Pandemic origins and a One Health approach to preparedness and prevention: solutions based on SARS-CoV-2 and other RNA viruses

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Supporting information for:

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Table S.1. List of individuals interviewed and affiliation

Part of the Task Force's information gathering strategy involved interviews of expert international scientists with diverse backgrounds, interests, and experience. These interviews were confidential and available to Task Force members alone for the purpose of broadening our insights and perspectives on the relevant issues addressed in the manuscript. We acknowledge the value of these discussions and thank the individuals interviewed for the gift of their valuable time. The manuscript itself is a product of the Task Force members alone, who bear sole responsibility for its content, conclusions, and recommendations.

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Table S. 2. Representative emerging RNA virus pathogens affecting humans, 1967 - 2015 (excluding coronaviruses).

Virus	Family*	Year of outbreak /virus discovery	Zoonotic	Ancestral or Reservoir Host† [years to publication of discovery], (reference)	Intermediate, amplifying or alternate host [years to publication of discovery], (reference)	Repeated spillovers	Person-to-Person Trans-mission
Marburg	F	1967 (N)‡	Yes	Bats [40 yrs], (1-3)	Primates [<1 yr], (4)	Yes	Yes
Influenza A (H3N2)	O	1968 (N)	Yes	Aquatic birds [>20 yrs], (5, 6)	Unknown, possibly swine (6)	Yes	Yes
Lassa	A	1969 (N)	Yes	*Mastomys* rodents [5 yrs], (7)	N/A	Yes	Yes
Ebola	F	1976 (N)*	Yes	Bats† [29 yrs], (8)	Non-human Primates [23 yrs], (9)	Yes	Yes
HIV	R	1983 (N)	Yes	Non-human primates [6 yrs]**, (10)	N/A	Yes	Yes
Sin Nombre §	B	1993 (N)	Yes	Rodents†♦ [1 yr], (11)	N/A	Yes	No
Hendra	P	1994 (N)	Yes	Bats [serologically 2 yrs; by viral isolation 6 years], (12, 13)	Horses, including Koch's postulates [<1 yr], (14)	Yes	No
Nipah	P	1998 (N)	Yes	Bats† [serologically 3 yrs; by viral isolation 4 years], (15, 16)	Swine [epidemiological connection <1 yr; definitive proof & Koch's postulates ~2 yrs], (17, 18)	Yes	Yes

Influenza A (H1N1-pdm09)	O	2009 (K)	Yes	Swine[†]/Avian/ Human [7 yrs], (19)	Swine [<1 yr], (20)	Yes	Yes
Zika	FL	1947(N) 2007 (K) 2015 (K)	Yes	Non-human primates [0 yrs] [+], (21)	*Aedes* sp. mosquitos [22 yrs], (22, 23)	Yes	Yes

Key and notes:

N/A = not applicable, for example if no amplifier hosts are known.

*F = *Filoviridae*; O = *Orthomyxoviridae*; A = *Arenaviridae*; R = *Retroviridae*; P = *Paramyxoviridae*; B = *Bunyaviridae*; FL = *Flaviviridae*.

[†] Indicates the reservoir host can directly transmit infection to humans.

[‡] N = newly discovered; K = previously known.

**The SIV group of viruses was discovered in macaques in a paper published 6 years after the discovery of HIV-1. However, definitive evidence of the specific non-human primate reservoirs took 13 years for HIV-1 (the chimpanzee, (24)), and 6 years for HIV-2 (the sooty mangabey, (25)).

[§] Sin nombre virus (New World Hantavirus) is the first identified cause of Hantavirus pulmonary syndrome. Multiple Old World hantaviruses causing hemorrhagic fever syndromes have been identified since 2016.

♦Hantaviruses have been reported from >80 mammalian species, including 51 rodent spp. of at least 7 genera, 7 bat spp. and 20 shrew or mole spp. (order Soricomorpha) (26, 27). Some authors consider bats a likely ancestral origin of the viral family because bats are evolutionarily older mammals than rodents, so that viruses that coevolved with bats may have used conserved cell receptors to allow colonization of other mammal groups (28).

¶Influenza H1N1(pdm09) emerged in swine via reassortment of North American triple reassortant swine viruses (themselves derived by reassortment and acquiring gene segments from human, swine and avian influenza viruses) and Eurasian avian-origin swine viruses. The pdm09 H1 hemagglutinin is antigenically distinct from then circulating typical seasonal influenza H1N1 viruses and derived from the 1918 pandemic-like influenza viruses that have persisted in swine.

[+]Zika virus is unusual, in that it was discovered first in its reservoir host, and then decades later caused the first known outbreak in people.

Discussion: The information in Table S. 2. is derived from the experience with 10 RNA viruses from 7 virus families that emerged and resulted in disease outbreaks between 1967 (Marburg) and 2015 (Zika), exclusive of SARS-CoV and MERS-CoV which are described in Table S. 3. All examples in Table S. 2 originated from ancestor viruses present in bats, avian species, or mammals such as rodents or swine. All are zoonotic, i.e. the outbreak was due to initial transmission from animals to humans, including some directly from the reservoir host to people. Most infect humans by spillover transmission from secondarily infected intermediate hosts, including a mosquito vector in the case of Zika virus. And all have been documented to result in repeated spillovers, ranging from frequent to intermittent. In addition, 8 of the 10 are

transmitted human-to-human, resulting in larger outbreaks, local, regional or international spread, and serious illness and death in substantial numbers of people especially over multiple outbreaks.

Table S. 3. Human coronaviruses causing common colds, SARS, MERS, and COVID-19 and recent animal CoV spillover infections in humans

Human Coronaviruses [genus] & (reference)	Year of identification (emergence estimated by MRCA*)	Zoonotic	Ancestral or Reservoir Host (years to discovery).	Amplifier, intermediate or alternate host (years to discovery)	Repeated spillover	Person-to-Person Transmission
Common cold viruses (Endemic in humans)						
HCoV-NL63 (alpha-CoV) (29)	2003 (1218-1518*)	Yes	Bats (?)	?	?	Yes (endemic)
HCoV-229E (alpha-CoV) (30-33)	1966 (1718-1818*)	Yes	Bats (?)	Dromedary camels (50 yrs)	?	Yes (endemic)
HCoV-OC43 (beta-CoV) (33-35)	1967 (1898*)	Yes	? Rodents (?)	Cattle (39 yrs)	?	Yes (endemic)
HKU-1 (beta-CoV) (33)	2004 (?1400*)	Yes	? Rodents (?)	?	?	Yes (endemic)
Severe acute respiratory syndrome viruses (Epidemic/pandemic† in humans)						
SARS-CoV (beta-CoV) (36-39)	2003	Yes	Bats (15 yrs)	Masked palm civets (<1 yr)	Yes‡	Yes
MERS-CoV (beta-CoV) (40-44)	2012	Yes	Bats (2 yrs) Dromedary camels (1 yr)	Dromedary camels (1 yr)	Yes	Yes
SARS-CoV-2	2019	Yes	Bats (?)	?	Yes	Yes

(beta-CoV) (45-47)			(3 yrs)			
Recombinant viruses of unknown status						
CCoV-HuPn-2018 (48) HuCCoV-Z19 (alpha-CoV) (49)	2017-2018	Yes	Dogs (>4 yrs)	?	?	?
HuPDCoV (delta-CoV) (50)	2014-2015	Yes	Pigs (7 yrs)	?	?	?

* MRCA = Most Recent Common Ancestor analysis (Molecular Clock)

† Defined as a multi-continent and/or multi-country event, and consistent with the classical definition of an "epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people" excluding typical epidemic seasonal influenza (51).

‡ From (52): A ban on the sale of wildlife in wet markets in Guangdong imposed during the later period of the SARS outbreak, which ended in July 2003, was lifted in September 2003. Between 16 December and 30 January 2004, there were four new cases of SARS. Epidemiological linkage and phylogenetic data suggest that the associated viruses were new introductions from animals (53-55). These human cases were relatively mild and did not lead to secondary transmission, reflecting that the animal precursor virus is probably not well adapted to efficient human-to human transmission. This is probably a recapitulation of events in late 2002 in the run-up to the SARS outbreak in 2003. This time, the findings led to the reintroduction of the ban on wild-game animal markets and there have been no further naturally acquired human cases since then.

Discussion: Zoonotic common cold coronaviruses have infected humans for at least 800-1,000 years and are now endemic in people, transmitted from human-to-human by infectious respiratory droplets or aerosols, or contaminated fomites. These CoVs have crossed species from bats and other mammals to humans, causing mild upper respiratory tract infections in most and occasionally severe respiratory disease in susceptible immunosuppressed hosts. In addition, in the past 20 years three new human CoVs (SARS-CoV, MERS-CoV, and SARS-CoV-2) have been identified as the cause of severe lower respiratory tract infections, resulting in substantial mortality. Two of the 7 human CoVs, HCoV-OC43 and SARS-CoV-2, are very promiscuous and readily cross species from people to infect other species. Probable Intermediate hosts in which ancestral viruses adapted prior to infecting humans have been identified for H-CoV OC43, H-CoV 229E, SARS-CoV and SARS-CoV2. Identification of ancestral or intermediate hosts can take years.

SARS-CoV and SARS-CoV-2 have been traced to ancestral bat CoVs. MERS-CoV may have originated from an ancestral bat virus as well (41, 44), but since its identification in 2012 it has retrospectively been documented in dromedary camels for many decades. These animals were rapidly documented to be the most likely source of transmission to people because the early

cluster of MERS cases with severe pneumonia were primarily people in close contact with the animals (42, 43). MERS-CoV can also transmit human to human to a limited extent, with one exception, a large outbreak in Korea in 2015 introduced by an infected traveler from the Middle East who was hospitalized due to severe pneumonia. This triggered a nosocomial outbreak within multiple hospitals and medical facilities to staff, other patients, and visitors. Ultimately there were 186 cases with 38 fatalities. Five super-spreaders were responsible for 83% of the transmission events.

The recent isolation of a canine-feline recombinant alphacoronavirus from hospitalized children in Malaysia (CCoV-HuPn-2018) and a medical team worker in Haiti (HuCCoV-Z19) illustrates how CoVs readily recombine and cross species to infect humans and also how difficult it is to identify the zoonotic source of the virus. CCoV-HuPn-2018, isolated from children in Malaysia, contains genetic material from two strains of canine coronavirus, and a feline coronavirus. Feline CoV, canine CoV and a swine coronavirus, TGEV, are closely related, use the same receptor to enter cells and readily recombine. CCoV-HuPn-2018 presumably used the human version of the receptor (amino peptidase N) to enter cells. Like many RNA viruses, the barrier to crossing species is cellular entry; once in the cells, these viruses are generally capable of replicating. CCoV-HuPn-2018 has never been found in nature and so the zoonotic species that served as the source for the virus is not known. Careful surveillance will be required both to determine the zoonotic source of the virus, determine its prevalence in wildlife, domestic animals and humans, and to assess whether it transmits well enough from human-to-human to result in more than sporadic cases, and represents an outbreak risk or even more widespread infection.

Table S. 4. Characteristics of endemic and epidemic swine coronaviruses (CoVs) illustrating their projected spillover from bats, dogs and birds and their propensity to mutate and recombine, resulting in diverse variants and lineages differing in virulence, tissue tropisms and potential for interspecies infections (56, 57).

Swine Coronaviruses (abbreviation) [genus] &	**Year**	**Zoonotic**	**Ancestral or reservoir host**	**Intermediate, amplifying, alternate host**	**Evidence of repeated spillover**	**Comments**
Endemic						
Transmissible Gastroenteritis Virus (TGEV) [alpha-CoV] (57, 58)	1946	No	?	Dogs	Yes, multiple spillover events among	TGEV, canine CoV and feline CoV are single CoV species that cross-infect pigs, dogs and cats with multiple

					multiple species.	recombinant strains emerging
Porcine Respiratory CoV (PRCV) [alpha-CoV](57, 59)	1984	No	Swine	None	No	PRCV is an S gene variant of TGEV with 621-681nt deletion in S1 and loss of enteric tropism; largely displaced TGEV
TGEV/PRCV recombinant (60)	2007-2014	No	Swine	None	No	Variant TGEV strains dominant in US
Severe Acute Diarrhea Syndrome (SADS) [alpha-CoV] (61-64)	2016	No	Bats	Swine	?	Emerged in S China-killed piglets Infects human respiratory cells
Porcine Hemagglutinating encephalomyelitis virus (PHEV) [beta-CoV] (57)	1962	No	Rodents?	Cattle?	No	PHEV is closely related to bovine CoV and human CoV OC43 with a projected common ancestor
Porcine delta-CoV (PDCoV) [delta-CoV] (57, 65-68)	2009 (China) 2012 (HK) 2014 (USA)	Yes	Birds?	Sparrow (HKU17)	Endemic? Epidemic	Birds are likely host reservoir; 2 PDCoV strains spilled over into humans in 2014-15 (Table S. 3)
Epidemic/ Endemic						
Porcine Epidemic Diarrhea Virus (PEDV)-Europe [alpha-CoV] (57, 65, 69)	1977	No	Bats?	Swine	Yes	Epidemic-Moderately pathogenic Disappeared with isolated outbreaks Distinct species from TGEV

PEDV-SE Asia, China (57, 65)	1980s	No	Bats?	Swine	Yes	Endemic-Moderately pathogenic
PEDV- China (57)	2010	No	Bats?	Swine	Yes	Highly virulent PEDV
PEDV-USA (69)	2013	No	Bats?	Swine	Yes	Epidemic-Highly virulent strain from China; killed ~8 million pigs
Swine enteric CoV (SeCoV)-TGEV/PEDV recombinants-Europe (70)	2009	No	Swine	Swine	?	TGEV backbone with PEDV S

Discussion: The evolution of porcine CoVs has raised important questions about the evolution and adaptation of CoVs within animal host species and the implications for future spillover potential to humans. They further illustrate potential future scenarios for SARS-CoV-2 and its successors in humans:

1) Do coronaviruses re-emerge, increase in virulence or recombine after adaptation to a new host? The porcine epidemic diarrhea virus (PEDV) emerged in Europe, became increasingly rare in the next decade (56, 57) and then re-appeared in Asia. In 2010 a highly virulent variant PEDV re-emerged (Fig. 2, Table S1) in China and in 2013 caused an epidemic in the US killing over 8 million piglets. Emergence of a highly virulent variant of PEDV is of concern because it is now endemic worldwide. New recombinants of PEDV that express the PEDV S gene within a TGEV backbone (70, 71) demonstrate that two different CoV species can recombine when strains co-circulate in a host reservoir.

2) Do CoV variants emerge with altered tissue tropisms and disease potential? TGEV persistence in the swine reservoir has selected for recombinants that escape host immunity and have altered pathogenesis or virulence (58). The porcine respiratory CoV (PRCV) variant mutated from TGEV by a large deletion in the spike (S)1 sequence (621-681nt) that abolished sialic acid binding, altering tissue tropism (enteric to respiratory tract) and attenuating PRCV (57). Its rapid aerosol transmission and induction of TGEV neutralizing antibodies (intact RBD), led to not only displacement of TGEV, but also to TGEV/PRCV recombinants with reduced enteric virulence in US swine (60).

3) Which swine CoVs cause multispecies infections and spillover to humans or are future threats? Porcine delta-CoV (PDCoV) exemplifies one of the few mammalian CoVs that likely spilled over from birds and has a broad host range (57, 65, 67, 68). After potential spillover from a songbird reservoir to swine in China (65), it caused an epidemic in US swine, and is now

endemic in many countries (67, 68). The recent detection of zoonotic PDCoVs in Haitian children (72) and the delta-CoV avian-to-swine-to-human transmission ominously resembles influenza virus interspecies/zoonotic transmission, raising concerns that if Hu-PDCoV acquires sustained human-to-human transmission capability it could evolve into the next "WHO pandemic disease X". Recently a new CoV, Severe Acute Diarrhea Syndrome (SADS) virus caused fatal disease in piglets in China, likely via direct spillover from bats (61, 62, 64). However, the virus also replicates in primary human lung cells (73), raising concerns it may be a future human pandemic threat.

4) What are the consequences of multi-host reservoir communities for CoVs? TGEV, CCoV and FCoV are a single CoV species that cross-infects dogs, cats and pigs and persist in this animal host reservoir community, with emergence of recombinants that escape host immunity and have altered pathogenesis or virulence in the new host (58). A concern is the discovery of CCoVs (canine-feline-porcine-recombinant S) in humans in Haiti, Malaysia and Thailand (48, 49, 74). Additional examples are ungulate beta-CoVs circulating among cattle and in wild cervids that occasionally transmit infection to humans or even avian species (75-78). The spillover of SARS-CoV-2 from humans to cervids [White Tailed (WT) deer] in North America, may establish a new host reservoir community in nature (79, 80), with a possible spillback to a human already reported (81). Multi-host reservoir communities are epidemiologically important because they can perpetuate CoVs in animals and represent opportunities for future zoonotic spillback to humans. Broader host range favors CoV co-infections, providing opportunities for recombinants to emerge, possibly with increased fitness for other hosts, new tissue tropisms, or enhanced transmission and/or virulence properties.

Table S. 5. Ancestral bat CoVs related to SARS-CoV-2

This table lists the bat SARS-related CoVs that are most closely related to SARS-CoV-2 based on sequence identity of the whole genome, or different genes involved in binding to host cells. These include several CoVs with high overall percent sequence homology with SARS-CoV-2, even greater homology with the S protein, and the use of ACE2 as the cell receptor. None of these have been shown to express a functional furin cleavage site (FCS) similar to that which facilitates cell entry of SARS-CoV-2. However some possess FCS-like motifs, suggesting this cleavage strategy may readily evolve in nature.

Virus strain	Source of Sample (Year of Collection)	Overall % sequence shared with SARS-CoV-2)	% sequence identity S/RBP* with SARS-CoV-2 (nucleotide)	S protein binds to Human ACE2	Furin cleavage site within S protein	Evidence of mutations at FCS site
RaTG13 (82)	Yunnan, China (2013)	96.1%	97.5%/89.2%	No*	No	Yes

RmYN02 (83)	Yunnan, China (2019)	93.3%	71.8%/61.3%	No	No	Yes
RpYN06 (84)	Yunnan, China (2019-2020)	94.5%	76.3%/60.9%	No	No	Yes
PRC-31 (85)	Yunnan, China 2018	90.7%	74.9/64.2%	No	No	Yes
BANAL 52/ 103/236 (45)	Laos 2020	96.8%	S1[#]-NTD[#]: 97.96%/ S1[#]-RBD: 97.32%	Yes	No	Yes

*Although no isolate of RaTG13 exists to test its binding efficacy, analyses of cryo-EM spike protein structure suggests it likely binds inefficiently to human ACE2 and would therefore be unable to infect people (86, 87).

[#]S = Spike Protein; RBP = RNA binding protein

Table S. 6. Published reports on the origins of COVID-19

This table summarizes the results from 35 published papers exploring whether COVID-19 likely resulted from a spillover event from an animal host naturally infected with SARS-CoV-2 or a laboratory leak of the virus. All hypotheses and a variety of publication types are represented, including scientific consensus reports, peer-reviewed literature publications, and online non-peer reviewed articles. When information was available to the Task Force regarding the status of peer-review by a scientific journal, the information has been included in the table.

Origin pathway hypothesis	**Evidence presented**	**Publication type**	**Peer-reviewed**
Wildlife-intermediate host-human. **Likely origin in wildlife farms/trade/market**	Mammals of species/genera known to harbor SARSr-CoVs shipped into Huanan Seafood Market; Wildlife farms supplying market were located in provinces where closest relatives to SARS-CoV-2 have been reported (Yunnan, Guangxi, Guangdong); data on animal and human testing subsequently used in studies that conclude origin in wildlife farming/ trade/market.	Consensus report from WHO-convened teams of international scientists (88)	No
	Live mammals of species and genera known to harbor SARSr-CoVs were sold at Huanan	Journal article (89)	Yes

	Seafood Market and other markets in Wuhan through December 2019.		
	Genomic evidence that SARS-CoV-2 may have spilled over twice from animals to people – suggests long-term transmission cycles in a reservoir from which multiple spillovers to people could occur, e.g. a wildlife farm or market system.	Online discussion board (90)	No
	Series of SARS-CoV- and SARS-CoV-2-related viruses reported in bats in China and Southeast Asia, suggesting a wide potential geographic region from which the clade could have originated.	Multiple journal articles (46, 47, 84, 85, 91-93)	Yes
	BANAL bat SARSr-CoVs from Laos bats: closest relatives of SARS-CoV-2; highest known proportion of receptor binding domain residues interacting with human ACE2 other than SARS-CoV-2 itself.	Journal article (45)	Yes
	Analysis of mutations at the point in the Spike protein where the FCS of SARS-CoV-2 is found suggest this site is evolutionarily "volatile" and that the relevant amino acid motif (RRAR) in SARS-CoV-2 is functionally suboptimal.	Journal 'review' article (94)	Yes
	Discovery of a novel alpha-CoV in rats with a polybasic cleavage site almost identical to that found in SARS-CoV-2, sampled in wildlife farms, train stations and hotels in Southern China.	Journal article (95)	Yes
	Environmental sampling from Huanan Seafood Market during Jan-March 2020 yields sequence of four types of animal CoVs (hedgehog HKU31-related CoV; rabbit HKU14-related CoV; canine CoV; rat CoV), further suggesting this market was actively trading CoV-infected live farmed animals, including wildlife.	Preprint article (96)	Undergoing peer review
	Analysis of SARSr-CoV bat host distribution, human population density, and serological evidence of bat virus spillover suggests that bat-to-human transmission could occur across an area of ~5.1 million km^2 of China, SE Asia, and S. Asia where ~499 million people live. Data indicate a median of >66,000 people are	Journal article (97)	Yes

	infected each year by bat SARSr-CoVs in this catchment area.		
	Analysis of early Wuhan cases proposes first known case is not an office worker who lived near WIV, but a Huanan Market worker. Geolocation of residences of early cases suggests epicenter around the Huanan Seafood Market and corrects for the bias introduced later by the inclusion of the category 'association with Huanan Market' as a criterion for inclusion of a case.	Journal article (98)	Yes
	Analysis of spike protein sequences in European bats demonstrates clear pathway for natural evolutionary origin of furin cleavage site (FCS) and suggests natural origin of FCS in SARS-CoV-2.	Journal article (99)	Yes
	Survey of 748 individuals of 23 species of farmed wildlife in Guangdong Province, China. 4 novel CoVs characterized: bamboo rats had CoVs similar to Canine and rodent CoVs; pheasants had CoVs similar to poultry CoVs; civet had CoVs close to dolphin CoV. Authors conclude wildlife farms are a key risk for CoV recombination and spillover, including zoonotic risk.	Journal article (100)	Yes
	SARS-CoV-2 testing of 1380 environmental samples and samples from both live and dead animals (including many from taxa not known and/or unlikely to harbor SARSr-CoVs) collected at Huanan Seafood Market in Jan. 2020. 73 environmental samples positive, three live viruses isolated. No SARS-CoV-2 detected in animal swabs from 18 species. Data suggest Huanan Seafood Market was an early epicenter for COVID-19 transmission.	Preprint article (101)	Undergoing peer review
	Spatial analysis of COVID-19 cases reported in December 2019 demonstrated they lived closer to the Huanan Seafood Market than expected by chance, whether the individuals are epidemiologically linked to the market or not. Majority (31/33) of virus positive environmental samples tracked to the western section where wildlife sold, with 5 samples	Journal article (102)	Yes

	positive for SARS-CoV-2 (the most from any specific site) obtained from a stall known to sell live animals in late 2019, including from cages and objects directly related to live animal sales. Five positive samples were also obtained from the adjacent stall.		
	Analysis of genome diversity between lineage A and B of SARS-CoV-2 in Wuhan December 2019 and January 2020 suggests at least two cross-species transmission events likely in intermediate host animal reservoirs prior to the outbreak in people.	Journal article (103)	Yes
	Analysis of SARS-CoV-2 related BANAL viruses from bats in Lao PDR shows that they do not evolve FCS during serial passage in human cells *in vitro*, suggesting that the lab leak scenario of a bat-CoV acquiring FCS during inadvertent or deliberate cell culture in a lab is unlikely. Paper also shows FCS not acquired during serial infection of humanized mice, or infection of primates in lab, suggesting other species may have been involved, or a bat-CoV with FCS was present in nature.	Preprint article (104)	Undergoing peer review
Laboratory origin[#]			
	Two articles by the same authors review the information published in a Masters' and a Ph.D thesis, and in the literature, on the origin of RaTG13 and the death of miners at the Mojiang mine, China. The authors raise the question of a laboratory origin because it is possible that Chinese scientists have not released full information, and because scientists publishing the RaTG13 sequence (47) came to different conclusions on the cause of death than the students do in the theses.	Journal commentary 'perspectives article' article (105) and 'general article' (106)	Yes
	Hypothesizes mis-match in RBD sequence data and 'unexpected reads' for RaTG13 and other bat-CoVs.	Journal commentary article* (107)	Yes

	Analysis of RaTG13 sequence does not rule out genetic manipulation.	Journal commentary article* (108)	Yes
	Analysis of Illumina machine sequencing read contaminants from machines used by WIV and other Chinese institutions suggests it provides evidence of viruses in samples/nucleic acid extractions. The possibility that this phenomenon could represent 'lane leakage' of PCR product common in Illumina machines is not considered.	Preprint article (109)	No
	Hypothesizes that anomalies exist in the sequence data of RaTG13 uploaded online and suggests a laboratory origin.	Preprint article, (110)	No
	Metagenomic analysis of raw reads of WIV-submitted RaTG13 genomes. Finds 10.3% of reads are fecal microbial sequences and hypothesizes this is insufficient for a bat fecal sample, and more consistent with virus in bat cell culture at WIV.	Preprint article (111)	No
	Reports contaminant sequences (SARS-CoV-2, primate, hamster) in Illumina reads in an Antarctic soil study. Hypothesizes these likely indicate culture of SARS-CoV-2 in hamster/primate cell lines, and "there are unpublished results that may be key to identifying the origin of SARS-CoV-2".	Preprint article (112)	No
	Analysis of sequence data from early Wuhan patients deleted from NIH genomics database suggests an intention to cover up origin information by means of "a less than wholehearted effort to maximize information about viral sequences from early in the Wuhan epidemic". It does not indicate whether this analysis points towards lab or wildlife market origin. No explanation for the deletion of sequences is given by the submitters, although the article states that there are valid reasons to delete data from the NIH database.	Preprint article (113)	Undergoing peer review
	Review of the furin cleavage site in SARS-CoV-2. Puts forward hypothesis that this could have been artificially inserted in a laboratory.	Journal 'perspectives' article (114)	Yes

	Analysis of RaTG13 genome hypothesizes the data shows that the CGGCGG repeat codon is 'improbable' and therefore indicates this was a laboratory construct. Concerns raised by other scientists resulted in a formal 'expression of concern' being posted by the Editor (115).	Journal 'opinion' article (116)	Yes
	Hypothesizes that the negative SARS-CoV-2 testing data from WIV employees reported in the Joint WHO-China origins study report (88) are invalid and either "misleading or simply untrue".	Preprint article (117)	No

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https://onlinelibrary.wiley.com/page/journal/15211878/homepage/productinformation.html

[#]The list of articles in the "Laboratory origin" section is incomplete, for sake of space. Numerous other non-peer reviewed articles have been published, some with DOI numbers, and many uploaded to preprint servers, of a similar nature to some of those listed. These include articles listing questions and criticisms of the Joint WHO-China COVID-19 origins study report (88), and others that are self-published online reviews and opinion pieces on the origins of COVID-19 that hypothesize a laboratory leak, cover up of data or other nefarious activity that may indicate a laboratory origin. To our best knowledge, all peer-reviewed papers, or preprints of papers that are known to be undergoing peer review in scientific journals, and that suggest a lab origin for COVID-19 are listed.

Discussion: Determining the origins of a novel emerging infectious disease (EID) is a challenging process. Mounting evidence from multiple outbreaks suggests that most EIDs are zoonotic (118), and emerge in biodiverse regions with high human population density and growth and are undergoing rapid development (119). These regions, known as EID hotspots, include many low- and middle-income countries with limited resources devoted to healthcare, epidemiological capacity to identify clusters of cases of potential concern, modern methods for etiological diagnosis of such cases, or technical expertise or policy rationale to rapidly report an apparent outbreak to WHO (120). For EIDs caused by novel viral agents, like COVID-19, their discovery often lags their initial transmission from an animal host to humans (the 'spillover' event), leading to difficulties in collecting and collating data, samples and evidence to analyze the details of the spillover event. Even in countries with a significant proportion of GDP spent on research or healthcare, the origins of outbreaks caused by novel agents can be difficult to identify, with substantial delays in resolution of competing hypotheses (121, 122).

Tracing the origins of zoonotic EIDs often involves generating and retrospectively testing hypotheses on pathways of transmission from animals to people, and on the underlying drivers that led to the initial spillover. It can require years of research to analyze trends in underlying causal factors, and specifically test hypotheses that have been put forward. For example, while

the spillover events that led to the HIV/AIDS pandemic likely occurred around 1920, the outbreak was first identified in the early 1980s after it had become pandemic. It took 6-13 years from that point to identify the likely animal origins of HIV-2 and HIV-1, respectively, (123) and around 2 decades from the original discovery of HIV-1 and HIV-2 before conflicting hypotheses on the drivers of AIDS emergence were resolved (123, 124). The discovery of Nipah virus as the cause of a febrile encephalitis outbreak in Malaysia was delayed for over 2 years after the likely initial spillover event (125), hampered by the similarity of symptoms with other known human pathogens and an unsuccessful search for the known agents rather than a previously unknown virus (17, 126, 127). Further work to test conflicting hypotheses on the underlying drivers of the Nipah virus outbreak took another 5 years (125).

Increasing evidence has shown that the causative agent of COVID-19, like most of the emerging viral infectious diseases, appears to be zoonotic. Viruses related to SARS-CoV-2 have been found in rhinolophid and other insectivorous bats (45, 47, 93) and pangolins (46, 128-130). However, to date, the closest known relatives of SARS-CoV-2 have only 96.8% overall sequence identity (45), and lack certain functional elements of the virus (e.g. a furin cleavage site), suggesting that the true progenitor of SARS-CoV-2 has not yet been discovered. While some have taken the latter to indicate the virus could have been constructed in a laboratory, there is increasing evidence of the widespread presence of similar polybasic cleavage sites in many bat viruses, including some recent findings of SAR-CoV-2 related viruses just a mutation short of possessing a fully functional furin cleavage site. There is substantial evidence that SARS-CoV-2 is able to infect multiple non-human species, including farmed domestic and wild animals, free-ranging wildlife, captive wildlife, and pet species (131), although for most the spillover has been from humans to the new host, with just a few instances of well documented spillback to humans. This presents the opportunity for mutation or recombination as the virus adapts to the new host, with the possibility of acquiring properties relevant for zoonotic transmission and altered virulence in humans.

During the outbreak of SARS in 2002-2003, evidence of SARS-CoV infection in several captive wildlife species, including masked palm civets, raccoon dogs and ferret badgers was found. These samples were collected in live animal markets where early human cases had been identified, raising the likelihood that a zoonotic spillover event was involved (37, 132). The higher viral prevalence in civets compared to other mammals in the markets, and the similarity of virus sequences from humans and civets suggested they were a natural reservoir and the direct source of human infection, or were an amplifier host for SARS-CoV (21). These studies did not clarify whether other species were involved in SARS-CoV transmission to humans and did not identify the reservoir host species from which SARS-CoV originated. Limited serologic studies of civets from animal markets and civet farms in mid-2003 revealed 13% (4/31) seropositivity in the markets but no positives from the farms. Subsequent studies in 2004 on samples of convenience, limited as well by regulatory constraints during a major culling of farmed civets, showed nearly 80% (14/18) of samples from a market were positive for SARS-CoV, but none of 75 samples from 6 different farms in 3 different regions of China, suggesting civets were incidentally infected in the markets (133). Bats were identified as the likely host of

SARSr-CoVs in 2005 (39), but it took a further 10 years to demonstrate that bat SARSr-CoVs closely related to SARS-CoV could bind to the human ACE2 receptor, and thus provide strong evidence of the origin of SARS-CoV in bats (36).

We remain in an early stage in our understanding of the origin of SARS-CoV-2 and the pathway it took from the likely bat reservoir host of its ancestral clade of viruses (47, 93) to people. While SARS-CoV-2 testing of environmental samples, live animals and frozen carcasses from the Huanan Seafood Market has now been published, no positive samples from animals were reported (101). The only live mammals of species known to harbor SARSr-CoVs that were sampled at the market just after the COVID-19 outbreak began (a weasel and 'stray cats') were negative (88). Samples taken from six frozen 'badger' carcasses (likely a farmed ferret badger species) were negative as well (88). Extensive sampling of wildlife, domestic animals, zoo animals and farmed wildlife was conducted in China before and during the COVID-19 outbreak, and samples from around 80,000 animals were tested for SARS-CoV-2 by PCR and/or serology. Although these samples were all negative for SARS-CoV-2, they were largely from species not known and/or unlikely to harbor SARSr-CoVs, were from regions where bats are not known to harbor CoVs closely related to SARS-CoV-2, or were of inadequate sample size to rule out infection in the overall animal populations (88). Definitive evidence of a role for intermediate host species in the emergence of COVID-19 remains elusive.

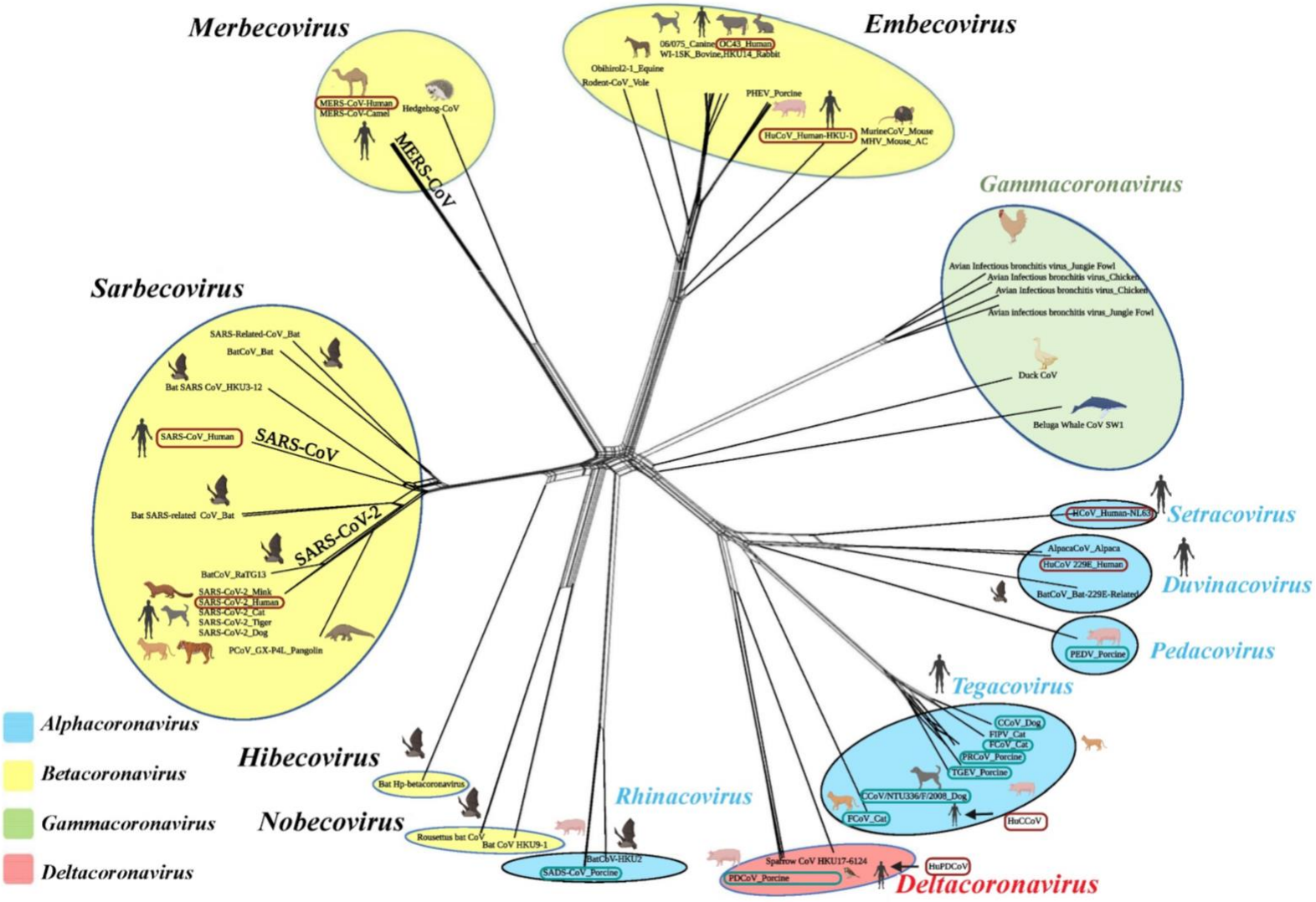
Our taskforce followed the same broad strategy as the Joint WHO-China Study of the Animal Origins of COVID-19 in assessing available evidence for different pathways by which SARS-CoV-2 could have emerged in people, and concluding which are most likely and least likely, based on the data available (88). Since the Joint WHO-China Study conducted its work, there has been an increased focus on the possibility that SARS-CoV-2 had a laboratory origin, or its spillover occurred via a laboratory or research-associated pathway. Table S.6 shows that there are substantially more published data available than at the time the Joint WHO-China Study conducted its work, and that the number of papers focused on both an origin via wildlife farming, the wildlife trade and a laboratory-related incident have also increased substantially. However, the majority of papers focused on the latter are in the form of opinion pieces, editorials, or from non-peer-reviewed sources. By contrast almost all of the papers that point towards a zoonotic origin via the wildlife trade or direct spillover from wildlife without a laboratory or research involvement are in peer-reviewed journals or are undergoing peer-review, and provide reproducible or verifiable evidence. Our taskforce therefore concludes that the balance of available evidence strongly supports a so-called 'natural' origin of SARS-CoV- 2 and that COVID-19 resulted from a spillover from wildlife (likely bats), with or less probably without involvement of an intermediate host (likely a farmed wildlife species such as a raccoon dog, ferret badger, civet or related species) to humans (particularly people involved in wildlife farming or trade). We also conclude that there is no verifiable direct evidence for a laboratory- or research-related origin, and that the circumstantial evidence is weak.

Table S.7: Proof-of-concept and return on investment from novel virus discovery in wildlife.

Many of the COVID-19 therapeutics, treatments or vaccines currently in clinical trials or in use have been shown to have broad efficacy against other CoVs *in vitro* and in animal models. Each product below has been shown to be effective against bat SARSr-CoVs discovered, isolated and characterized via NIH/NIAID- and USAID-funded sampling of bats in China. This information has guided further development of products for therapeutic use.

Therapeutic, vaccine or treatment tested	**Citation**
Remdesivir (formerly GS-5734), drug treatment for COVID-19	(134)
Molnupiravir (NHC, EIDD-1931 and prodrug EIDD-2801), drug treatment for COVID-19	(135, 136)
Adagio ADG20 (formerly ADG2). Monoclonal antibody treatment for COVID-19.	(137)
DH1047, a broadly-neutralizing RBD-specific antibody.	(138)
Chimeric NTD/RBD spike mRNA vaccines.	(139)
Neutralizing antibody vaccine for pandemic and 'pre-emergent' CoVs, cited as proof-of-concept for a Universal vaccine initiative.	(140)

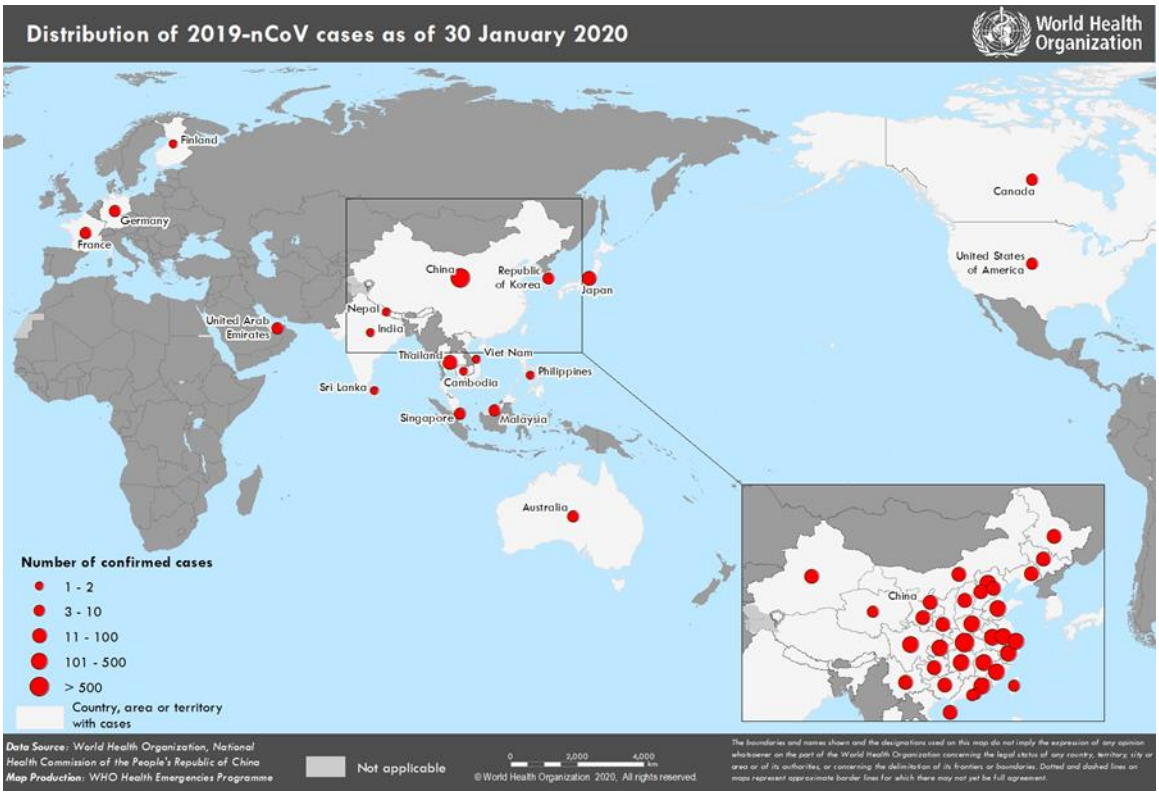
Fig. S 1. Phylogenetic grouping of animal and human coronaviruses.



Adapted from (141)

Figure legend: This phylogenetic grouping of coronaviruses (CoVs) is based on 78 full-length sequences of the spike protein encoding genes of human and animal CoVs. The 4 genera are color coded including the Alphacoronavirus and subgenera in blue (Duvinacovirus, Pedacovirus, Rhinacovirus, Setracovirus, and Tegacovirus); Betacoronavirus and subgenera in yellow (Embecovirus, Hibecovirus, Merbecovirus, Nobecovirus, and Sarbecovirus); Gammacoronavirus in green; and Deltacoronavirus in rose. Coronaviruses discussed in detail in the manuscript are identified by a red box to indicate human CoVs or a green box to indicate animal CoVs.

Fig. S. 2. Early spread of COVID-19 through January 30, 2020



Reproduced with permission: Novel Coronavirus (2019-nCoV). Situation Report – 10 https://cms.who.int/docs/default-source/coronaviruse/situation-reports/20200130-sitrep-10-ncov.pdf?sfvrsn=d0b2e480_2 (Accessed April 22, 2022)

Discussion: One of the first widely disseminated reports of an unexplained cluster of pneumonia cases in December 2019 in Wuhan, China, was published December 30, 2019 by the International Society for Infectious Diseases on its online platform, ProMed Mail (142). It cites an "urgent notice" issued by the Wuhan Municipal Health Commission of unexplained pneumonia cases in Wuhan involving 27 patients, including 7 described as critically ill, with a possible connection to the Huanan Seafood Market (HSM) in Wuhan. The report notes that the Chinese Center for Disease Control and Prevention (China CDC) was beginning an investigation and clearly indicates that health care workers and health authorities were aware of the growing number of affected patients well before the December 30, 2019 message from health authorities in Wuhan City.

On January 1, 2020, the WHO China Country Office informed WHO Headquarters in Geneva of the Wuhan outbreak. Four days later, on January 5, 2020, WHO issued its first Disease Outbreak Notification (DON) which noted that the WHO China Country Office had become aware of the outbreak on December 31, 2019, and WHO Headquarters was now involved (143). It indicated that as of January 3, 2020 there were 44 patients including 11 who were severely ill, and cited media reports indicating that "the concerned market in Wuhan was closed on 1 January 2020 for environmental sanitation and disinfection". According to preliminary information from the

Chinese investigation team there was “no evidence of significant human-to-human transmission and no health care worker infections”.

The next follow-up DON, published on January 12, 2020, again mentioned the association of the outbreak with HSM, and reiterated there were no infections in healthcare workers nor evidence of human-to-human transmission (144). It reported the first death among confirmed cases in a patient with “serious unspecified underlying medical conditions”. At this time the sequence of the novel coronavirus identified as the cause of the outbreak was posted online, allowing the rapid creation of PCR diagnostics by other countries to track and confirm cases around the world.

On January 23, 2020, the WHO Emergency Committee convened at the request of the Director-General, as required under the International Health Regulations, to assess the significance of the ongoing outbreak (145). There were unclarified “divergent views on whether this event constitutes a PHEIC [Public Health Emergency of International Concern] or not”, even though human-to-human transmission was now confirmed and announced by Chinese authorities (146). The statement released after the meeting said “the source is still unknown (most likely an animal reservoir)”. By this time there were 557 known cases with 17 deaths, however no action to declare a PHEIC was taken by WHO. In contrast, “as part of initial efforts to contain the outbreak, the Chinese government announced a cordon sanitaire for the city of Wuhan, Hubei Province, starting on 23rd January 2020, one day before LNY [Lunar New Year] holidays” (147). This action restricted all non-essential movement into and out of Wuhan, as travel from airports, train stations, long-distance bus stations, and commercial ports were all suspended. Over the next few days these restrictions were extended to other cities in Hubei province, and then to cities outside of Hubei.

On January 29, 2020, a peer reviewed paper describing the first 425 patients in Wuhan with the novel-coronavirus infection was published online (148). The median age of the patients was 59 years, 56% were male, and 55% of cases with onset before January 1, 2020 were linked to HSM compared to 8.6% of cases from January 1 to January 22, 2020. The mean incubation period was 5.2 days (95% CI, 4.1 to 7.0) and the doubling time for cases was 7.4 days. The basic reproductive number (R0) was estimated to be 2.2 (95% CI, 1.4 to 3.9), indicative of an expanding outbreak. The report concluded that human-to-human transmission from patients to close contacts had been ongoing since mid-December 2019.

On January 30, the Emergency Committee recommended to the WHO Director that WHO should declare the outbreak was a PHEIC, which was promptly announced (149). The committee recommended that Chinese authorities “[c]ontinue to identify the zoonotic source of the outbreak, and particularly the potential for circulation”. WHO Situation Report 10, released the same day, reported there 7,818 confirmed infections, including 7,736 in China, with 1,370 severe cases and 170 deaths, and 82 confirmed infections in 18 countries outside of China, but no reported fatalities (150). On January 30, 2020, the US CDC announced the first well-documented human-to-human transmission of the virus in the US involving a recent traveler to China who became ill after returning home and passed the infection to his wife

(151). As Figure S. 2 depicts, the rapidly spiraling increase of cases in China, both within and outside of Wuhan, and in multiple countries around the world should have been an alarming finding, as internal and international travel during the Chinese holiday had proceeded unimpeded as usual throughout most of January 2020.

By the end of January, although domestic travel in China was now dramatically curtailed, international travel out of China continued. The New York Times subsequently reported that over 380,000 people flew from China to the US during January 2020, only one quarter of whom were US Citizens. The US banned travel from China beginning February 2, 2020 (152), yet almost 40,000 travelers from China arrived in the US over the subsequent two months. The introduction of the virus to the US, carried by infected, asymptomatic or mildly ill travelers from China occurred early and undoubtedly often throughout January 2020. By the time the first domestically acquired case transmitted from human-to-human was confirmed on January 20, 2020 (https://www.cdc.gov/media/releases/2020/p0121-novel-coronavirus-travel-case.html, accessed May 18, 2022), there were certainly many more infected individuals dispersed around the country.

The optimal time to control an incipient outbreak is as early as possible, when the number of cases is small and the number of contacts with potentially acquired infection is still limited, allowing implementation of efficient, focused public health measures to identify cases and contacts, isolate them until they no longer are contagious, and break the chain of transmission. There were many accomplishments in this early phase of the outbreak, including rapid identification of the agent, sequencing the genome, developing molecular diagnostic tests, identifying an epidemiological association with a particular market, initial suspicions the infection was zoonotic in origin, and establishing that infection was transmitted from person to person. For WHO the declaration of a PHEIC within a month of the initial report of the outbreak was a historic record, although it is difficult to explain the delay of even 1 week by the Emergency Committee. January 30, 2020 represents a landmark date, when every public health agency in every country around the world should have and could have realized there was an urgent public health crisis demanding its full attention and mobilization to implement known effective measures to identify cases and prevent spread.

Although it is difficult to establish the exact chronology from available documents, it is likely that clinicians in Wuhan had become aware of the initial cluster of severe pneumonia cases before the end of December, and possibly by mid-December. They then, in a prescient manner, likely took advantage of the genomics capacity in Wuhan by submitting samples of respiratory secretions for next generation sequencing. This allowed the first identification of a novel coronavirus related to SARS-CoV, and at least a partial sequence of the causative virus was already known when WHO became engaged. Additional serious problems contributed to the uncontrolled pandemic that followed. Information provided by the Chinese authorities was not always timely or fully forthcoming. Following the initial “urgent notice” of the outbreak, subsequent public statements did not reflect the concerns of the health community. Of particular import was the failure to provide early clear information on the extent of human-to-human transmission or the frequency of asymptomatic or mild infections.

On December 30, 2019, the day the "urgent notice" was posted by the Wuhan Municipal Health Commission, Dr. Li Wenliang, an ophthalmologist at Wuhan Central Hospital, used social media to inform his medical school classmates about cases of severe pneumonia being admitted to his hospital, and warning them to take precautions to prevent becoming infected while caring for these patients. Soon after, on January 1, 2020, Dr. Li was detained by police for "rumor-mongering", although he was subsequently released two days later after signing a police document admitting to an illegal act consisting of "untrue statements" on social media (153). He returned to work at the hospital, developed symptoms of COVID-19 on January 10, 2020, and was admitted to the hospital on January 12, 2020. He died of the infection on February 6, 2020, having attracted a large following of supporters on social media.

On January 10, the first sequence of the virus was published on Virological.org by Prof. Edward Holmes on behalf of a Chinese group led by Dr. Yong-Zhen Zhang from Fudan University in Shanghai (154). Dr. Zhang had already submitted the sequence data to GenBank on January 5, 2020, and it was published on January 13, 2020 (155). But it has been suggested by some that the sequence was already known and could have been released two or more weeks earlier. The virus isolate obtained from patients in Wuhan in early January was not shared with researchers outside of China. The rapid ramp up of product research and development that began in mid-January was based on the initial and multiple additional sequences posted by researchers around the world, and initially utilized early samples of the virus obtained from patients who presented outside of China (156).

Figure S. 3. Ecology and phylogeny of selected coronaviruses.

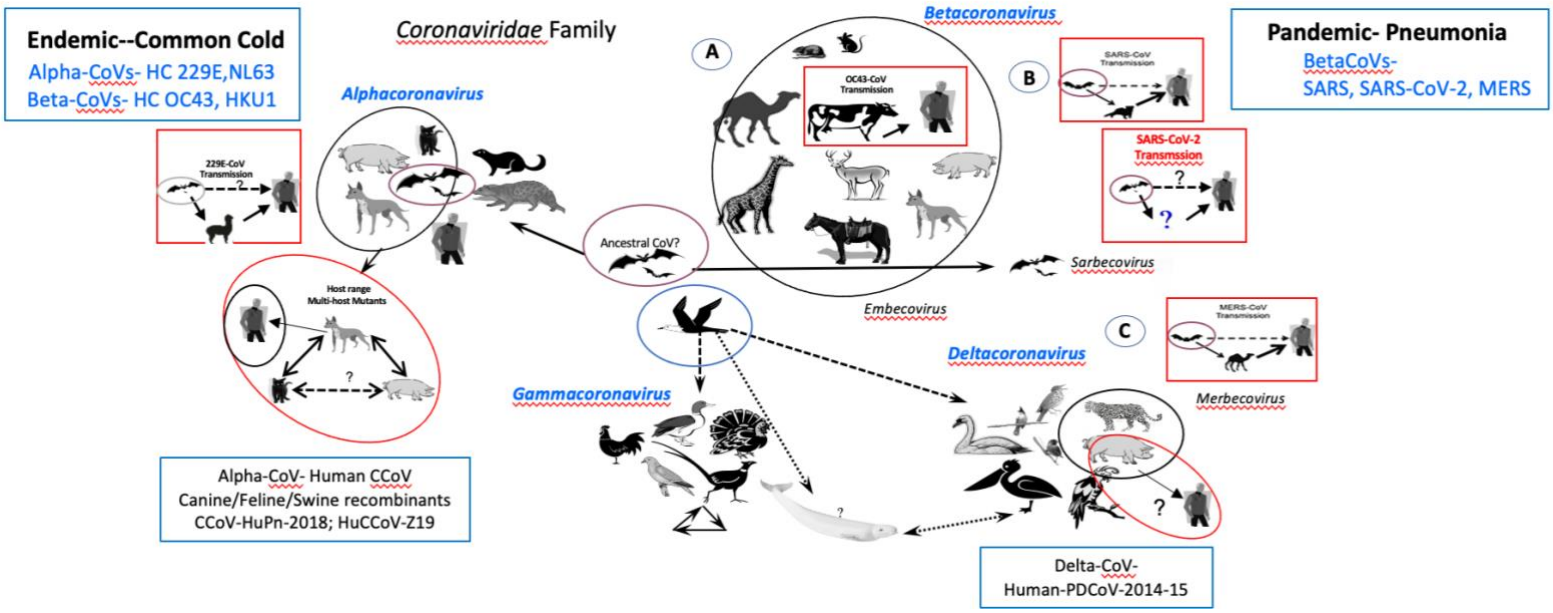
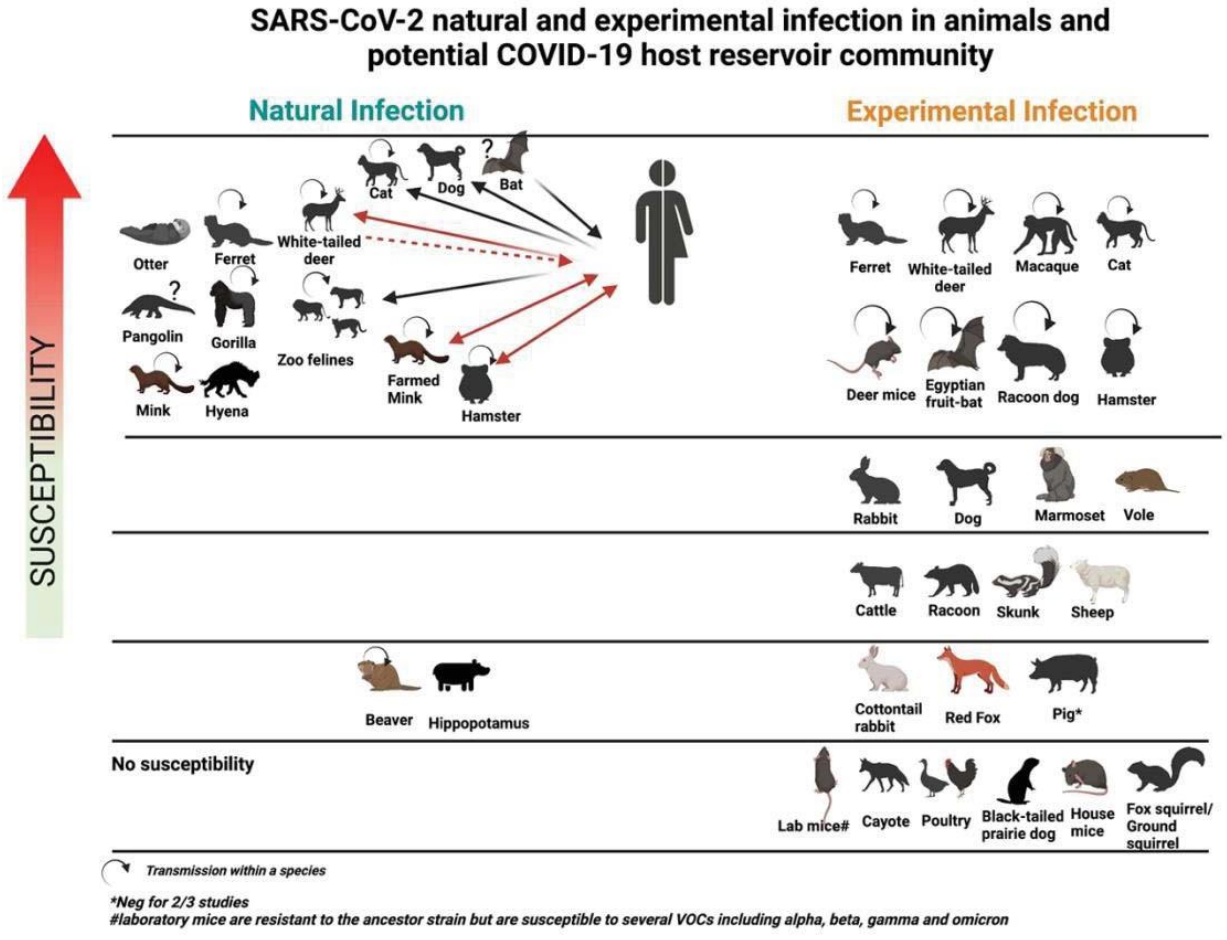


Figure modified from (157, 158).

Discussion: The 4 coronavirus genera and 3 subgenera of beta-coronaviruses detailed in **Fig. S. 1** are shown illustrating the emergence of most alpha-coronaviruses, and sarbecovirus and merbecovirus beta-coronaviruses from bats, the embecoviruses from cattle, and the gamma and delta-coronaviruses from birds (see **Fig 2** for timeline). The red boxes or ovals denote zoonotic coronavirus spillovers to humans.

Figure S. 4: Varying susceptibility of animal species to natural or experimental challenge infection with SARS-CoV-2. Black arrows show one-way transmissions between animals and humans. Red arrows indicate reverse zoonosis of SARS-CoV-2 back to humans.



Discussion: As part of the epidemiological investigation of the source of introduction of SARS-CoV-2 into the human population multiple animal species have been surveyed to assess

evidence of natural infection or tested for their susceptibility to experimental infection. Susceptibility varies considerably, and several species have emerged as important *in vivo* models to study COVID-19 pathogenesis and pathology, and to use in the development of vaccines and therapeutics. Multiple species have also been shown to transmit infection to others members of the same species. At least 2 species (farmed mink, hamsters) have been shown to transmit infection to humans (159, 160). At least 1 species (White-tailed deer) has acquired infection via spillover from humans with widespread dissemination of infection within the deer population, at least in North America (80), with preliminary evidence of spillback to humans (81). The evidence for this stems from the isolation of a highly divergent variant of SARS-CoV-2 from deer samples obtained in Canada with 76 consensus mutations, followed by a search for similar variants in human patients. This yielded a human sample with plausible epidemiological links to the deer samples in that it was collected in the same geographical region and time-period, from a case that had close contact with deer in the week prior to symptom onset and no known contact with people who tested positive for SARS-CoV-2 prior to or after contact with deer. Whether this remains an isolated incident or an indication of the spillover-spillback potential involving humans and White-tailed deer (or possibly from another species due to cross-species transmission in nature) remains to be seen.

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