
In 2013, affected Iowa swine farms.
Strain is **99% identical to Chinese** strain.

Swine Acute Diarrhea Syndrome aka Porcine Enteric Alphacoronavirus (PEAV) is 5th porcine-CoV identified.

Emerged from HKU2-Bat-CoV in China, 2016

ELSEVIER

Virus Research

Volume 285, August 2020, 198024

Review

Swine enteric alphacoronavirus (swine acute diarrhea syndrome coronavirus): An update three years after its discovery

Yong-Le Yang, Jia-Qi Yu, Yao-Wei Huang

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https://doi.org/10.1016/j.virusres.2020.198024

Get rights and content

Highlights

- A summary of the research progress in SeACoV (SADS-CoV) from 2017 to 2020.
- Bat-derived SeACoV was most recently recognized prior to SARS-CoV-2 associated with COVID-19.
- Focusing on the etiology, epidemiology, evolutionary perspective, potential for interspecies transmission, pathogenesis and diagnosis.

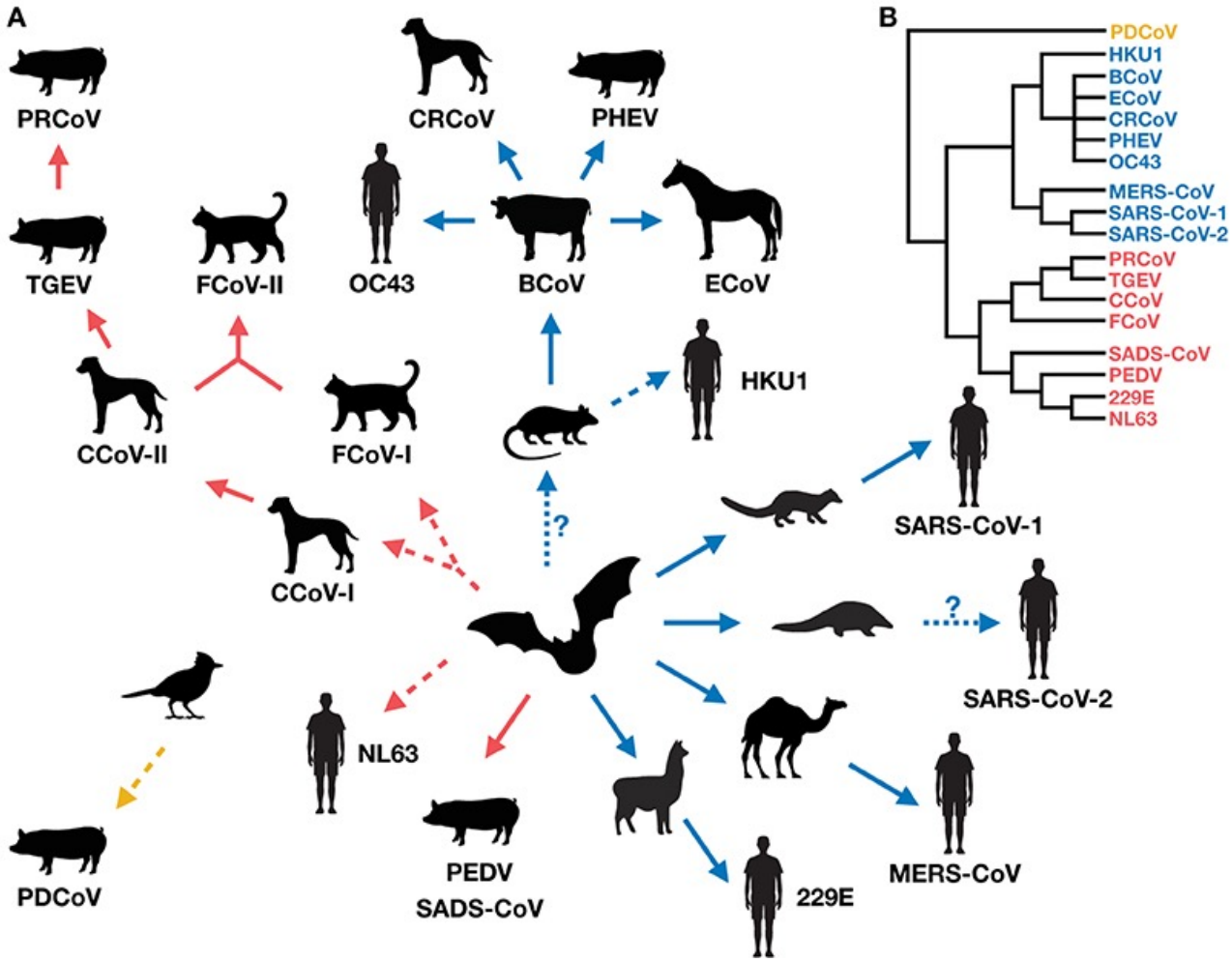
Explosive fecal-oral spread.

MINI REVIEW article
Front. Public Health, 30 September 2021 | https://doi.org/10.3389/fpubh.2021.717941

Cross-Species Transmission of Coronaviruses in Humans and Domestic Mammals, What Are the Ecological Mechanisms Driving Transmission, Spillover, and Disease Emergence?

Nicole Nova*

Department of Biology, Stanford University, Stanford, CA, United States



Genus	Species
ALPHACORONAVIRUS	
	Human coronavirus 229E
	Human coronavirus NL63
	Porcine epidemic diarrhea virus (PEDV)
	Transmissible gastroenteritis virus (TGEV)
	Porcine respiratory coronavirus (PRCV)
	Feline infectious peritonitis virus (FIPV)
	Canine enteric coronavirus (CCoV)
	Rhinolophus bat coronavirus HKU2
BETACORONAVIRUS SUBGENUS	
Embecovirus (Lineage A)	Human coronavirus HKU1
	Human coronavirus OC43
	Bovine coronavirus (BCoV)
	Porcine hemagglutinating encephalomyelitis virus (PHEV)
	Canine respiratory coronavirus (CRCoV)
	Feline enteric coronavirus (FCoV)
	Murine hepatitis virus (MHV)
Sarbecovirus (Lineage B)	Severe acute respiratory syndrome (SARS) related coronavirus (SARS-CoV-1, SARS-CoV-2)
Merbecovirus (Lineage C)	Middle east respiratory syndrome (MERS) related coronavirus
Nobecovirus (Lineage D)	Bat coronaviruses
Hibecovirus	Bat Hp-betacoronavirus Zhejiang 2013
GAMMACORONAVIRUS	
	Infectious bronchitis virus (IBV)
	Bluecomb virus of turkey
DELTACORONAVIRUS	
	Porcine deltacoronavirus (PdCV)
	Avian coronaviruses

Frontiers Vet Sci., 18 Oct 2021, Parkhe and Verma

nature

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nature > articles > article

Article | Open Access | Published: 17 November 2021

Independent infections of porcine deltacoronavirus among Haitian children

John A. Lednicky, Massimiliano S. Tagliamonte, Sarah K. White, Maha A. Elbadry, Md. Mahbubul Alam, Caroline J. Stephenson, Tania S. Bonny, Julia C. Loeb, Taina Telisma, Sonese Chavannes, David A. Ostrov, Carla Mavian, Valery Madsen Beau De Rochars, Marco Salemi & J. Glenn Morris Jr

Nature **600**, 133–137 (2021) | Cite this article

14k Accesses | **21** Citations | **82** Altmetric | Metrics

Evidence for Natural Spillover Events for SARS-CoV-1 and MERS-CoV

SARS-CoV-1

- **Animal antibody & viral genome evidence—**
- Viruses from palm civets in animal market in Guangdong, China had **genome sequences 99.8% identical to SARS-CoV**.
- 80% of palm civets tested positive for SARS-CoV antibodies.
- **Occupational antibody evidence—**
- Study of 800 people in Guangdong found that **people who traded masked palm** civets had highest positivity rates, **73%**, of IgG antibodies to SARS-CoV.

MERS-CoV

- **Animal antibody evidence—**
- **Dromedary camels** throughout Middle East and parts of Asia **tested positive** for MERS-CoV antibodies.
- **Archived camel blood specimens** dating back decades **tested positive** for MERS-CoV antibodies.
- **Occupational antibody evidence—**
- Study of over **10,000 adults** from all 13 provinces of **Saudi Arabia** found MERS-CoV antibodies in **0.15% of samples**.
- In camel shepherds, antibody seropositivity rates were 15 times higher and for **slaughterhouse workers**, they were **23 times higher** than the general population, respectively.

Evidence for Natural Spillover Event for SARS-CoV-2

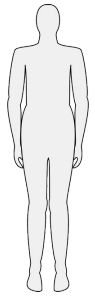
- **Neither the virus nor antibodies to the virus have been identified in animals sampled in Wuhan in 2019 or early 2020**.
- Liu et al, found *zero* out of 457 samples taken from 18 species of animals sampled in Wuhan in early 2020 tested positive for SARS-CoV-2. (Nature (April 3, 2023) Surveillance of SARS-CoV-2 at the Huanan Seafood Market)
- **No correlation has been observed between human occupational exposures to animals and higher rates of infection or seropositivity to the virus**.
- By early 2020, Chinese physicians had conducted serological surveys of thousands of people to assess prevalence rates of SARS-CoV-2 antibodies. None of these studies included data on occupation.

Coronavirus Spillover Events: SARS-CoV-1, MERS-CoV, SARS-CoV-2

SARS-CoV-1
2002-2003

Rhinolophus (Horseshoe) bats

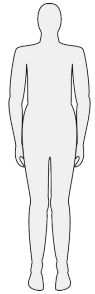
Masked palm civet cats



MERS-CoV
2012-

Neoromicia cf. *zuluensis* bats

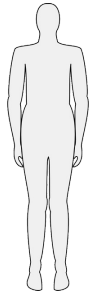
Dromedary camels



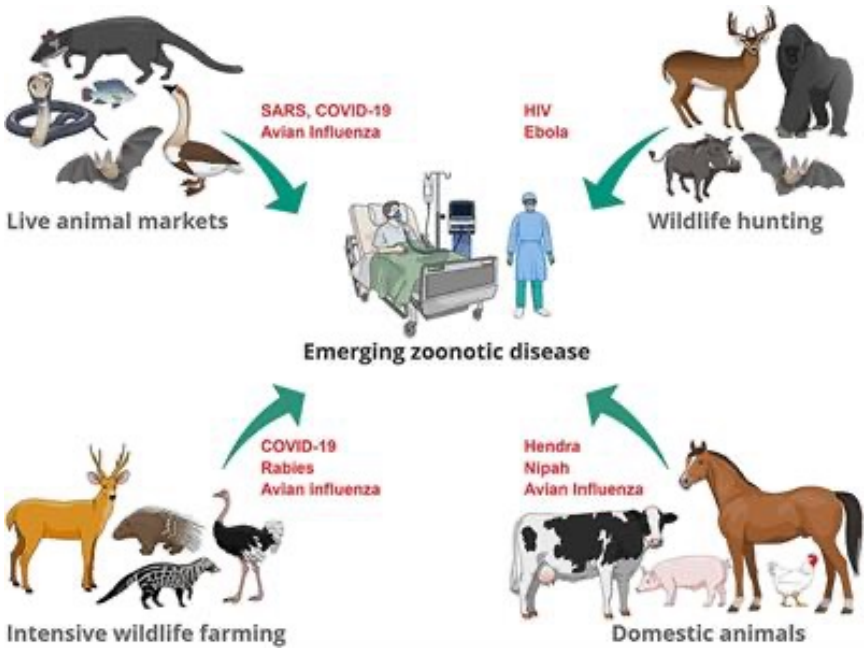
SARS-CoV-2
2019-

Rhinolophus (Horseshoe) bats

????



Did SARS-CoV-2 Result from a Natural Spillover Event or from a Laboratory-Acquired Infection?



2nd One Health Analysis

Humans

Individual

COVID-19 generates unusual disease characteristics including loss of taste and smell, widespread dermatological manifestations, and “long COVID.”

Clinical Manifestations of SARS-CoV-2 are Vast

EBioMedicine 58 (2020) 102887

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Review

The four horsemen of a viral Apocalypse: The pathogenesis of SARS-CoV-2 infection (COVID-19)

Pere Domingo[a,*], Isabel Mur[a], Virginia Pomar[a], Héctor Corominas[b], Jordi Casademont[c], Natividad de Benito[a]

[a] Infectious Diseases Unit, Hospital de la Santa Creu i Sant Pau, Institut de Recerca del Hospital de la Santa Creu i Sant Pau, Av. Sant Antoni Mª Claret, 167, 08025 Barcelona, Spain
[b] Departments of Rheumatology, Hospital de la Santa Creu i Sant Pau, Institut de Recerca del Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[c] Internal Medicine, Hospital de la Santa Creu i Sant Pau, Institut de Recerca del Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

ARTICLE INFO

Article History:
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Available online 29 July 2020

Keywords:
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SARS-CoV-2
ACE2
RAS
Hyperinflammatory state
Hypercoagulability
Acute lung injury
Adult distress respiratory syndrome

SUMMARY

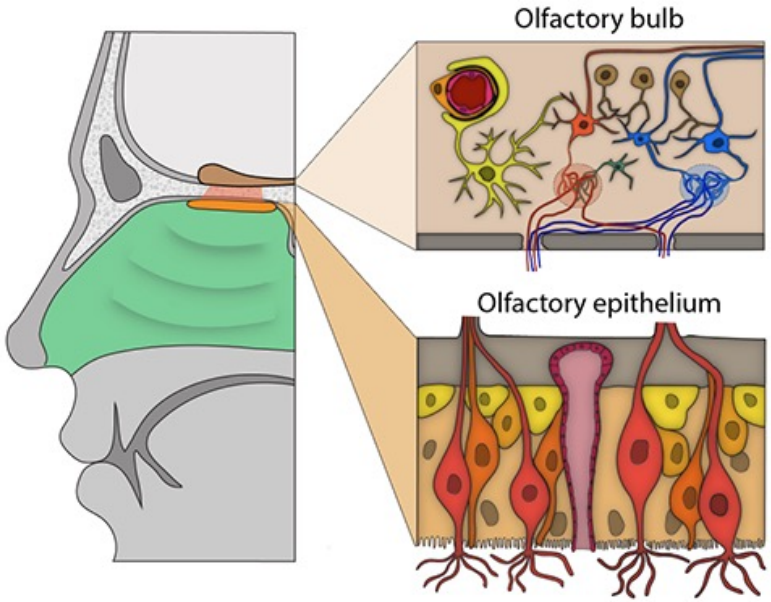
The pathogenesis of coronavirus disease 2019 (COVID-19) may be envisaged as the dynamic interaction between four vicious feedback loops chained or happening at once. These are the viral loop, the hyperinflammatory loop, the non-canonical renin-angiotensin system (RAS) axis loop, and the hypercoagulation loop. Severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 lights the wick by infecting alveolar epithelial cells (AECs) and downregulating the angiotensin converting enzyme-2 (ACE2)/angiotensin (Ang-1−7)/Mas1R axis. The viral feedback loop includes evading the host's innate response, uncontrolled viral replication, and turning on a hyperactive adaptative immune response. The inflammatory loop is composed of the exuberant inflammatory response feeding back until exploding in an actual cytokine storm. Downregulation of the ACE2/Ang-(1−7)/Mas1R axis leaves the lung without a critical defense mechanism and turns the scale to the inflammatory side of the RAS. The coagulation loop is a hypercoagulable state caused by the interplay between inflammation and coagulation in an endless feedback loop. The result is a hyperinflammatory and hypercoagulable state producing acute immune-mediated lung injury and eventually, adult respiratory distress syndrome.

Clinical *Similarities* between SARS, MERS, and SARS-CoV-2

- Median incubation period: 5-6 days
- Asymptomatic cases exist with all 3.
- Initial symptoms: fever, cough, chills, fatigue
- Respiratory: dyspnea, pneumonia, acute respiratory failure, ARDS
- Cardiac: acute myocardial infarction
- Gastrointestinal: nausea, vomiting, diarrhea
- Renal: Acute renal impairment
- Immune: Lymphopenia
- Hematologic: Thrombocytopenia

Clinical *Differences* between SARS-CoV-1, MERS-CoV, and SARS-CoV-2

- Nervous System: SARS-CoV-2 reported to cause **loss of smell and taste**.
- Dermatologic: SARS-CoV-2 has **many reports of** erythematous **rashes**, vesicular lesions, urticarial lesions, and other involvement. Not clear if from direct viral or systemic inflammatory effects.
- No **dermatologic** involvement reported with **SARS-CoV-1 or MERS-CoV**.
- Chronic sequelae: SARS and MERS have been reported to cause chronic fatigue, reduced pulmonary function, anxiety depression.
- **SARS-CoV-2 has extensive reports of long-term effects called "Long COVID"** including brain fog, loss of smell/taste, encephalopathy, cough, dyspnea, palpitations, heart failure, myocarditis, pericarditis, anxiety, depression.
- Global Case Fatality rates: SARS (9.6%), MERS (34.5%), SARS-CoV-2 (2%)



Olfactory neurons do not express ACE2 receptors
but olfactory epithelium cells do.

How COVID-19 Causes Loss of Smell

Olfactory support cells, not neurons, are vulnerable to novel coronavirus infection

By KEVIN JIANG | July 24, 2020 | Research

This article is part of Harvard Medical School's continuing coverage of medicine, biomedical research, medical education and policy related to the SARS-CoV-2 pandemic and the disease COVID-19.

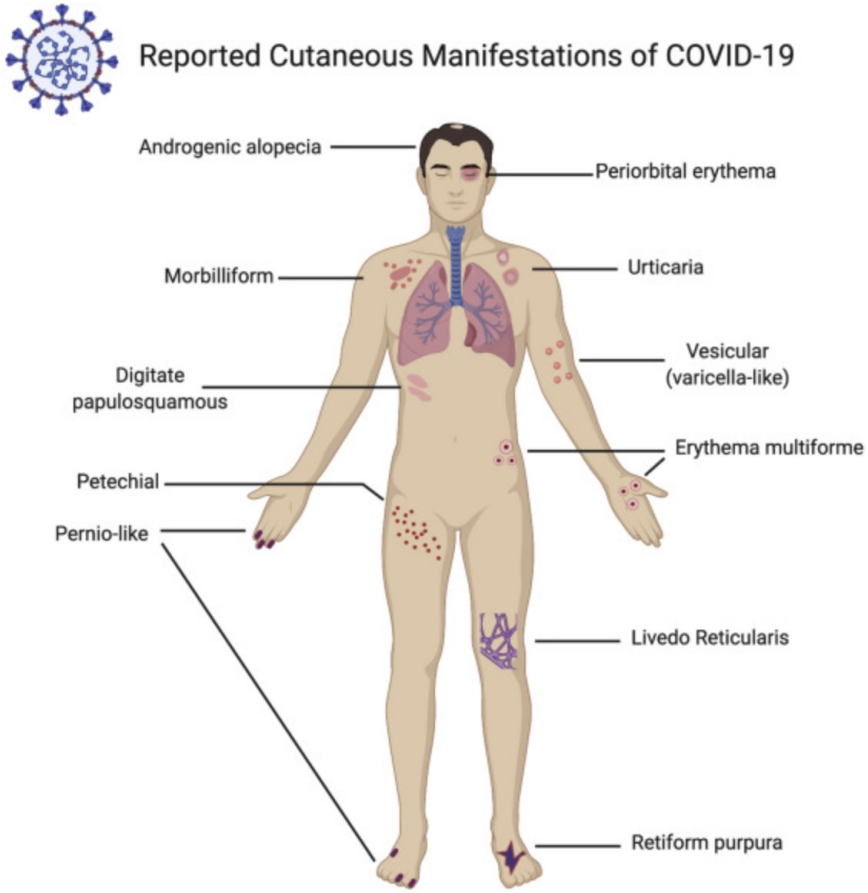


Fig 1 Reported cutaneous manifestations of coronavirus disease (*COVID-19*). These skin findings have been reported by clinicians as potential signs of COVID-19. Most of these highly variable and rare findings reported in case reports and small case series may not be specific to severe acute respiratory syndrome coronavirus 2 infection. We urge caution and continued scholarship moving forward to decipher what impact COVID-19 has on skin.

JAAD, Vesely and Perkins. July 15, 2020 83(4): E321-E322.

What Is 'Covid Toe'? Maybe a Strange Sign of Coronavirus Infection

Dermatologists say the lesions should prompt testing for the virus, even though many patients have no other symptoms.

Give this article

Chilblains, the painful red inflammations that are normally associated with exposure to cold air. A similar condition has been showing up in Covid-19 patients. Science Source

New York Times, May 1, 2020

Coronavirus FAQ: What is long COVID? And what is my risk of getting it?

November 18, 2021 · 12:53 PM ET

MICHAELEEN DOUCLEFF

6-Minute Listen

+ PLAYLIST

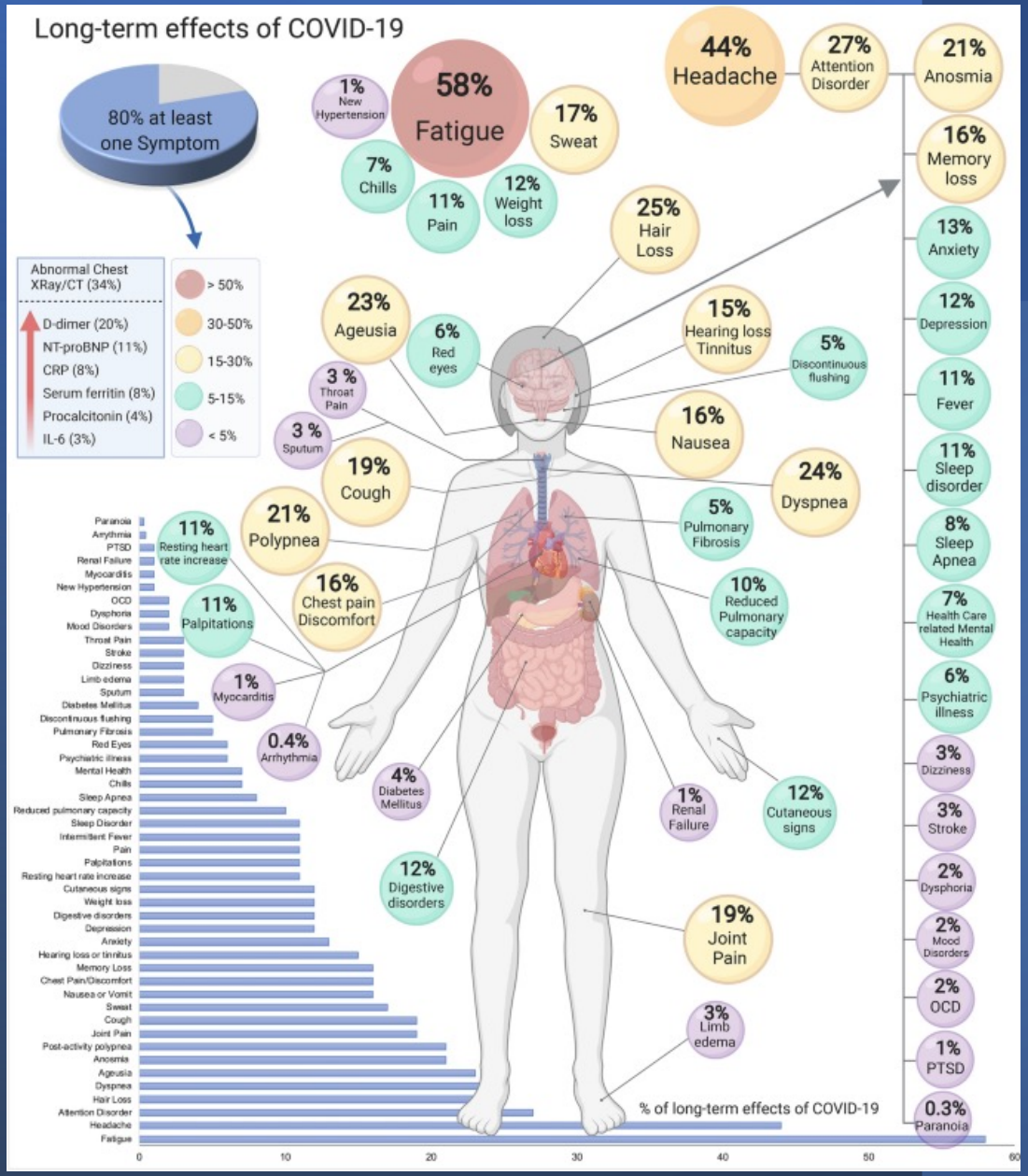
RLT_Images/Getty Images

OPEN

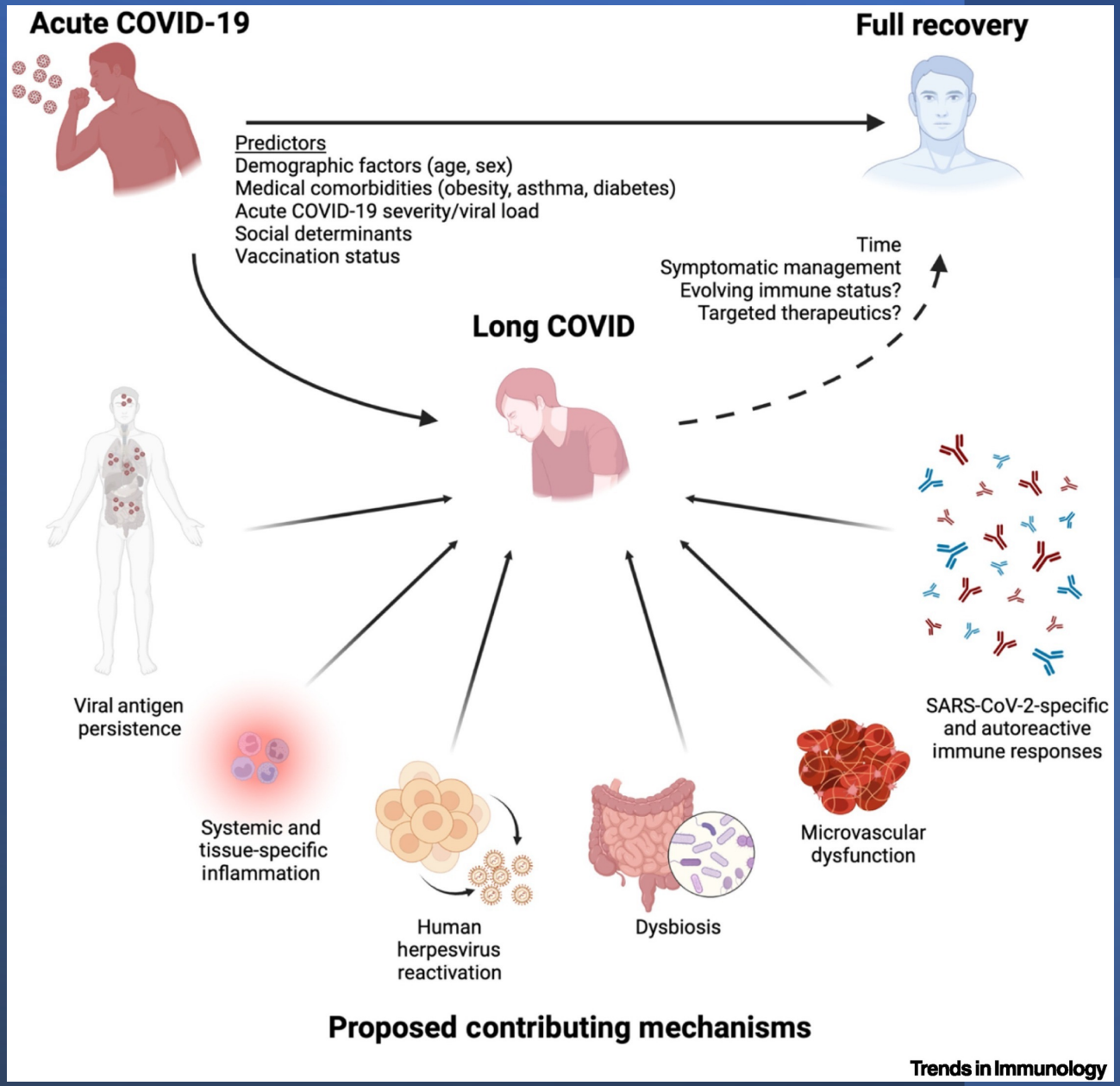
More than 50 long-term effects of COVID-19: a systematic review and meta-analysis

Sandra Lopez-Leon[1], Talia Wegman-Ostrosky[2], Carol Perelman[3], Rosalinda Sepulveda[4], Paulina A. Rebolledo[5,6], Angelica Cuapio[7] & Sonia Villapol[8,9]✉

COVID-19 can involve persistence, sequelae, and other medical complications that last weeks to months after initial recovery. This systematic review and meta-analysis aims to identify studies assessing the long-term effects of COVID-19. LitCOVID and Embase were searched to identify articles with original data published before the 1st of January 2021, with a minimum of 100 patients. For effects reported in two or more studies, meta-analyses using a random-effects model were performed using the MetaXL software to estimate the pooled prevalence with 95% CI. PRISMA guidelines were followed. A total of 18,251 publications were identified, of which 15 met the inclusion criteria. The prevalence of 55 long-term effects was estimated, 21 meta-analyses were performed, and 47,910 patients were included (age 17–87 years). The included studies defined long-COVID as ranging from 14 to 110 days post-viral infection. It was estimated that 80% of the infected patients with SARS-CoV-2 developed one or more long-term symptoms. The five most common symptoms were fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%). Multi-disciplinary teams are crucial to developing preventive measures, rehabilitation techniques, and clinical management strategies with whole-patient perspectives designed to address long COVID-19 care.



Scientific Reports. Lopez-Leon S, Wegman-Ostrosky T, et al. (2021) 11:16144



Trends in Immunology (2022) 43(4): 268-270.

Open Forum Infectious Diseases

Article Contents

ACCEPTED MANUSCRIPT

The protective effect of covid-19 vaccination on post-acute sequelae of covid-19 (pasc): a multicenter study from a large national health research network

Sokratis N. Zisis, M.D ✉, Jared C. Durieux, M.S, M.D.S, M.P.H, Christian Mouchati, M.D, Jamie A. Perez, Ph.D, Grace A. McComsey, M.D, FIDSA ✉

Open Forum Infectious Diseases, ofac228, https://doi.org/10.1093/ofid/ofac228

Published: 07 May 2022 **Article history** ▾

Abstract

Background

COVID-19 vaccines have been proven to decrease the severity of acute phase infection, however little is known about its effect on Post-Acute Sequelae of COVID-19 (PASC).

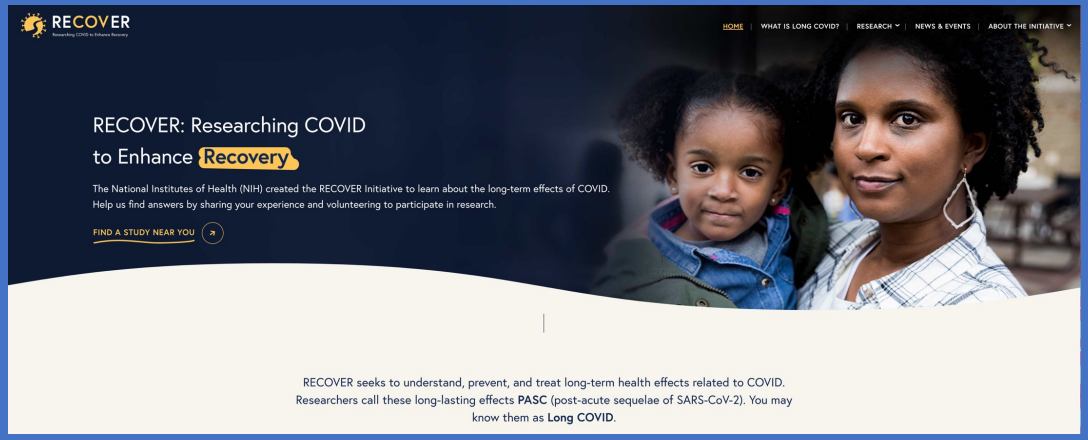
NEWS | 04 March 2021

US health agency will invest $1 billion to investigate 'long COVID'

The National Institutes of Health will fund researchers to track people's recovery, and will host a biospecimen bank.

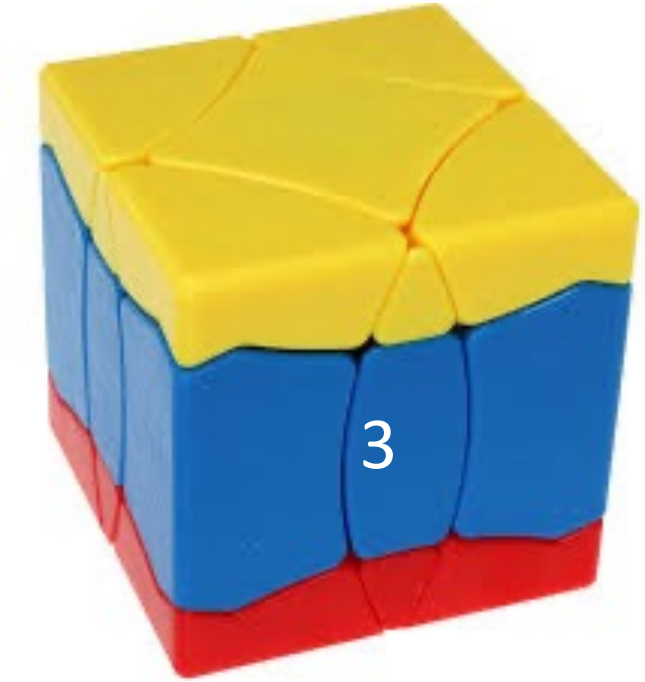
Nidhi Subbaraman

US National Institutes of Health director Francis Collins has announced an initiative to study the effects of COVID-19 that can last for weeks or months. Credit: Saul Loeb/CNP via Zuma Wire



3rd One Health Analysis

Environment



Microbial/Cellular

SARS-CoV-1 and MERS-CoV primarily transmitted by respiratory droplets;
SARS-CoV-2 primarily by airborne transmission.

Environmental Transmission

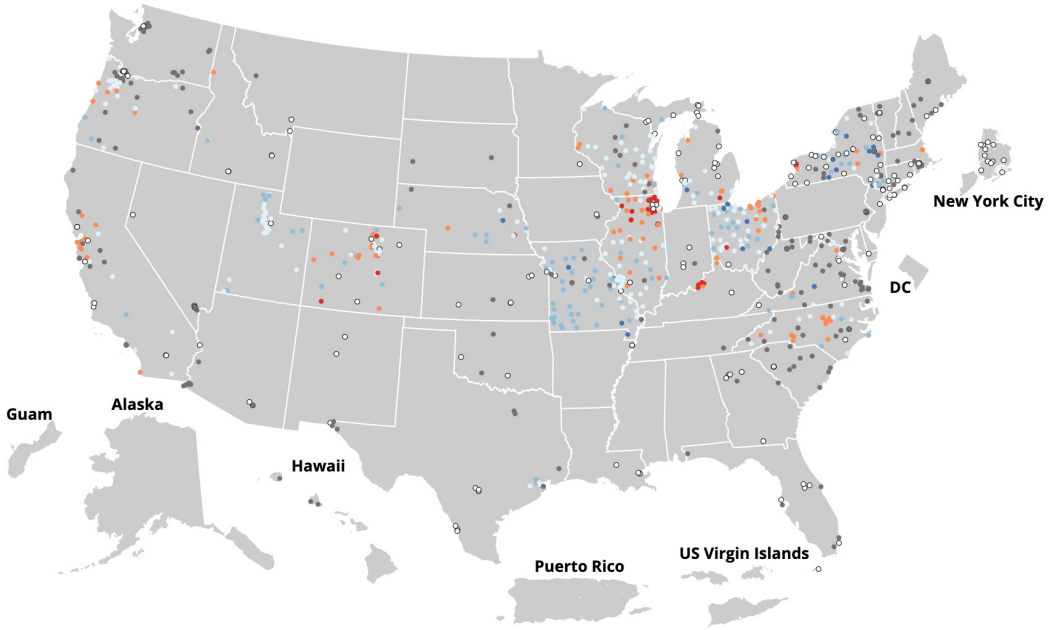
	SARS-CoV-1	MERS-CoV	SARS-CoV-2	Delta Variant	Omicron Variant
Estimated R_0	1.7 to 3.6	0.45 to 8	2.5 to 6.1	3.2 to 8 Mean 5.08	3 to 9.4
Primary Mode of Spread	Respiratory Droplets	Respiratory Droplets	Airborne (Indoors)	Airborne (Indoors)	Airborne (Indoors)
Airborne Transmission Possible	Yes	Yes	Yes	Yes	Yes
Wastewater Detection (Urine & Feces)	Yes	Yes	Yes	Yes	Yes

R_0 = number of people that 1 infected person will infect.
Public health goal: $R_0 < 1$.
(Comparison: Measles R_0 often cited as ranging from 12 to 18)

CDC National Wastewater Surveillance System Provides Early Warning of Viral Spread

Current virus levels in wastewater by site
This metric shows whether SARS-CoV-2 levels at a site are currently higher or lower than past historical levels at the same site. 0% means levels are the lowest they have been at the site; 100% means levels are the highest they have been at the site. Public health officials watch for increasing levels of the virus in wastewater over time and use these data to help make public health decisions.

⚠ **Note:** Sites began collecting data at different times. Sites that began reporting wastewater data after December 1, 2021 are not comparable to sites that started reporting data on or before December 1, 2021. The data history for these new sites is not long enough to reflect the same surges as the other sites.



Current SARS-CoV-2 virus levels by site, United States

Current virus levels category	Num. sites	% sites	Category change in last 7 days
New Site	177	25	5%
0% to 19%	21	3	– 30%
20% to 39%	123	18	– 22%
40% to 59%	231	33	0%
60% to 79%	114	16	18%
80% to 100%	35	5	21%

Total sites with current data: 701
Total number of wastewater sampling sites: 897

How is the current SARS-CoV-2 level compared to past levels calculated?

Select legend categories to filter points on the map.

New site | 0% to 19% | 20% to 39% | 40% to 59% | 60% to 79% | 80% to 100% | No recent data

CDC COVID Data Tracker: Wastewater Surveillance

Indoor air quality is important for disease prevention.

frontiers in Public Health

ORIGINAL RESEARCH
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Critical Role of the Subways in the Initial Spread of SARS-CoV-2 in New York City

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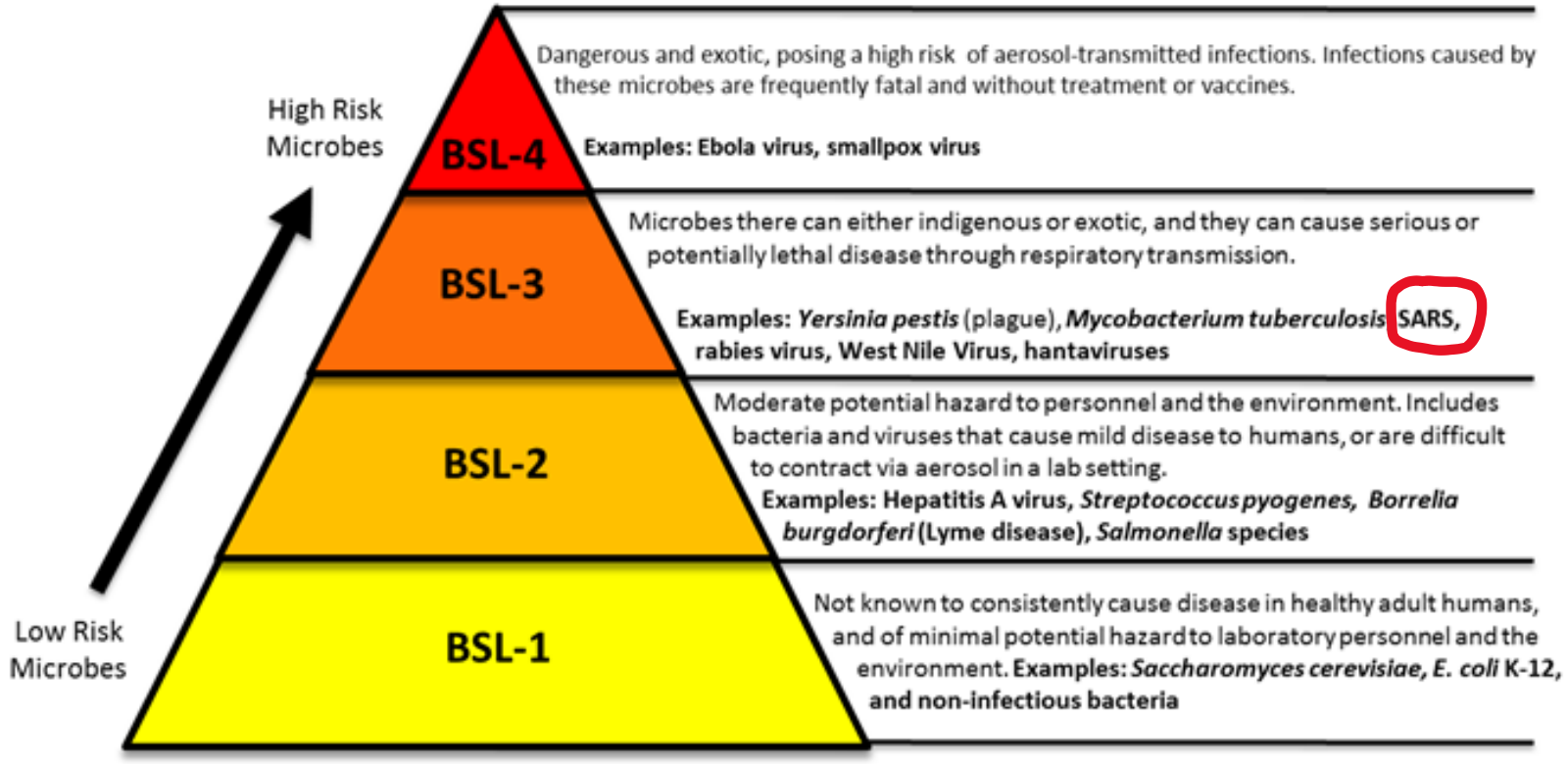
Fourth One Health Analysis

Biosafety/Biosecurity/Bioethics

Political, Social, Economic Factors

Furin cleavage sites have been inserted into spike proteins of SARS-CoV-1 since 2005.
Furin cleavage site in SARS-CoV-2 is suggestive but not conclusive to be from laboratory insertion.

BIOSAFETY



https://biosafety.utk.edu/biosafety-program/the-biosafety-program/biosafety-manual/2-principles-of-biosafety/

MIT Technology Review

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PANDEMIC TECHNOLOGY PROJECT

Inside the risky bat-virus engineering that links America to Wuhan

China emulated US techniques to construct novel coronaviruses in unsafe conditions.

By Rowan Jacobsen June 29, 2021

MS TECH | AP

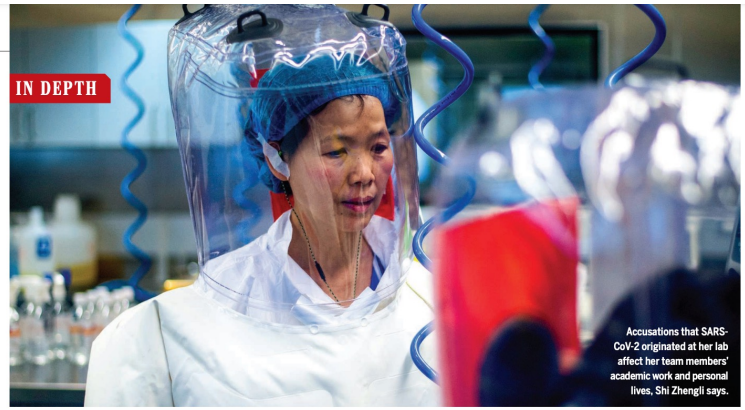
Research with SARS in Wuhan, China done in BSL 2 labs.

The NIH decided the risk was worth it. In a potentially fateful decision, it funded work similar to Baric's at the Wuhan Institute of Virology, which soon used its own reverse-genetics technology to make numerous coronavirus chimeras.

Unnoticed by most, however, was a key difference that significantly shifted the risk calculation. The Chinese work was carried out at biosafety level 2 (BSL-2), a much lower tier than Baric's BSL-3+.

What caused the covid-19 pandemic remains uncertain, and Shi says her lab never encountered the SARS-CoV-2 virus before the Wuhan outbreak. But now that US officials have said the possibility of a lab accident needs to be investigated, the spotlight has fallen on American funding of the Wuhan lab's less safe research. Todaya chorus of scientists, including Baric, are coming forward to say this was a misstep. Even if there is no link to covid-19, allowing work on potentially dangerous bat viruses at BSL-2 is "an actual scandal," says Michael Lin, a bioengineer at Stanford University.

Rowan Jacobsen. MIT Technology Review. June 29, 2021



Accusations that SARS-CoV-2 originated at her lab affect her team members' academic work and personal lives, Shi Zhengli says.

COVID-19

Wuhan coronavirus hunter Shi Zhengli speaks out

China's "Bat Woman" denies responsibility for the pandemic, demands apology from Trump

By **Jon Cohen**

lab has isolated and grown in culture only three bat coronaviruses related to one that in- | emy of Sciences, of which WIV is part, and evolutionary biologist Kristian Andersen of | Down

Q: Given that coronavirus research in most places is done in BSL-2 or BSL-3 labs--and indeed, you WIV didn't even have an operational BSL-4 until recently--why would you do any coronavirus experiments under BSL-4 conditions?

A: The coronavirus research in our laboratory is conducted in BSL-2 or BSL-3 laboratories.

After the BSL-4 laboratory in our institute has been put into operation, in accordance with the management regulations of BSL-4 laboratory, we have trained the scientific researchers in the BSL-4 laboratory using the low-pathogenic coronaviruses as model viruses, which aims to prepare for conducting the experimental activities of highly pathogenic microorganisms.

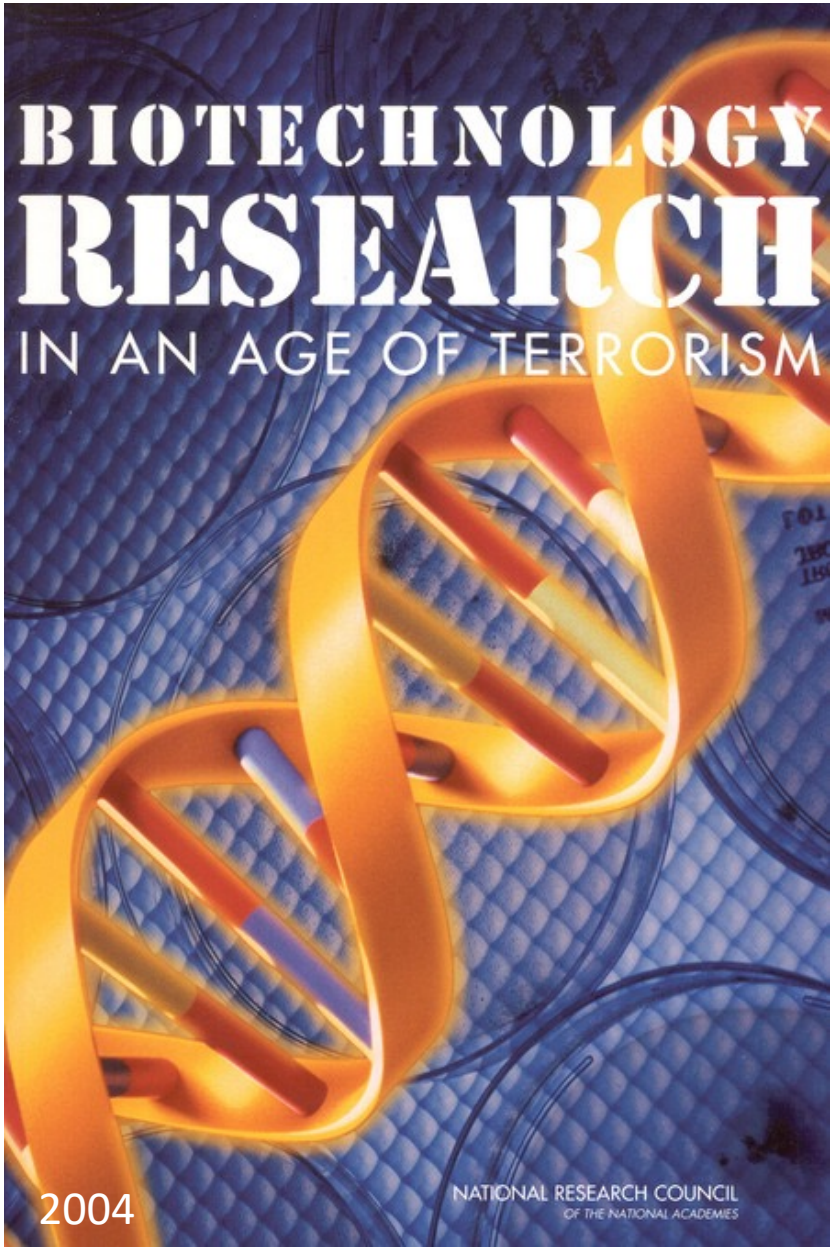
After the COVID-19 outbreak, our country has stipulated that the cultivation and the animal infection experiments of SARS-CoV-2 should be carried out in BSL-3 laboratory or above. Since the BSL-3 laboratories in our institute do not have the hardware conditions to conduct experiments on non-human primates, and in order to carry out the mentioned research, our institute had applied to the governmental authorities and obtained the qualification to conduct experiments on SARS-CoV-2 for Wuhan P4 laboratory, in which the rhesus monkey animal model, etc. have been carried out.

The experimental activities are supervised by our institute's biosafety committee and complied with the biosafety regulations.

Research carried out in BSL 2 labs.
After pandemic, should be done in BSL 3 labs.

Science (2020) 369(6503): 487-488.
In depth interview: https://www.science.org/pb-assets/PDF/News%20PDFs/Shi%20Zhengli%20Q&A-1630433861.pdf

Biosecurity and Bioethics



Outlined 7 Experiments of Concern

Seven Experiments of Concern That Should Not Be Done

- Show how to render a vaccine ineffective
- Confer resistance to therapeutically useful antibiotics or antivirals
- Enhance the virulence of a pathogen or make a nonpathogen virulent
- Increase transmissibility of a pathogen
- Alter the host range of a pathogen
- Enable to evasion of diagnostic/detection modalities
- Enable the weaponization of a biological agent or toxin

NIH Gain of Function Research Definition

"…improves the ability of a pathogen to cause disease…"

Gain-of-Function Research

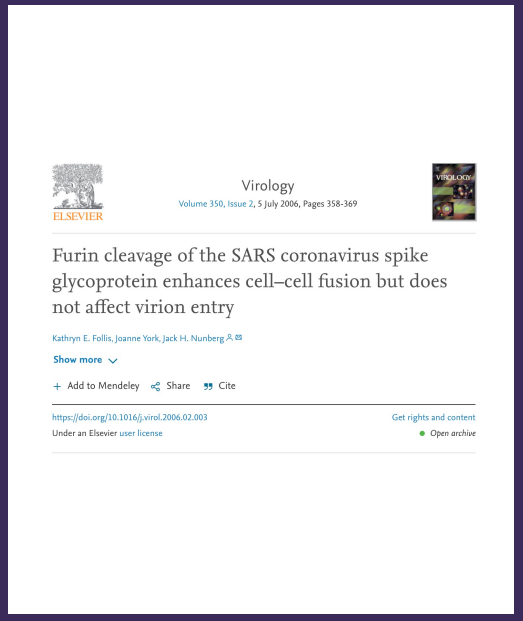
Gain-of-function (GOF) studies, or research that improves the ability of a pathogen to cause disease, help define the fundamental nature of human-pathogen interactions, thereby enabling assessment of the pandemic potential of emerging infectious agents, informing public health and preparedness efforts, and furthering medical countermeasure development.

Gain-of-function studies may entail biosafety and biosecurity risks; therefore, the risks and benefits of gain-of function research must be evaluated, both in the context of recent U.S. biosafety incidents and to keep pace with new technological developments, in order to determine which types of studies should go forward and under what conditions.

To address the biosafety and biosecurity risks associated with undertaking such research and ensure that they are adequately considered and appropriately mitigated to safely realize the potential benefits, the Department of Health and Human Services (HHS) adopted a pre-funding review mechanism in 2017. The HHS Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens (P3CO) is intended to guide HHS funding decisions on proposed research that is reasonably anticipated to create, transfer, or use PPPs resulting from the enhancement of a pathogen's transmissibility or virulence in humans (enhanced PPPs). Enhanced PPP do not include naturally occurring pathogens that are circulating in or have been recovered from nature, regardless of their pandemic potential.

- Department of Health and Human Services Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens

This page last reviewed: June 03, 2021



ELSEVIER

Virology

Volume 350, Issue 2, 5 July 2006, Pages 358-369

Furin cleavage of the SARS coronavirus spike glycoprotein enhances cell–cell fusion but does not affect virion entry

Kathryn E. Follis, Joanne York, Jack H. Nunberg

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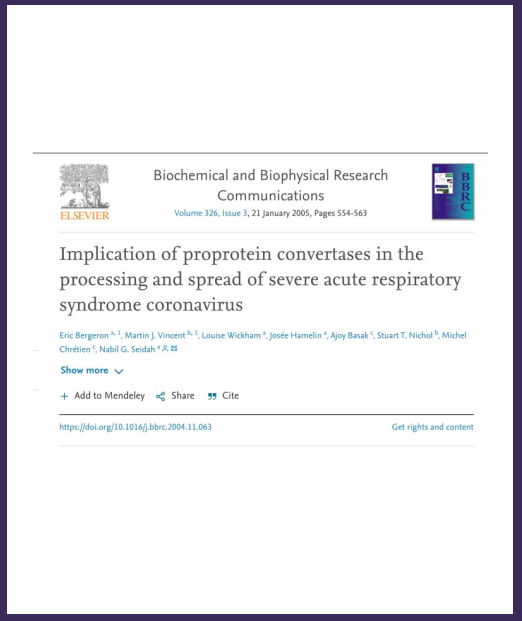

ELSEVIER

Biochemical and Biophysical Research Communications

Volume 326, Issue 3, 21 January 2005, Pages 554-563

Implication of proprotein convertases in the processing and spread of severe acute respiratory syndrome coronavirus

Eric Bergeron, Martin J. Vincent, Louise Wickham, Josée Hamelin, Ajoy Basak, Stuart T. Nichol, Michel Chrétien, Nabil G. Seidah

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American Society for Microbiology

Journal of Virology

Volume 82, Issue 23, 1 December 2008, Pages 11985-11991

https://doi.org/10.1128/JVI.01412-08

VIRUS-CELL INTERACTIONS

Entry from the Cell Surface of Severe Acute Respiratory Syndrome Coronavirus with Cleaved S Protein as Revealed by Pseudotype Virus Bearing Cleaved S Protein

Rie Watanabe[1], Shutoku Matsuyama[1], Kazuya Shirato[1], Masami Maejima[1], Shuetsu Fukushi[2], Shigeru Morikawa[2], and Fumihiro Taguchi[1,*]

[1]Departments of Virology III

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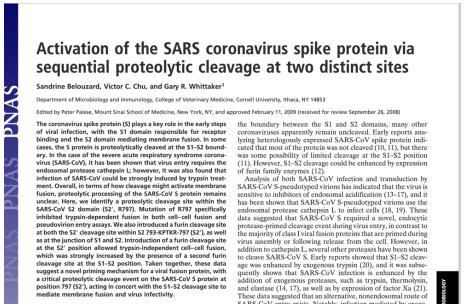


PNAS

Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites

Sandrine Belouzard, Victor C. Chu, and Gary R. Whittaker[1]

Department of Microbiology and Immunology, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853

Edited by Peter Palese, Mount Sinai School of Medicine, New York, NY, and approved February 11, 2009 (received for review September 26, 2008)

The coronavirus spike protein (S) plays a key role in the early steps of viral infection, with the S1 domain responsible for receptor binding and the S2 domain mediating membrane fusion. In some cases, the S protein is proteolytically cleaved at the S1–S2 boundary. In the case of the severe acute respiratory syndrome coronavirus (SARS-CoV), it has been shown that virus entry requires the endosomal protease cathepsin L; however, it was also found that infection of SARS-CoV could be strongly induced by trypsin treatment. Overall, in terms of how cleavage might activate membrane fusion, proteolytic processing of the SARS-CoV S protein remains unclear. Here, we identify a proteolytic cleavage site within the SARS-CoV S2 domain (S2′, R797). Mutation of R797 specifically inhibited trypsin-dependent fusion in both cell–cell fusion and pseudovirion entry assays. We also introduced a furin cleavage site at both the S2′ cleavage site within S2 793-KPTKR-797 (S2′), as well as at the junction of S1 and S2. Introduction of a furin cleavage site at the S2′ position allowed trypsin-independent cell–cell fusion, which was strongly increased by the presence of a second furin cleavage site at the S1–S2 position. Taken together, these data suggest a novel priming mechanism for a viral fusion protein, with a critical proteolytic cleavage event on the SARS-CoV S protein at position 797 (S2′), acting in concert with the S1–S2 cleavage site to mediate membrane fusion and virus infectivity.

the boundary between the S1 and S2 domains, many other coronaviruses apparently remain uncleaved. Early reports analyzing heterologously expressed SARS-CoV spike protein indicated that most of the protein was not cleaved (10, 11), but there was some possibility of limited cleavage at the S1–S2 position (11). However, S1–S2 cleavage could be enhanced by expression of furin family enzymes (12).

Analysis of both SARS-CoV infection and transduction by SARS-CoV S-pseudotyped virions has indicated that the virus is sensitive to inhibitors of endosomal acidification (13–17), and it has been shown that SARS-CoV S-pseudotyped virions use the endosomal protease cathepsin L to infect cells (18, 19). These data suggested that SARS-CoV S required a novel, endocytic protease-primed cleavage event during virus entry, in contrast to the majority of class I viral fusion proteins that are primed during virus assembly or following release from the cell. However, in addition to cathepsin L, several other proteases have been shown to cleave SARS-CoV S. Early reports showed that S1–S2 cleavage was enhanced by exogenous trypsin (20), and it was subsequently shown that SARS-CoV infection is enhanced by the addition of exogenous proteases, such as trypsin, thermolysin, and elastase (14, 17), as well as by expression of factor Xa (21). These data suggested that an alternative, nonendosomal route of

Virologists have been inserting furin cleavage sites into SARS spike proteins since 2005.

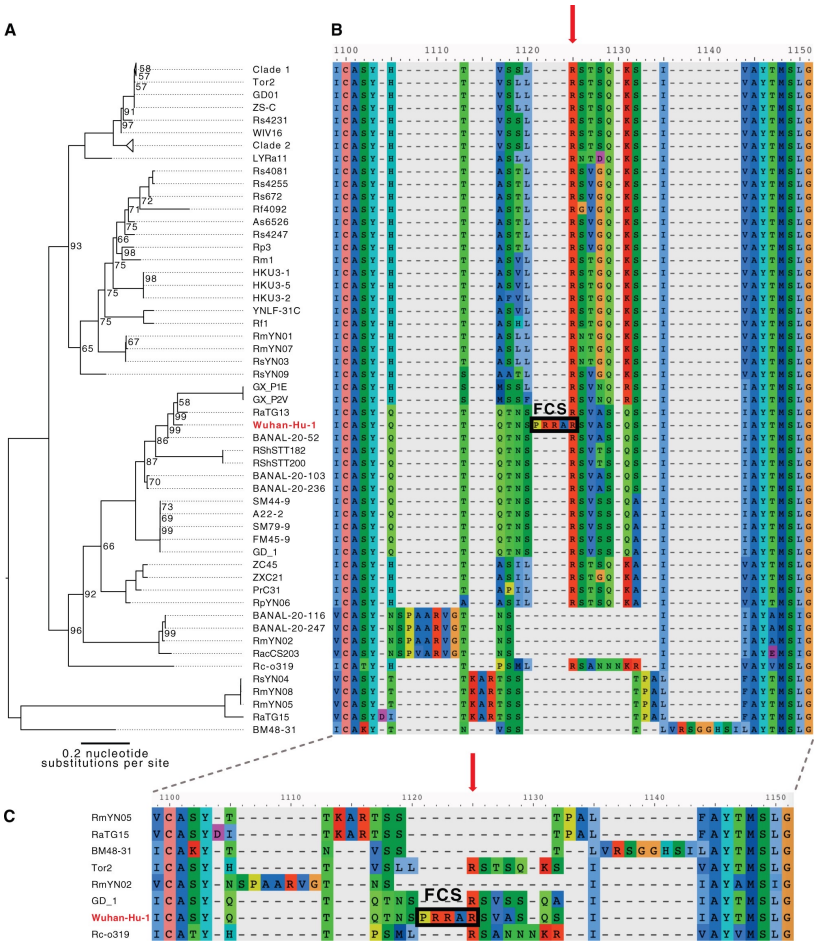
Laboratory biosafety levels not mentioned in papers.

SARS-CoV-1, MERS-CoV, SARS-CoV-2 Comparison

Features	SARS-CoV-1	MERS-CoV	SARS-CoV-2
Human Receptor Binding Site	ACE2	DPP4	ACE2
Furin Cleavage Site (FCS)	No	Yes	Yes
Location of FCS	N/A	S1/S2 junction & S2’	S1/S2 junction

Was a furin cleavage site inserted into SARS-CoV-2?

Fig. 1. Phylogenetic tree of the spike gene (A) and alignments of the S1/S2 region of the FCS by codon sequences (B). ...



Comparison with other Sarbecoviruses.

Naturally-occurring or Genetically engineered?

Mol Biol Evol, Volume 39, Issue 1, January 2022, msab327, https://doi.org/10.1093/molbev/msab327

One Health Mini Analysis Recap

One Health Factors:

Animals
(Domestic & Wild)

Humans

Environments

Biosafety/Biosecurity/Bioethics

Complexity Factors:

Populations

Individuals

Microbial/Cellular

Political/Social/Economic Factors

Time Factor: Years

One Health Mini Analysis Findings

- Coronavirus epidemics have been occurring in domesticated food animals at least since the early 1930s.
- Most transmission has been fecal-oral, but aerosolization possible.
- Natural spillover data (animal antibodies and antibodies from occupational exposures) exists for SARS-CoV-1 and MERS-CoV, but not for SARS-CoV-2.
- COVID-19 generates unusual disease characteristics including loss of taste and smell, widespread dermatological manifestations, and “long COVID.”
- SARS-CoV-1 and MERS-CoV primarily transmitted by respiratory droplets; SARS-CoV-2 primarily by airborne transmission.
- Furin cleavage sites have been inserted into spike proteins of SARS-CoV-1 since 2005.
- Furin cleavage site in SARS-CoV-2 is suggestive but not conclusive to be from laboratory insertion.

NIH lifts 3-year ban on funding risky virus studies

New proposals that make pathogens more dangerous will go through special review

19 DEC 2017 · BY JOCELYN KAISER

A researcher works on a study of the H5N1 avian influenza virus. CDC/GREG KNOBLOCH/SCIENCE SOURCE

Where do we go from here?

According to the WHO, COVID-19 has infected > 520M and killed >6M globally.

In the US alone, >81M cases and >1M deaths.

It behooves us to develop policies to reduce the risks of another pandemic happening soon.

Both origin possibilities (natural spillover and laboratory accident) must be examined and addressed.

Gain of function research must be examined and addressed.

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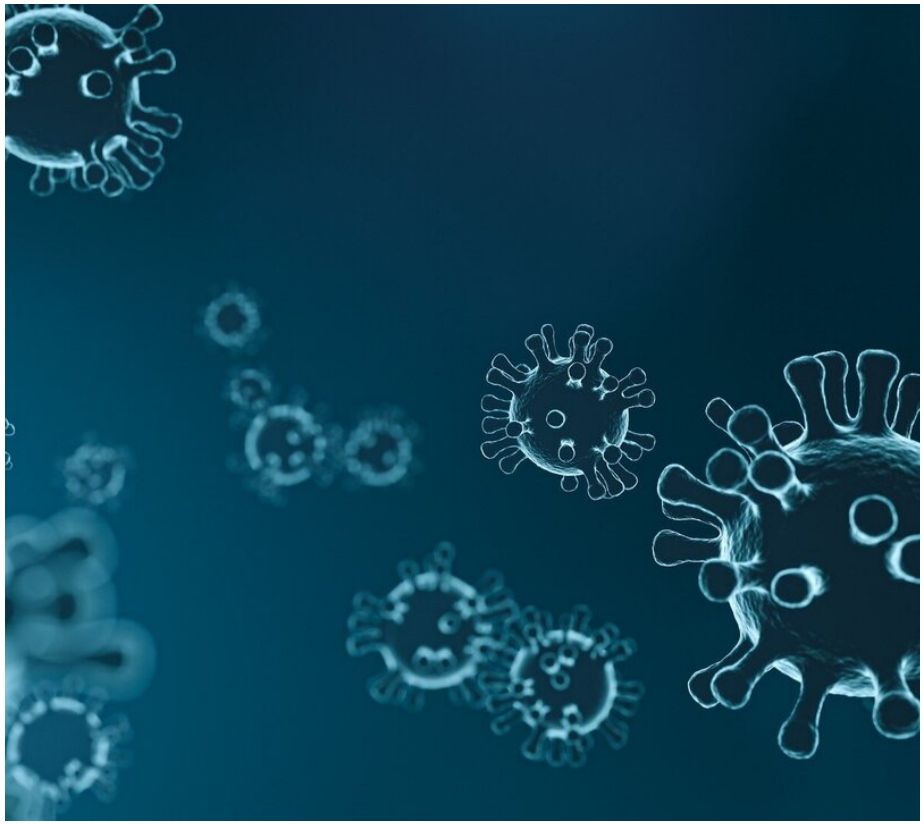
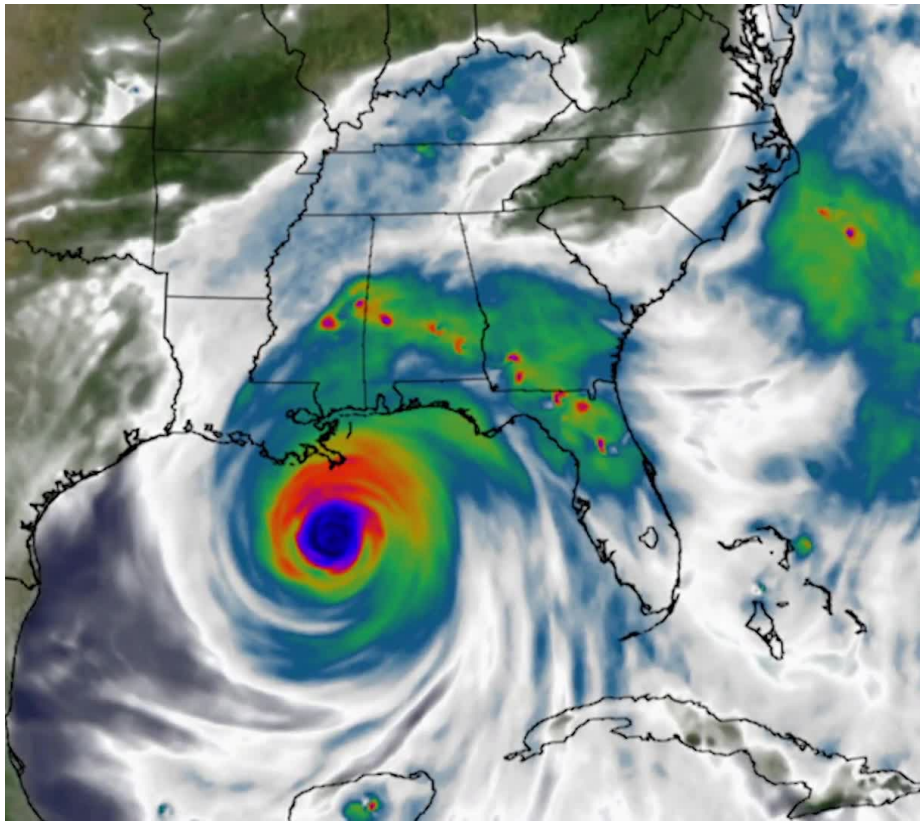
LAB-GENERATED PANDEMICS ARE A CONSTANT THREAT

The rapidly increasing power and rapidly decreasing cost of advanced biotechnology has made lab-generated pandemics a threat to the survival of the human species. Remarkably, despite the major risks to the public, dangerous "gain-of-function" research that enhances potential pandemic pathogens (ePPP research) is subject to almost no national or international oversight. Moreover, to date, the public largely

Predicting Pandemics vs. Predicting Hurricanes





Predicting hurricanes does not include manipulating clouds; surveillance only.

We must learn to live sustainably on Earth.

One Health recognizes that life is interconnected.

The One Health matrix revealed the connections between animals, humans, and environments.

What should we do?

- Societal challenges require political solutions.
- Bipartisan inquiry into the pandemics' origins and public health responses.
- We must learn from our mistakes if we are to develop effective policies to prevent future catastrophes.
- Scientific inquiries must be safe, secure, transparent, and ethical.

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Welcome to "Bats, Ducks, and Pandemics: An Introduction to One Health Policy".

One Health is the concept that human, animal, and environmental/ecosystem health are linked. The concept provides a useful framework for examining complex health issues such as food safety and security, emerging and vector-borne diseases, and antimicrobial resistance. It can be used to analyze government policies to determine if they are effective in improving health and well-being.

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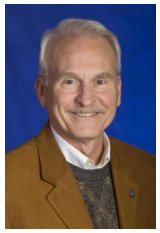

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Becky Barrentine

Dick Seifman

http://www.onehealthinitiative.com

Thank you! Questions?

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