Twitter Thread by Michael Lin, MD PhD ■



Michael Lin, MD PhD ■
@michaelzlin

There have been a lot of stories recently on the search into COVID19/SARSCoV2 origins, but they have been written to tell stories of intrigue or mystery, not to summarize known facts.

Thus I thought it might be useful to succinctly summarize what we actually know...

1/n

I'll say from the outset we know zero about where sarscov2 itself came from, so the only facts we can list are those that could be proximally relevant. That is, each of these facts is either about SARSCoV2 discovery or just one potential step removed from SARSCoV2 origins.
2/n

First, the briefest bit of background: SARSCoV2 is in the clade or coronaviruses called the sarbecoviruses, named after its first known member, SARSCoV1, the cause of SARS discovered in 2002. SARSCoV1 and SARSCoV2 are 80% identical.

3/n

They essentially cause the same range of pathologies (flu-like disease which then progresses sometimes to inflammatory pneumonia and sometimes systemic inflammation), but with very different outcome distributions

4/n

Now, on to the circumstantial facts.

1. The 1st known case of SARSCoV2 disease was detected on 2019/12/8 in Wuhan, China. Most cases in the next 3 wks were linked to the Huanan seafood market, but the 1st case, and 4 of the first 5, were not.
https://t.co/ALUpEboqwT

5/n

2. The closest known sarbecovirus to SARSCoV2 is RaTG13 (96%), which was isolated from a Mojiang mine in 2013 by WIV scientists. WIV scientists were alerted to the mine after 3 miners contracted a SARS-like pneumonia and died.
https://t.co/AIL9op3A2Z

6/n

3. The wild bat-resident precursor to SARSCoV2 has not yet been found but it is not RaTG13 itself, whose 96% similarity still suggests 50 years of divergence from SARSCoV2.
https://t.co/nGkVuhTdqj

7/n

4. The first paper on RaTG13 by Shi Zhengli of WIV (2020/2, https://t.co/FcpkqN8Dph) did not discuss where RaTG13 came from; this was figured out by DRASTIC (2020/5, https://t.co/CT9PKSSRUp).

8/n

Although RaTG13 is not the wild precursor to SARSCoV2, details about where, when, and why it was isolated is relevant to SARSCoV2, as it provides a plausible path for the transport (knowing or unknowing) of SARSCoV2 to Wuhan.

9/n

5. Zhengli Shi's group at WIV was sent serum samples from the sick miners to test for antibodies that react to SARSCoV1. The PhD thesis of Huang Canping recorded that 4 miners' sera were positive for SARSCoV1-reactive antibodies.
https://t.co/k0puaoaZZK

10/n

6. Note antibodies raised against SARSCoV2 cross-react to SARSCoV1 and vice versa. Thus a positive reaction to SARSCoV1 antigens, if true, in the miners' serum would indicate some sort of sarbecovirus, which could have at least 20% divergence from SARSCoV1
https://t.co/6sI0zgXpuI

7. I verified the original statement in Huang's thesis about the miners being seropositive for sarbecovirus. Whether the miners were infected with a sarbecovirus is relevant for assessing whether it's worth attempting to find SARSCoV2 sequences in the miner serum samples.
11/n

2012 年 11 月，云南省墨江哈尼族自治县通关镇的一个废弃的铜矿矿洞中，矿工群体中暴发重症肺炎疫情。其中 6 人感染，共造成 3 人死亡。中国疾病预防控制中心、云南省疾病预防控制中心以及其他医疗机构和相关科研单位采集了病人以及矿洞中蝙蝠、老鼠和环境等样本并进行病原检测和病因分析。4 名患者咽拭子和全血标本中，SARS 冠状病毒、流行性出血热、登革热（1-4 型）、乙型脑炎及黄病毒、甲病毒病原核酸检测均为阴性（成都军区疾病预防控制中心）；4 名病例和 4 名曾经进入矿洞但未发病人员的血标本检测结果无异常发现（广东钟

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南山实验室）；对矿洞内蝙蝠进行解剖，对蝙蝠粪便进行检测，均未发现异常（中国科学院武汉病毒学研究所）；4 名病例血液标本检测结果显示：4 人均携带 SARS 病毒 IgG 抗体，其中出院 2 人的抗体水平较高，住院 2 人的抗体水平较低（中国科学院武汉病毒学研究所）。时隔半年之后，金奇实验室再次进入该矿洞采集蝙蝠和野鼠样本并进行病原检测，从野鼠样本中，得到一株 Henipa-like virus 基因组全长序列[99]。但是，该病毒与这次疫情暴发之间的相关性，并未得到论证。因此，造成此次疫情暴发的病因尚未明了，虽经多方努力，迄今成了一桩不了了之的悬案。

8. However, Zhengli Shi said in 2020.11 that the miners were seronegative for SARSCoV1 antibodies in 2012. That contradicts Huang's thesis, so only one can be correct. Shi said the sera were also negative for SARSCoV2 antibodies when retested in 2020. https://t.co/5ZZG2P8ieL
12/n

9. It is not known if the miner serum samples that yielded the 9 sarbecoviruses have since been tested to see if they contained SARSCoV2, but now we know the SARSCoV2 sequence, it would be straightforward to do the PCR.
13/n

10. Thus whether the wild precursor to SARSCoV2 was in the Mojiang mine is unknown, regardless of whether Huang or Shi is correct. But if Huang is correct, it's worth PCRing from the miners' sera to look for it. If Shi is correct, it's not worth

doing so.
14/n

11. Shi reported obtaining sequences of 9 sarbecoviruses (including RaTG13) out of 293 coronaviruses from 1322 bat guano samples from the mine 2012-2015. Shi said next-gen sequencing in 2018 allowed recovery of more RaTG13 sequence.
https://t.co/5ZZG2P8ieL
15/n

12. Shi has not said if next-gen sequencing has now been attempted on those 1322 samples to look for SARSCoV2.
16/n

13. Shi has not said if WIV attempted to culture those 9 sarbecoviruses. But WHO's Embarek may know: "They never succeeded to culture a virus out of the bat feces sample." Not clear if he was speaking loosely, but this implies an attempt.
https://t.co/AGMBrQk4P2
17/n

14. Besides WIV, Wuhan CDC was also involved in bat collection and virus sampling of the Mojiang mine and various caves
https://t.co/FlISgPwxZb
18/n

15. Regarding a potential wildlife origin, sequencing of thousands of animal samples in and around Wuhan and in suppliers to Wuhan markets have not found SARSCoV2, per the WHO joint report 4/2021
19/n

Table 9. Survey of wildlife (captive) in China for SARS-CoV-2 NAT, post-epidemic in Wuhan (after March 2020).

	Nucleic Acid Testing (NAT)	
	Hubei Province	Nationwide
Number of species	74	208
Specific types of animals	Yunnan horse, Pony, Kangaroo, Arctic fox, Dezhou donkey, leopard, Ocelot, Tibetan macaque, Red-necked kangaroo, Skunk, Sichuan horse, Elephant, Giant panda, Siberian tiger, Sheep, Auricular fox, African lion, Baboon, Dog, Civet, Nutria, Porcupine, River muntjac, Golden monkey, Black bear, Red fox, Fruit bat, Pangolin, Tiglon, South China tiger, Ring-tailed lemur, Raccoon, Yellow muntjac, Grey kangaroo, Muntjacs, Snub-nosed monkey, Grey wolf, Dwarf musk deer, Bactrian camel, Mongolian horse, Red deer, Yak, Sika deer, Stump-tailed macaque, Squirrel, Argali, Grey goat, Muskrat, Black goat, Capybara, Red squirrels, Squirrel monkey, Prairie dog, Guinea pig, Pig-footed bandicoot, Northwest wolf, Tibetan wild ass, Meerkat, Xiang Pig, Panda, Alpaca, Chinese Hare, Wild boar, Bamboo rat, Brown bear, etc.	Green guenons, Green iguanas, Green monkeys, Bactrian camels, Horned owls, Dwarf musk deer, Hyenas, Falcons, Cheetahs, Cinnamon bittern, Northwest wolves, Blue macaws, Cockatoos, Snub-nosed monkey, Leopards, Festival-tail monkeys, Wildebeest, Muntjacs, Grey parrots, Grey rock rats, Grey owls, Grey wolves, Grey kangaroos, Grey monkeys, Reeves's muntjac, Yellow monkeys, Ringtail raccoons, Ring-tailed lemur, Ring-necked pheasants, Rat snakes, South China tigers, Masked foxes, Tiger frogs, Red foxes, Red-beaked blue magpies, Red-faced monkey, Orangutan, Red-cheeked bamboo rat, Black bear, Chimpanzee, Black swan, domestic chicken, Beauty rat snake, spider monkey, Black eyebrow monkey, Black monkey, Black panther, Black spotted frog, Black and white colobus monkey, Black and whitetegu, Brown winged crow cuckoo, Hippopotamus, River muntjac, Porcupine, nutria, Gecko, Civet, badger, Gansu zokor, Crested eagle, Yellow baboon, Scarlet parrot, African elephant, Auricle fox, Crocodile lizard, Sheep, East African baboon, Siberian tiger, Panda, Asian elephant, King snake, Giant anteater, Great ewe, Great egret, Pangolin, River horse, Skunk, Red kangaroo, Red lemur, Red-bellied lemur, Pond heron, Toad, Striped Water Snake, Tibetan macaque, De Brazza's monkey, Fruit bat, Leopard cat, Leopard, Zebra, White rhino, White-headed langur, White fallow deer, Lion, Hoolock gibbon, White eyebrow monkey, Dezhou donkey, White-faced monk monkey, White peacock, Northern white-cheeked gibbon, Tiger, White fox, White bellied langur, Kangaroo, White nose monkey, Yunnan horse, Pony, Hamadryas baboons, etc.
Total sample size	3643	27 000
Test results	Negative	Negative

16. The only other sarbecovirus to have entered humans is SARSCoV1, so its transmission path is often cited as a model. It jumped from civets to humans in wildlife markets in Guangdong province, and its ultimate reservoir is believed to be bats. https://t.co/i1gAVqV58k

20/n

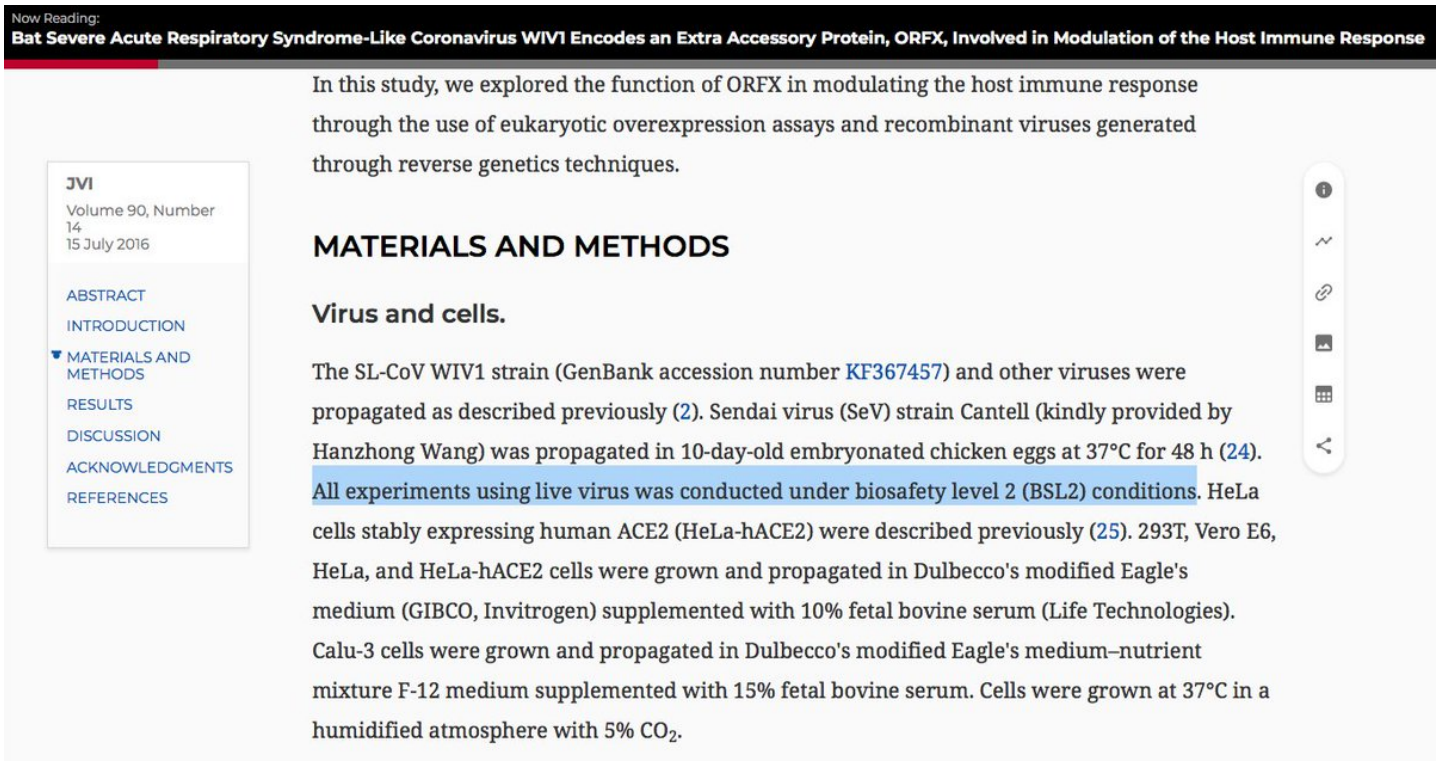
17. However WIV1 and WIV16, the closest known bat-resident viruses to SARSCoV1 (95/95%), have the ability to infect human cells directly. So in-civet evolution was not necessary; direct bats to humans was possible too. https://t.co/UHrpCSTqSU

21/n

18. Regarding virus engineering, Shi's lab had made chimeric sarbecoviruses by inserting newly discovered spike sequences into the WIV1 backbone, and assessing for retained ability to to infect human cells (WIV1 already had this capability).
https://t.co/Ee74nn4euo
22/n

19. They have not reported using other backbones to perform chimeric virus work, so the above is the closest known work to "gain-of-function" studies.
23/n

20. Cultures of WIV1 were done at BSL2 level (gloves, lab coats, eye protection and masks depending on perceived risk). The paper that describes the virus production method (and referenced by the chimeric virus paper) is
https://t.co/UHrpCSTqSU
24/n



And that's it. That's all the circumstantial facts. We have no direct facts on SARSCoV2 origins. On one hand we have facts on RaTG13 providing an example path that SARSCoV could have taken to Wuhan, and on the other the precedence of SARS1 that's non-specific to Wuhan.
25/n

There's some negative circumstantial data: the virus-negative animal samples, and the failure to report results of easy searches for SARSCoV2 in samples in WIV's possession that a lab interested in papers or solving the mystery of the century would do.
26/n

And now my opinion: I think BSL2 for work on WIV1 (95% identifcal to SARSCoV1) is an actual scandal, recorded in print. Shi's whole reason to study WIV1 was that it was an actual bat virus but like SARSCoV1 can replicate in human cells. https://t.co/o7F2mdTooo
27/n

Being 95% identical to SARSCoV1, you should just treat it the same: There is an exceedingly high likelihood it would create a deadly epidemic if it got into a human. Indeed the conclusion of her Nature paper on WIV1 is that it or something similar could be the next SARS.
28/n

region. The new isolate was named SL-CoV-WIV1. and RSKT cells than in Vero E6 cells (Fig. 4).

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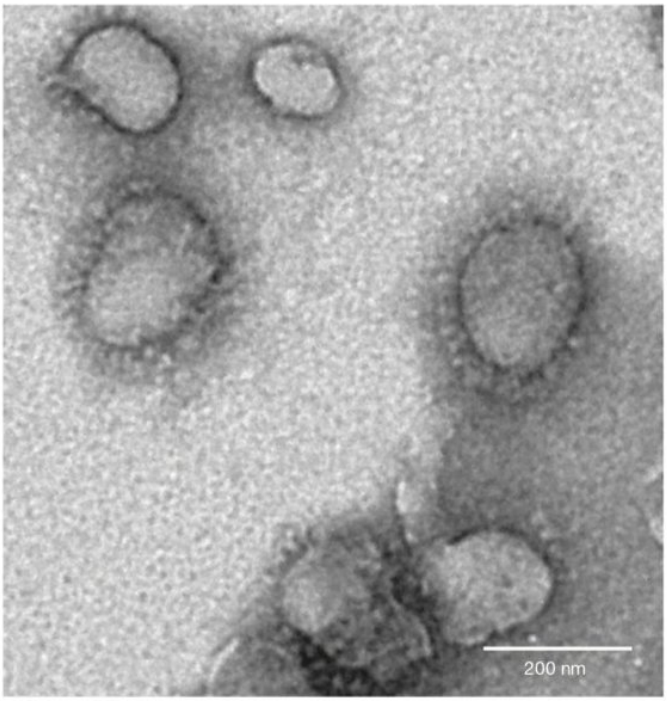


Figure 2 | Electron micrograph of purified virions. Virions from a 10-ml culture were collected, fixed and concentrated/purified by sucrose gradient centrifugation. The pelleted viral particles were suspended in 100 µl PBS, stained with 2% phosphotungstic acid (pH 7.0) and examined directly using a

culture infectious dose 50 ($TCID_{50}$) WIV1 at dilutions of 1:10 to 1:40, further confirming the close relationship between WIV1 and SARS-CoV.

Our findings have important implications for public health. First, they provide the clearest evidence yet that SARS-CoV originated in bats. Our previous work provided phylogenetic evidence of this[5], but the lack of an isolate or evidence that bat SL-CoVs can naturally infect human cells, until now, had cast doubt on this hypothesis. Second, the lack of capacity of SL-CoVs to use of ACE2 receptors has previously been considered as the key barrier for their direct spillover into humans, supporting the suggestion that civets were intermediate hosts for SARS-CoV adaptation to human transmission during the SARS outbreak[24]. However, the ability of SL-CoV-WIV1 to use human ACE2 argues against the necessity of this step for SL-CoV-WIV1 and suggests that direct bat-to-human infection is a plausible scenario for some bat SL-CoVs. This has implications for public health control measures in the face of potential spillover of a diverse and growing pool of recently discovered SARS-like CoVs with a wide geographic distribution.

Our findings suggest that the diversity of bat CoVs is substantially higher than that previously reported. In this study we were able to demonstrate the circulation of at least seven different strains of SL-CoVs within a single colony of *R. sinicus* during a 12-month period. The high genetic diversity of SL-CoVs within this colony was mirrored by high phenotypic diversity in the differential use of ACE2 by different strains. It would therefore not be surprising if further surveillance reveals a broad diversity of bat SL-CoVs that are able to use ACE2, some of which may have even closer homology to SARS-CoV than SL-CoV-WIV1. Our results—in addition to the recent demonstration of MERS-CoV in a Saudi Arabian bat[25], and of bat CoVs closely related to MERS-CoV in China, Africa, Europe and North America[3,26,27]—suggest that bat coronaviruses remain a substantial global threat to public health.

So then in their next paper they grow this virus in the lab under BSL2 conditions! BSL2 can be gloves and lab coats and not mouth pipetting, and cleaning up spills, and that's it. No masks or goggles unless you feel like it. 29/n

So while WIV workers don't seem to have gotten infections by WIV1, they may have dodged a bullet then. And it raises the question if they were performing other viral culture experiments at BSL2, experiments that may have been contaminated with SARSCoV2 without them knowing.
n/n

@Ayjchan @R_H_Ebright

@R_H_Ebright I recall you pointed out the BSL2 problem so I tagged you for credit

Follow-up: in case it was unclear, the above known facts do not identify a source for SARSCoV2. You could lean one way or another based on other assumptions you select. But to say something like "the facts rule this way or that way" is unwarranted at this time IMHO.

Adding correction to main thread (thx to those who alerted me). Entry "9. It is not known if the miner serum samples that yielded the 9 sarbecoviruses" had an editing error: The phrase "that yielded the 9 sarbecoviruses" was meant to go in entry #12 about guano samples.

Regarding retesting of bat samples for SARSCoV2 in point #12, Shi did reply to Science Magazine: "We tested all bat samples that we collected... 2,007 samples were positive for coronavirus. We did not find any viruses whose gene sequence is more similar to SARSCoV2 than RaTG13."

However it sounds like Shi may be describing their pre-epidemic screen using pan-coronavirus primers, rather than retesting with SARSCoV2-specific primers which could be more sensitive, or repeating with next-gen sequencing methods.

A paper published yesterday describes the sale of wild-captured mammals at several Wuhan markets in 2019. Those animals were likely removed before they could be tested, as market managers told authorities that all animals sold were farmed (per WHO report)
https://t.co/d01QpCuajv

The list of wild mammals observed is below. Based on my quick search through wikipedia, they are all found in Yunnan except for the hedgehog, hare, coypu (farmed apparently), mink (also farmed), and red squirrel. SD=0 suggests the authors just apply an estimate to all months.

Species on sale	Monthly mean (and SD) number of individuals sold	Price (mean ±SD) $ per individual
Mammals		
Raccoon dog (*Nyctereutes procyonoides*)[W,R,E,†]	38.33 ± 17.24 (n = 30)	63.32 ± 15.46 (n = 5)
Amur hedgehog (*Erinaceus amurensis*)[R,E,†]	332.14 ± 190.62 (n = 28)	2.66 ± 0.41 (n = 5)
Siberian weasel (*Mustela sibirica*)[W,R,E,†]	(10.06 ± 12.09, n = 31)	11.24 ± 3.07 (n = 5)
Hog badger (*Arctonyx albogularis*)[W,R,E,†]	(6.81 ± 5.37, n = 31)	72.79 ± 34.08 (n = 5)
Asian badger (*Meles leucurus*)[W,R,E,†]	12.24 ± 7.39 (n = 29)	59.77 ± 15.89 (n = 5)
Chinese hare (*Lepus sinensis*)[W,R,E,†]	168.96 ± 89.06 (n = 29)	16.87 ± 2.88 (n = 5)
Pallas's squirrel (*Callosciurus erythraeus*)[R,P,†]	16.52 ± 4.87 (n = 23)	25.74 ± 7.59 (n = 5)
Masked palm civet (*Paguma larvata*)[E,†]	10.69 ± 8.42 (n = 29)	62.73 ± 15.25 (n = 5)
Chinese bamboo rat (*Rhizomys sinensis*)[F,†]	42.76 ± 20.68 (n = 29)	18.64 ± 7.58 (n = 5)
Malayan porcupine (*Hystrix brachyura*)[E,†]	10.00 ± 0.00 (n = 29)	68.06 ± 14.23 (n = 5)
Chinese muntjac (*Muntiacus reevesi*)[F,†]	10.00 ± 0.00 (n = 29)	142.62 ± 49.67 (n = 5)
Coypu (*Myocastor coypus*)[F]	5.00 ± 0.00 (n = 29)	28.70 ± 5.08 (n = 5)
Marmot (*Marmota himalayana*)[F]	15.00 ± 4.29 (n = 20)	81.37 ± 11.70 (n = 5)
Red fox (*Vulpes vulpes*)[F,†]	30.00 ± 0.00 (n = 25)	60.96 ± 21.68 (n = 5)
Mink (*Neovison vison*)[F]	10.37 ± 1.92 (n = 27)	34.62 ± 14.78 (n = 5)
Red squirrel (*Sciurus vulgaris*)[R,P,†]	16.43 ± 9.51 (n = 28)	26.04 ± 8.14 (n = 5)
Wild boar (*Sus scrofa*)[W,R,E,*,†]	(4.17 ± 5.77, n = 29)	319.57 ± 55.95 (n = 5)
Complex-toothed Flying Squirrel (*Trogopterus xanthipes*)[F,P,†]	5.17 ± 27.85 (n = 29)	28.11 ± 9.64 (n = 5)
Birds		
Collared crow (*Corvus torquatus*)[R,P]	9.14 ± 20.18 (n = 29)	54.74 ± 8.43 (n = 5)
Spotted dove (*Spilopelia chinensis*)[R,E,†]	200.00 ± 0.00 (n = 29)	7.54 ± 1.10 (n = 5)
Eurasian magpie (*Pica pica*)[R,E,P,†]	21.54 ± 28.53 (n = 13)	10.21 ± 3.56 (n = 5)
Crested myna (*Acridotheres cristatellus*)[R,P,†]	60.34 ± 20.61 (n = 29)	15.39 ± 16.23 (n = 5)
Chukar partridge (*Alectoris chukar*)[E,†]	273.68 ± 45.24 (n = 19)	6.66 ± 1.38 (n = 5)
Ring-necked Pheasant (*Phasianus colchicus*)[E,†]	80.00 ± 0.00 (n = 26)	14.80 ± 5.44 (n = 5)
Peacock (*Pavo cristatus*)[E,P,*]	15.00 ± 0.00 (n = 15)	55.63 ± 20.33 (n = 5)
Guinea fowl (*Numida meleagris*)[F]	35.00 ± 15.81 (n = 10)	12.13 ± 5.17 (n = 5)
Reptiles		
Beauty rat snake (*Orthriophis taeniurus*)[R,E,†]	(7.00 ± 10.90, n = 28)	22.78 ± 15.36 (n = 5)
Red large-toothed Snake (*Dinodon rufozonatum*)[R,E,†]	(7.78 ± 11.56, n = 27)	10.06 ± 4.84 (n = 5)
Many-banded krait (*Bungarus multicinctus*)[R,E,†]	(3.18 ± 3.32, n = 27)	11.24 ± 3.41 (n = 5)
Ringed water snake (*Sinonatrix annularis*)[R,P,†]	(19.00 ± 39.21, n = 29)	3.25 ± 1.24 (n = 5)
Short-tailed pit viper (*Gloydius brevicaudus*)[R,E,†]	(5.96 ± 10.30, n = 27)	7.84 ± 1.93 (n = 5)
Chinese cobra (*Naja atra*)[R,E,†]	(59.04 ± 54.93, n = 28)	N/A
Monocled cobra (*Naja kaouthia*)[E,†]	(18.48 ± 48.50, n = 29)	20.42 ± 6.57 (n = 5)
Oriental rat snake (*Ptyas mucosa*)[E,†]	(11.76 ± 20.44, n = 29)	18.94 ± 3.21 (n = 5)
Sharp-nosed pit viper (*Deinagkistrodon acutus*)[E,†]	(3.69 ± 5.35, n = 26)	41.13 ± 16.65 (n = 5)
Siamese crocodile (*Crocodylus siamensis*)[E,*]	(2.07 ± 2.53, n = 27)	N/A
Big-eyed rat snake (*Ptyas dhumnades*)[R,E,†]	(121.10 ± 138.11, n = 29)	10.36 ± 2.09 (n = 5)
King rat snake (*Elaphe carinata*)[R,E,†]	(104.97 ± 85.07, n = 29)	N/A

Table 1. List of 38 species sold in Wuhan City markets between May 2017–Nov 2019, including the mean

The above 2 posts are relevant to fact #15, but some verification of this paper by a second source would be nice (if anybody was in Wuhan in 2019 and can provide photos of the illegal wildlife), that would be great.

I found additional verification that WIV routinely worked with the cross-species SARSCoV1-related WIV1 at BSL2. In fact they explain why in this obscure paper:
https://t.co/1v6SPPGv7z

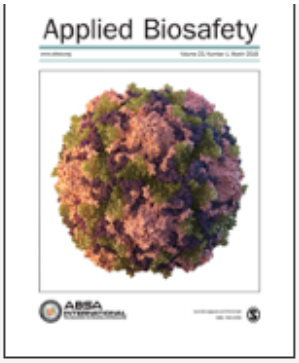
immunodeficiency virus type 1 (HIV-1), and hepatitis C virus.[4] Here, using bat severe acute respiratory syndrome (SARS)–like coronavirus (CoV) WIV1 as a surrogate, we report the evaluation tests of MCP at Wuhan National Biosafety Laboratory, which was designed and constructed with French cooperation and was the first BSL-4 laboratory certified by the China National Accreditation Service for Conformity Assessment (CNAS) in January 2017[5] and further approved by the National Health and Family Planning Commission of the People's Republic of China in August 2017.

Materials and Methods

Cells and Viruses

The African green monkey kidney cell line Vero-E6 was purchased from the American Type Culture Collection, maintained in Dulbecco's modified Eagle medium (DMEM; Gibco) supplemented with 10% fetal bovine serum (FBS; ThermoFisher, Waltham, Massachusetts) at 37°C with 5% CO2 in a humidified atmosphere.

The bat SARS-like CoV WIV1 strain was originally isolated with Vero-E6 from bat feces[6] and can replicate in human airways but lacks the virulence of epidemic SARS-CoV[7] so it can be handled in a BSL-2 laboratory. To prepare virus stocks, Vero-E6 monolayer was inoculated with WIV1, vesicular stomatitis virus (VSV), or poliovirus type I (PV-I) at the multiplicity of infection of 0.1 in DMEM + 2.5% FBS; 2 to 3 days later, the medium was collected and centrifuged at 5000 g for 10 minutes to remove cell debris. The supernatant was aliquoted and frozen at −80°C.



Information
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To cite this article:

Huajun Zhang, Chen Peng, Bobo Liu, Jun Liu, Zhiming Yuan, and Zhengli Shi. Applied Biosafety. Mar 2018. 32-38. http://doi.org/10.1177/153567601875889

Published in
Volume: 23 Issue 1: March 1, 2018

Keywords

MICRO-CHEM PLUS

disinfectant

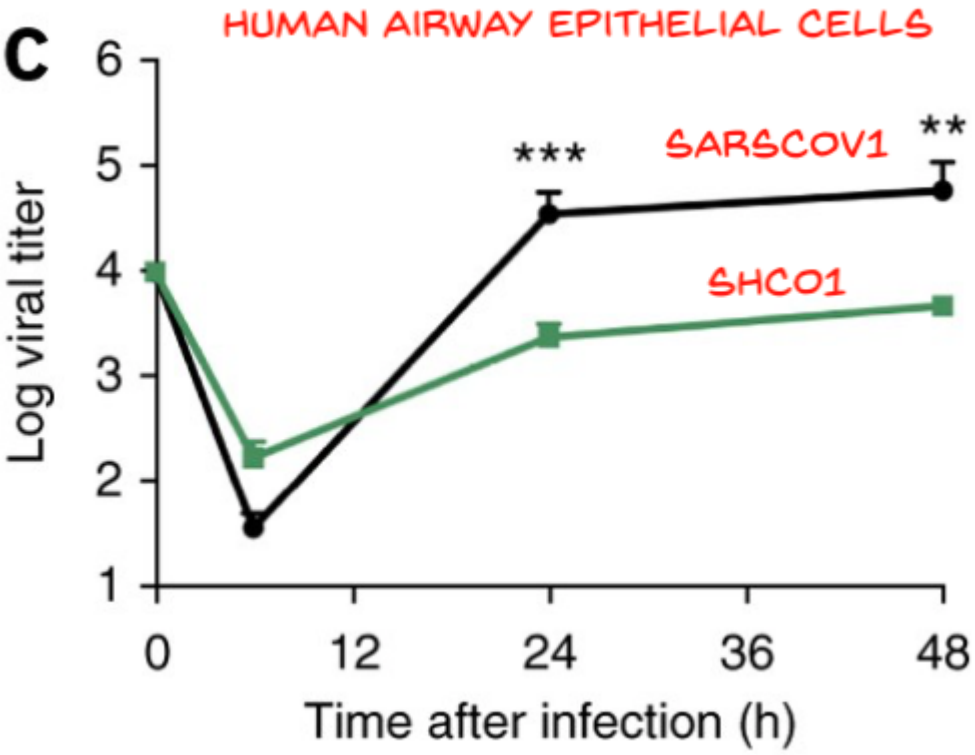
The claim is SARS-like bat coronavirus (SL-CoV) WIV1 "can replicate in human airways [sic] but lacks the virulence of epidemic SARS-CoV■ so it can be handled in a BSL-2 laboratory"

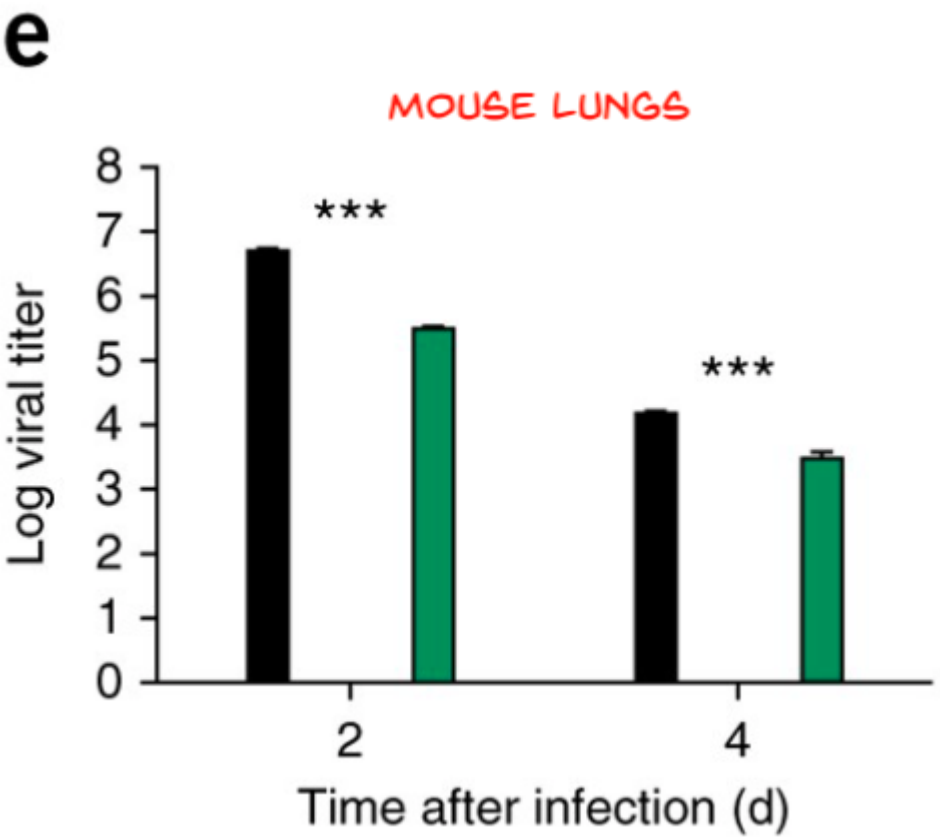
Pretty sure they meant human airway *cells*. Doubt they were squirting WIV1 down human throats...

Anyway they deemed it safe to handle WIV1 at BSL-2 because it "lacks the virulence of SARS-CoV".

They provide reference #7 to support that avirulence claim. As far as I could tell ref 7 says no such thing about WIV1. Instead it describes a related virus, SHC014...

There they define SHC014 as less virulent because it reaches 1 log lower titer than SARSCoV1 in human airway epithelial (HAE) cells, or in mouse lungs.



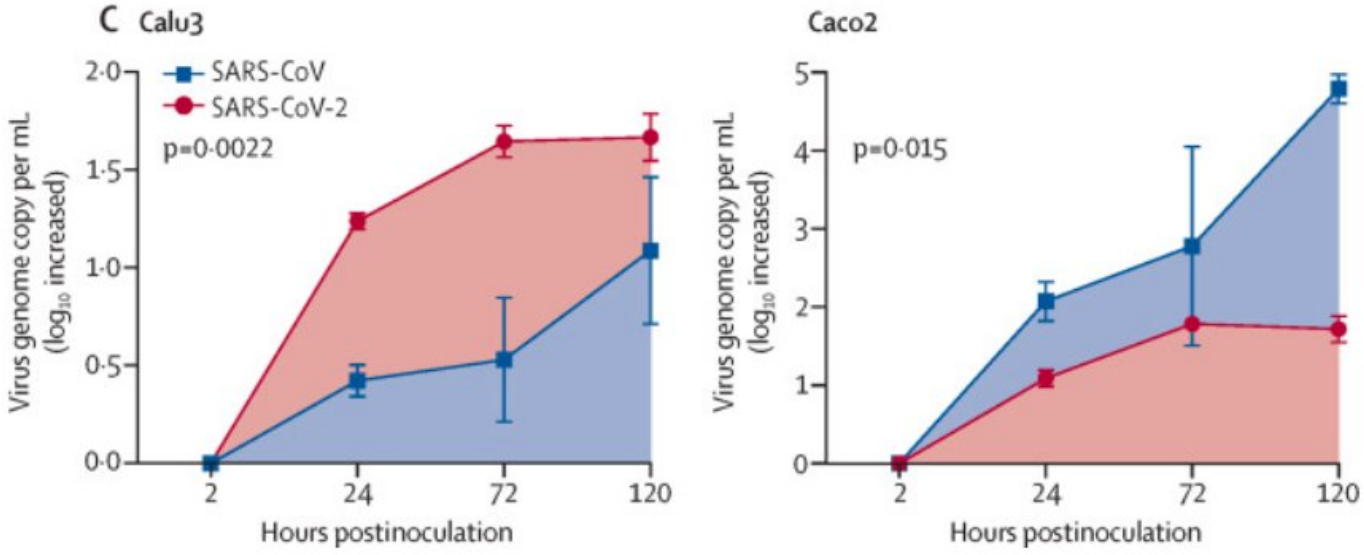


But replication to lower levels in cell culture or mouse lungs does not guarantee safety in humans. A virus could replicate poorly in cultured HAE cells or mouse lungs and do fine in a different cell type in the human body.

Or viruses that replicate poorly can still cause late-stage disease and be transmitted to others, if it means they are better at hiding away from the immune system in the early stages of the disease.

Just within the sarbecoviruses, we can try to figure out if viral levels in culture relate to pandemic potential by comparing SARSCoV1 with SARSCoV2...

Turns out you can't really conclude anything. SARSCoV1 replicates better in some cell types and SARSCoV2 better in others...
https://t.co/OpH6FnjDYY



It's odd to use viral levels as a definition for virulence anyway. Usually virulence means ability to cause pathology esp. death. So you might assess virulence better by cell death, not virus levels, in culture. Here SARSCoV2 looks consistently less potent than SARSCoV1:

figure 2A). SARS-CoV-2 replicated most robustly in non-human primate cells and pig cells, as shown by a 3 log or greater increase in mean viral load over a period of 120 h in VeroE6, FRhK4, and PK-15 cells. Similar to the human cell tropism profile, the cellular tropism of SARS-CoV-2 in non-human cells largely matched that of SARS-CoV, which was also capable of infecting and replicating in non-human primate, cat, rabbit, and pig cells (figure 2B). Importantly, SARS-CoV, but not SARS-CoV-2, could replicate in *Rhinolophus sinicus* primary bat kidney cells (RSK; p=0·048). With the recombinant human ACE2 protein blocking assay, we confirmed that, similar to SARS-CoV, infection of SARS-CoV-2 was dependent on ACE2 (appendix p 4).

In addition to cellular tropism and replication kinetics profiles, cell damage induced by SARS-CoV-2 was also assessed in nine human (figure 3A) and 16 non-human (figure 3B) cell lines. Among the 11 cell lines that supported SARS-CoV-2 replication (Calu3, Huh7, Caco2, 293T, U251, VeroE6, FRhK4, LLCMK2, CRFK, RK-13, and PK-15), SARS-CoV-2 only induced substantial cell damage in VeroE6 cells (28·7% viability at 120 hpi; p<0·0001) and FRhK4 cells (24·0% viability at 120 hpi; p<0·0001). Typical cytopathic effects in VeroE6 and FRhK4 cells included cell rounding, detachment, degeneration, and syncytium formation (figure 4).

Despite robust SARS-CoV-2 replication in Calu3 and Caco2 cells, substantial cell death was not detected up to 120 hpi (at 120 hpi, Calu3 viability was 103% and Caco2 viability was 104%). To understand if SARS-CoV-2 would induce cell death in cells that supported efficient virus replication at a delayed timepoint, cell viability of SARS-CoV-2-infected Calu3, Caco2, LLCMK2, PK-15, and RK-13 cells was assessed at 7 days postinfection; cell death was not detected in these cell types (appendix p 5).

Although SARS-CoV-2 and SARS-CoV were inoculated with the same MOI, SARS-CoV-2 induced less cell damage than did SARS-CoV (figure 3). This observation was supported by the significantly higher percentage of cell viability in VeroE6 and FRhK4 cells infected by SARS-CoV-2 than in those infected by SARS-CoV, at multiple timepoints. The AUC analysis also showed a significantly higher amount of viable cells on SARS-CoV-2 infection by comparison with SARS-CoV infection in both VeroE6 cells (p=0·016) and FRhK4 cells (p=0·0004) over the 120 h period (appendix p 6).

To sum up, Shi's lab cultured WIV1, a bat sarbecovirus that infects human cells, at BSL2 because they deemed it less virulent. But they showed no data to support this, and "virulence" assays they used for other viruses cannot predict pandemic or disease potential in humans anyway