Origin of Covid-19: Lab Leak

A case by Rootclaim, presented by Saar Wilf (Founder)

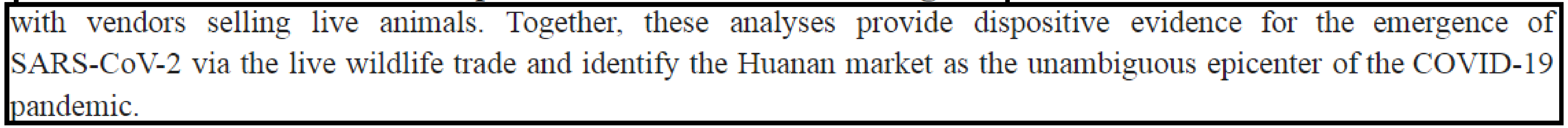
Rootclaim's Mission

Rootclaim attempts to solve the problem of intelligent people reaching contradictory conclusions while having access to the same evidence.

Former CDC chief Redfield says he thinks COVID-19 originated in a Chinese lab

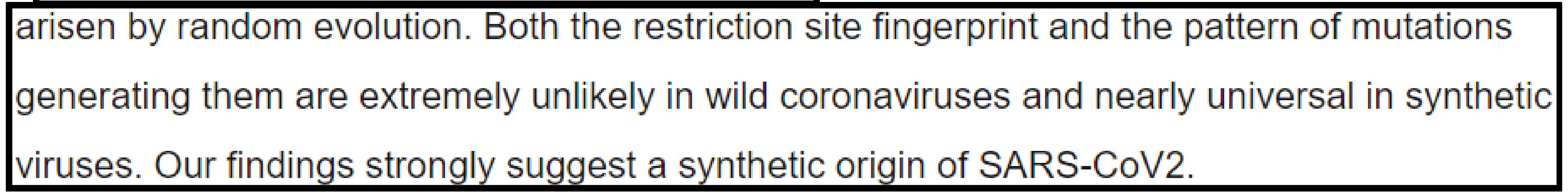
CDC chief says lab origin of Covid is 'one possibility,' but animal host is most common for coronaviruses

The Huanan market was the epicenter of SARS-CoV-2 emergence

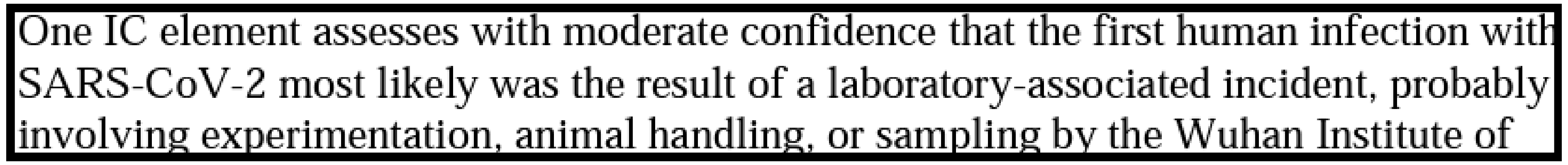


with vendors selling live animals. Together, these analyses provide dispositive evidence for the emergence of SARS-CoV-2 via the live wildlife trade and identify the Huanan market as the unambiguous epicenter of the COVID-19 pandemic.

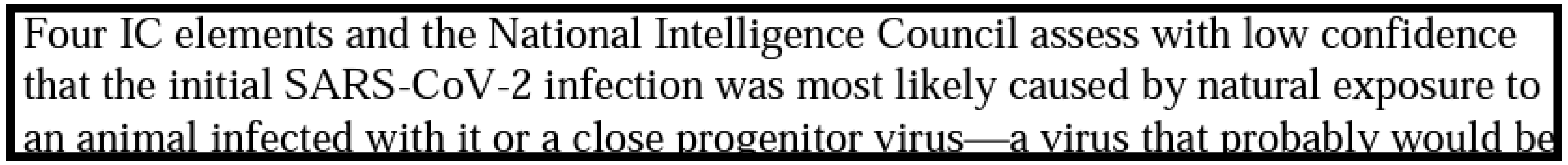
Endonuclease fingerprint indicates a synthetic origin of SARS-CoV-2



arisen by random evolution. Both the restriction site fingerprint and the pattern of mutations generating them are extremely unlikely in wild coronaviruses and nearly universal in synthetic viruses. Our findings strongly suggest a synthetic origin of SARS-CoV2.



One IC element assesses with moderate confidence that the first human infection with SARS-CoV-2 most likely was the result of a laboratory-associated incident, probably involving experimentation, animal handling, or sampling by the Wuhan Institute of



Four IC elements and the National Intelligence Council assess with low confidence that the initial SARS-CoV-2 infection was most likely caused by natural exposure to an animal infected with it or a close progenitor virus—a virus that probably would be

What Rootclaim Doesn’t Do

- Fact-Checking
- Investigative Journalism
- Leaks/Uncovering new evidence
- Conjecture when evidence is lacking

✗

Rootclaim excels when experts struggle to reach a consensus despite abundant evidence

☑

Human Inference Flaws

There are a few common flaws people experience when dealing with high uncertainty and multiple pieces of evidence.

Reliance on gut feelings and conventional wisdom to assess likelihoods

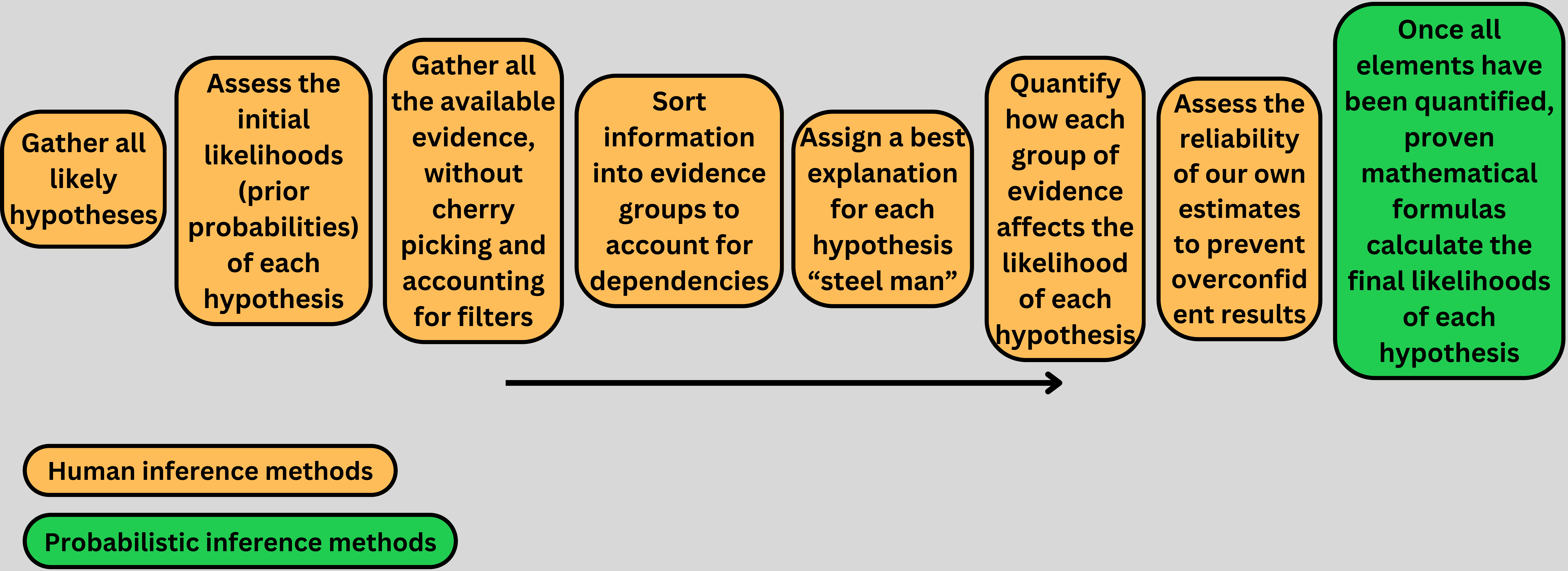
Weak intuition for compound probabilities

Ignoring filters on evidence

Ignoring priors - Prosecutor's fallacy

Overlooking dependencies

Rootclaim’s Methodology - Layout



- Gather all likely hypotheses
- Assess the initial likelihoods (prior probabilities) of each hypothesis
- Gather all the available evidence, without cherry picking and accounting for filters
- Sort information into evidence groups to account for dependencies
- Assign a best explanation for each hypothesis “steel man”
- Quantify how each group of evidence affects the likelihood of each hypothesis
- Assess the reliability of our own estimates to prevent overconfident results
- Once all elements have been quantified, proven mathematical formulas calculate the final likelihoods of each hypothesis

🟧 Human inference methods

🟩 Probabilistic inference methods

The goal of the Rootclaim methodology is to accurately quantify the strength of the evidence so it can be fed into a proven probabilistic model.

Example Rootclaim Cases

Murder of Tair Rada in 2006 (Israel)

Tair Rada, a 13-year-old Israeli schoolgirl, was found dead, covered in her own blood and her throat sliced, inside a locked bathroom stall in her school, Nofey Golan, in the town of Katzrin. Initial suspects were Roman Zdorov, a floorer temporarily working at the school and a new immigrant to Israel from Ukraine, as well as Tair's schoolmates. During the police investigation, Zdorov confessed to the crime but recanted soon after. Zdorov was convicted of the murder on 14th September 2010.

Conclusion: Ola Kravchenko murdered Tair Rada (98.4%)

Ghouta Chemical Attack in 2013 (Syria)

On August 21, 2013, rockets with chemical payloads landed around the neighborhood of Zamalka, located in Ghouta (an agricultural area outside of Damascus), resulting in hundreds of civilian casualties. There was initial skepticism that the Syrian government would have ordered such an attack, risking retaliation by the US. But information published by the US, UN, and Human Rights Watch during the following weeks convinced Western public opinion that the Syrian government was indeed responsible.

Conclusion: Opposition forces in Syria (Liwa al-Islam) carried out the chemical attack (96.4%)

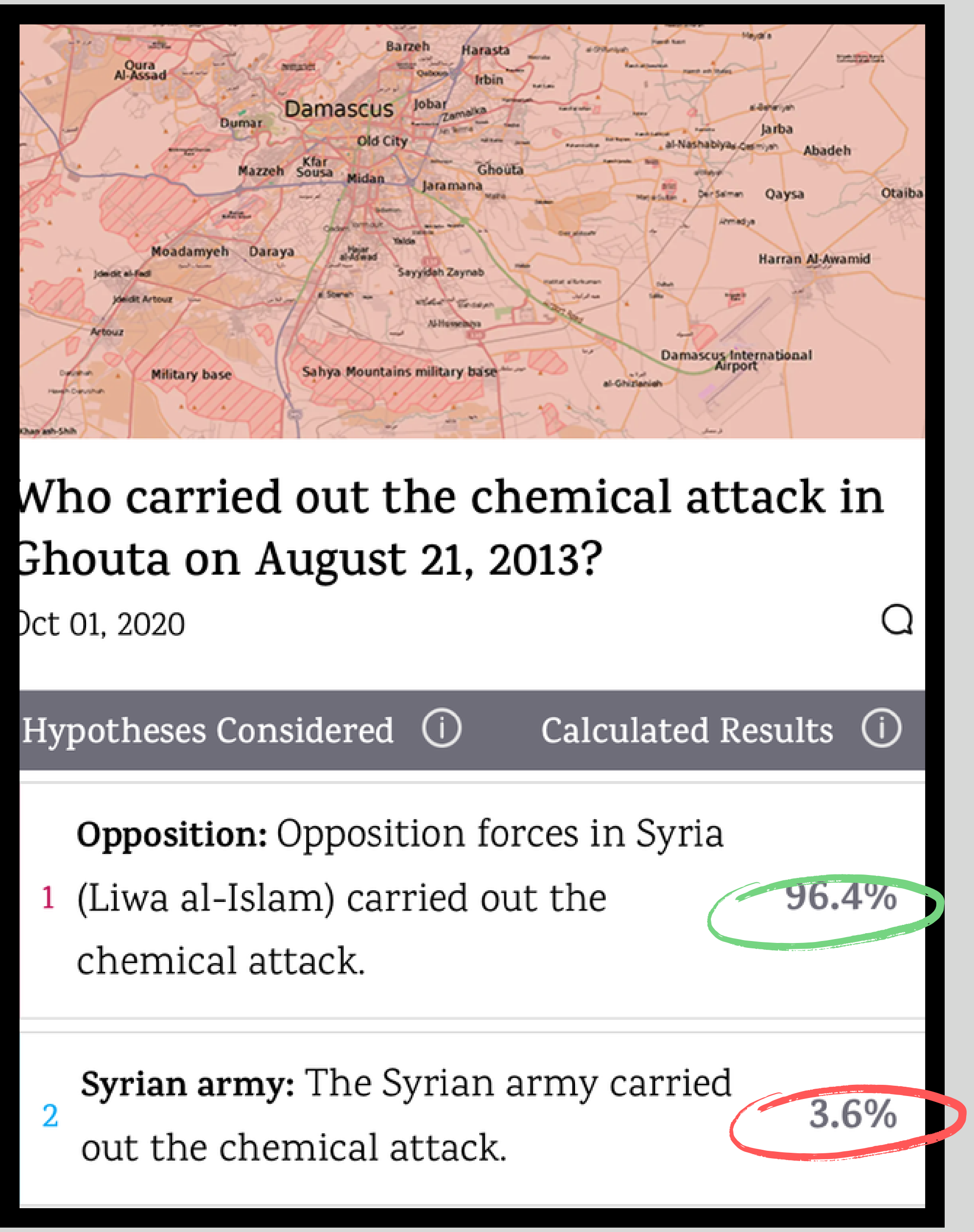
Why did authorities get these conclusions wrong?

	Chemical Attacks in Syria	Murder of Tair Rada	Origin of Covid-19
“Trapped Prior” (Confirmation Bias)	Only Syrian Government known to possess chemical weapons Opposition did have chemical weapons	Why would someone confess to a crime he didn’t commit? Confessions are common in wrongful convictions	Most viruses come from zoonosis, not lab eaks Advancements in GoF research increase the pandemic risk
Claimed “Smoking Gun” - In reality fabricated or “sharpshooter fallacy”	Part of Syrian chemical weapon found at the scene Appears fabricated - inconsistencies	Shoeprint claimed to have matched the suspect and the crime scene Weak matches combined to infer a strong match.	Huanan market as the epicenter Selection bias

Why did authorities get these conclusions wrong?

	Chemical Attacks in Syria	Murder of Tair Rada	Origin of Covid-19
Contrary Strong Evidence Dismissed	Video of the rocket launch claimed to be “fabricated” Fabricated videos are very rare	Mitochondrial DNA match of 1:700 - Dismissed as “10,000s of people” Since it matched a previously identified suspect - very strong evidence of guilt	Furin cleavage site insertion - “not impossible in nature” Impossibility is irrelevant, the likelihood is very low
Rare Coincidences Dismissed		Different suspect with desire to kill random people living close to the crime scene	Outbreak occurring next to a major coronavirus lab

Later Evidence Supported Rootclaim’s Conclusions ☑



Who carried out the chemical attack in Ghouta on August 21, 2013?

Oct 01, 2020

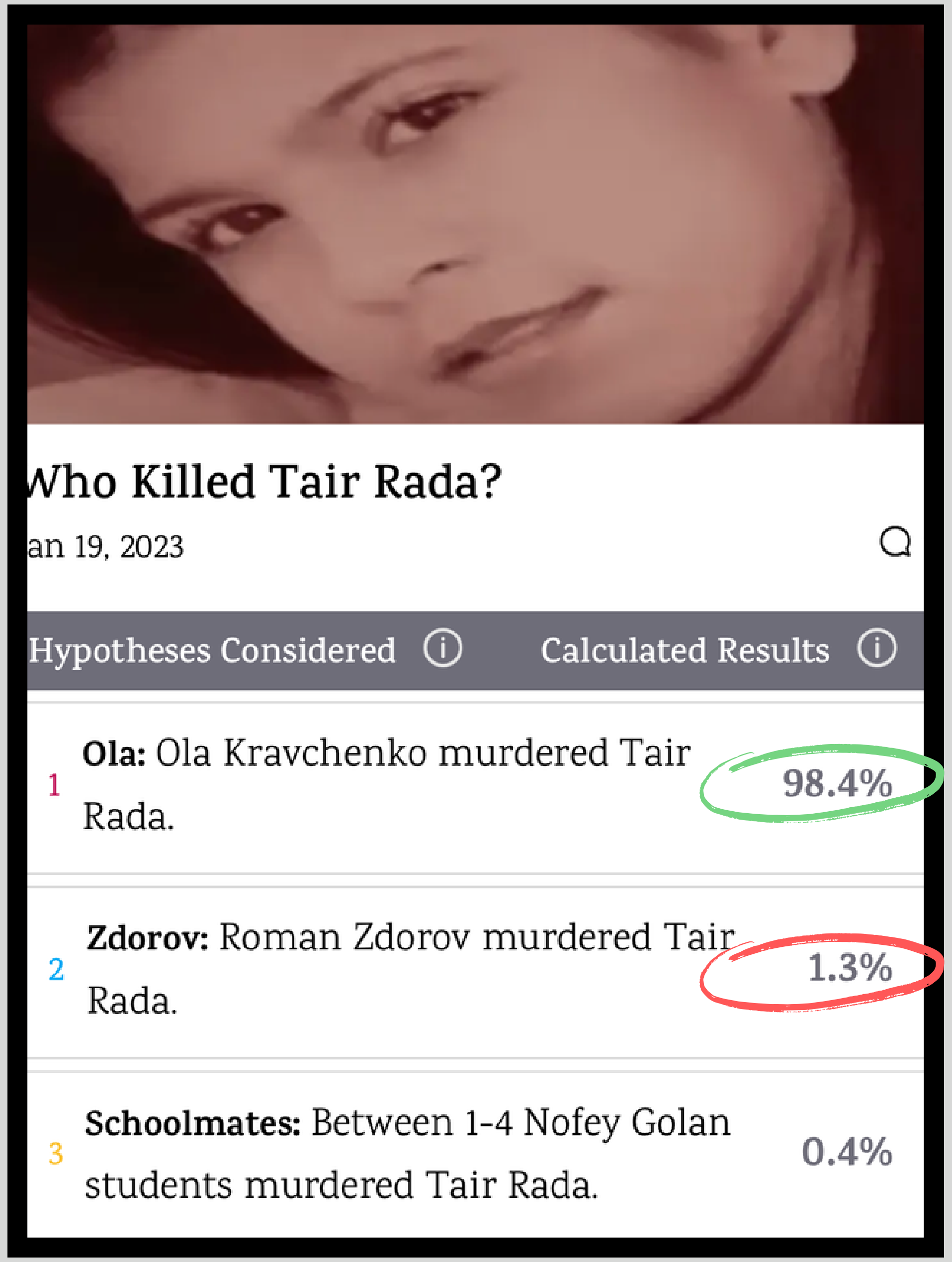
Hypotheses Considered ⓘ Calculated Results ⓘ

1 **Opposition:** Opposition forces in Syria (Liwa al-Islam) carried out the chemical attack. 96.4%

2 **Syrian army:** The Syrian army carried out the chemical attack. 3.6%

In June 2021, the videos were authenticated. They were matched to a field, within opposition-controlled territory, which was at the intersection of seven trajectories calculated from images of the impact sites.

#Syria: Alleged Liwa al-Islam rebels firing missiles 1 of 3



Who Killed Tair Rada?

an 19, 2023

Hypotheses Considered ⓘ Calculated Results ⓘ

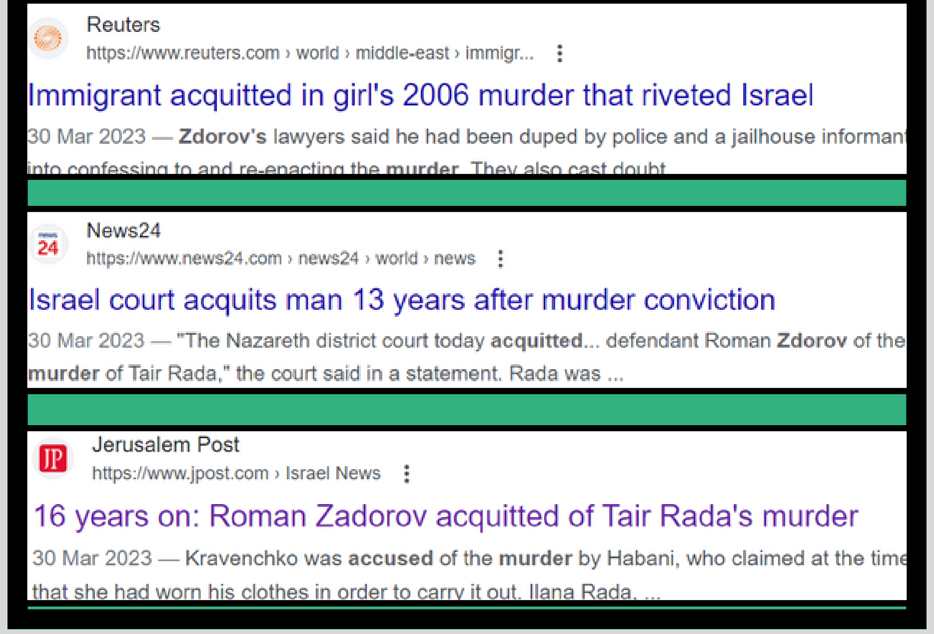
1 **Ola:** Ola Kravchenko murdered Tair Rada. 98.4%

2 **Zdorov:** Roman Zdorov murdered Tair Rada. 1.3%

3 **Schoolmates:** Between 1-4 Nofey Golan students murdered Tair Rada. 0.4%

The mtDNA was fully sequenced, strengthening the match from 1:700 to near certain.

After spending over a decade in prison, Zdorov’s conviction was overturned.



Reuters
https://www.reuters.com › world › middle-east › immigr...

Immigrant acquitted in girl's 2006 murder that riveted Israel

30 Mar 2023 — **Zdorov's** lawyers said he had been duped by police and a jailhouse informant into confessing to and re-enacting the **murder**. They also cast doubt

News24
https://www.news24.com › news24 › world › news

Israel court acquits man 13 years after murder conviction

30 Mar 2023 — "The Nazareth district court today **acquitted**... defendant Roman **Zdorov** of the **murder** of Tair Rada," the court said in a statement. Rada was ...

Jerusalem Post
https://www.jpost.com › Israel News

16 years on: Roman Zadorov acquitted of Tair Rada's murder

30 Mar 2023 — Kravenchko was **accused** of the **murder** by Habani, who claimed at the time that she had worn his clothes in order to carry it out. Ilana Rada, ...

Summary: Why Lab Leak IS Most Likely

Priors

Zoonosis is likely a more common cause, but lab leaks are more frequent than previously believed, and recent advances in Gain-of-Function (GoF) increase pandemic risk.

Lab leak: 23.5%

Location

Wuhan is a more probable origin under the lab leak hypothesis due to its prominence in GoF coronavirus research, whereas zoonotic outbreaks could have started in any other city.

Updated probability

Lab leak: 87.7%

Summary: Why Lab Leak IS Most Likely

WIV Activity

WIV has been likely conducting precisely the kind of research that would produce SARS-CoV-2

Updated probability

Lab leak: 96.9%

Market

Claims that the Huanan market is the epicenter are based on selection bias, and are contradicted by a substantial body of evidence

Updated probability

Lab leak: 94.8%

Summary: Why Lab Leak IS Most Likely

Genetics

The genetics of SARS-CoV-2 and especially the specific way in which the Furin Cleavage Site appears are highly unlikely to occur in nature

Updated probability

Lab leak: 99.9%

Other

Some behaviors of China and WIV match a lab leak and some don't. Same for missing evidence.

Updated probability

Lab leak: 99.5%

Note: "Genetics" will be discussed in Session 2, and "Behavioral" in Session 3

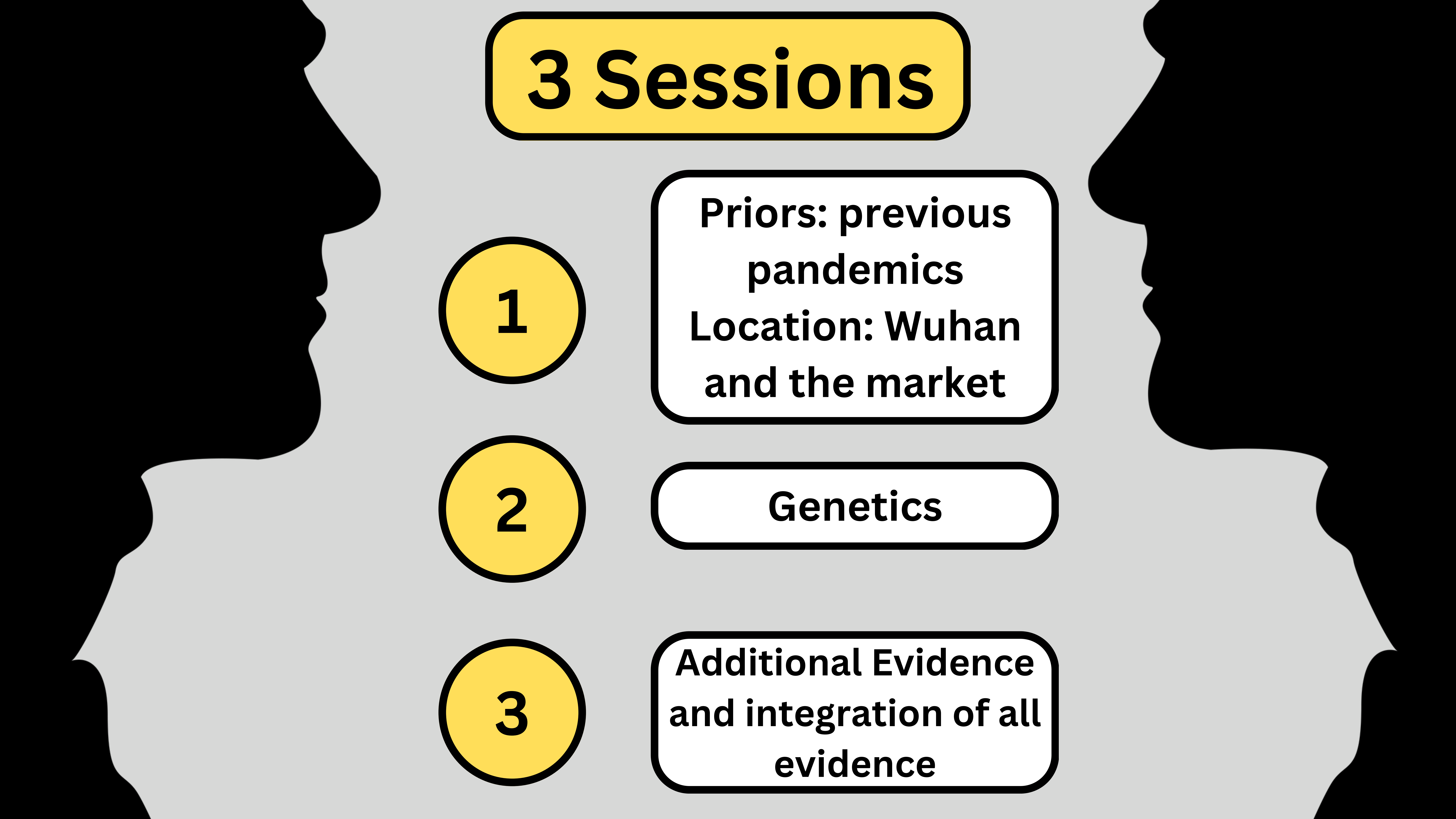
Results of other probabilistic analyses

Three analyses estimate the probability of a lab leak to be over 99%

- **M. Weissmann : “our point estimate of the probability of a laboratory-modified source, leaked in some lab mishap is ~99.96%”**
- **S. Quay : “The outcome of this report is the conclusion that the probability of laboratory origin for CoV-2 is 99.8%”**
- **L. Nemzer : “the estimated probability of a natural origin for SARS2 is ~0.001, which is 0.1%”**

Demaneuf & de Maistre : “under a reference set of input probabilities, the relative probabilities are at least 55% for a lab-related event”

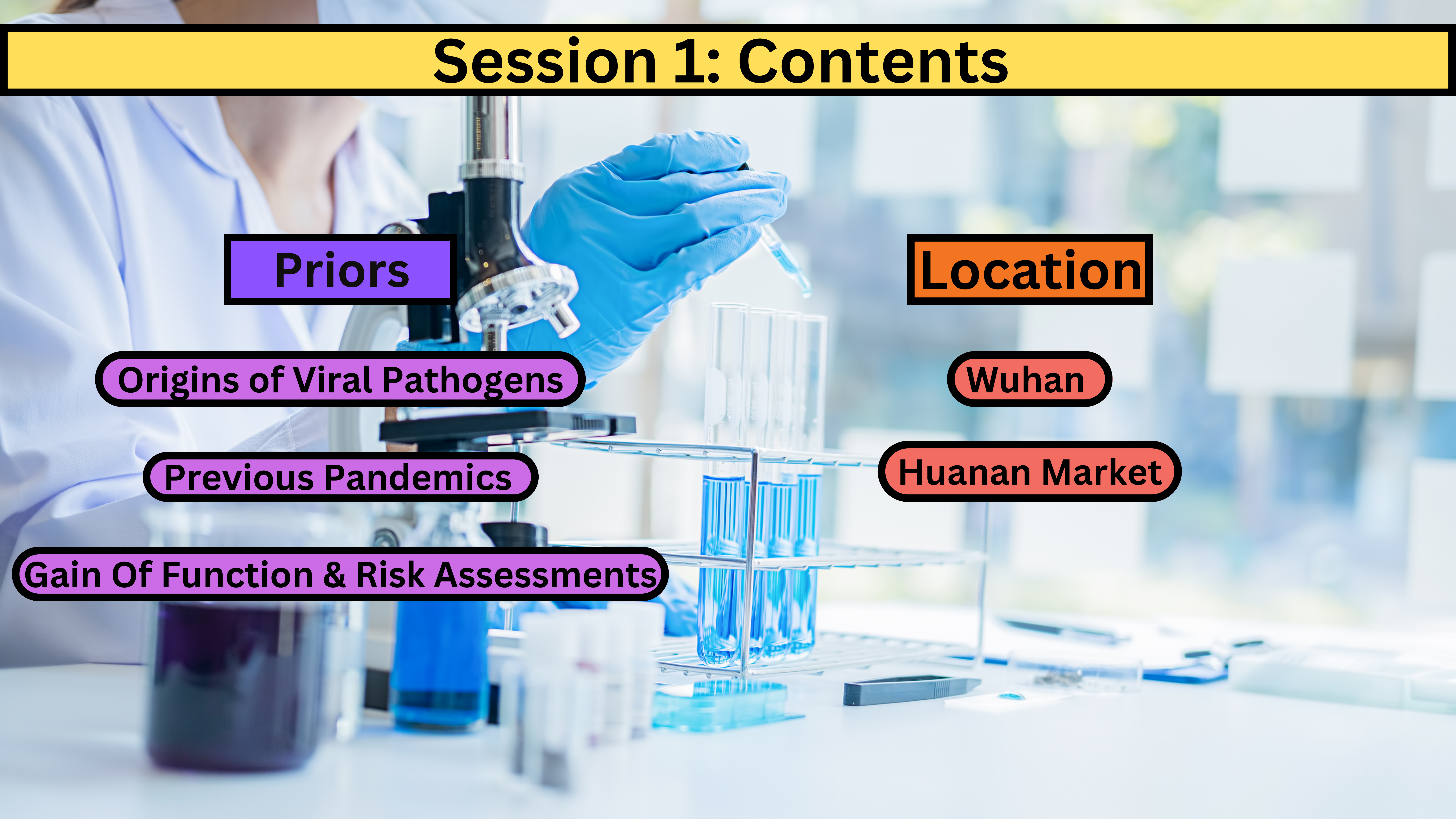
Note: Not included here are purely qualitative Bayesian analyses (Washburne : “The totality of the circumstances around the emergence of SARS-CoV-2 gives probable cause for a laboratory origin”) or analyses based solely on certain type of evidence (geographical for Seymour).



3 Sessions

1. Priors: previous pandemics
   Location: Wuhan and the market
2. Genetics
3. Additional Evidence and integration of all evidence

Session 1: Contents



Priors

- Origins of Viral Pathogens
- Previous Pandemics
- Gain Of Function & Risk Assessments

Location

- Wuhan
- Huanan Market

What is “Prior Probability”?

Priors are an initial estimate of a hypothesis's probability, before examining the specific evidence of the case.
Explicitly requiring it prevents prosecutor’s fallacy.

Your friend went for a routine exam and got a HIV+ result. You find out this type of test is 99% accurate - that is, the probability that the test would indicate that a person has HIV when he doesn’t is only 1%

what is the probability that your friend really has HIV?

Common answer:
99%

In reality:

Only 0.1% of the population has undiagnosed HIV

It is actually 10x more likely the test produced a false positive.

“Extraodinary claims require extraordinary evidence” - Carl Sagan

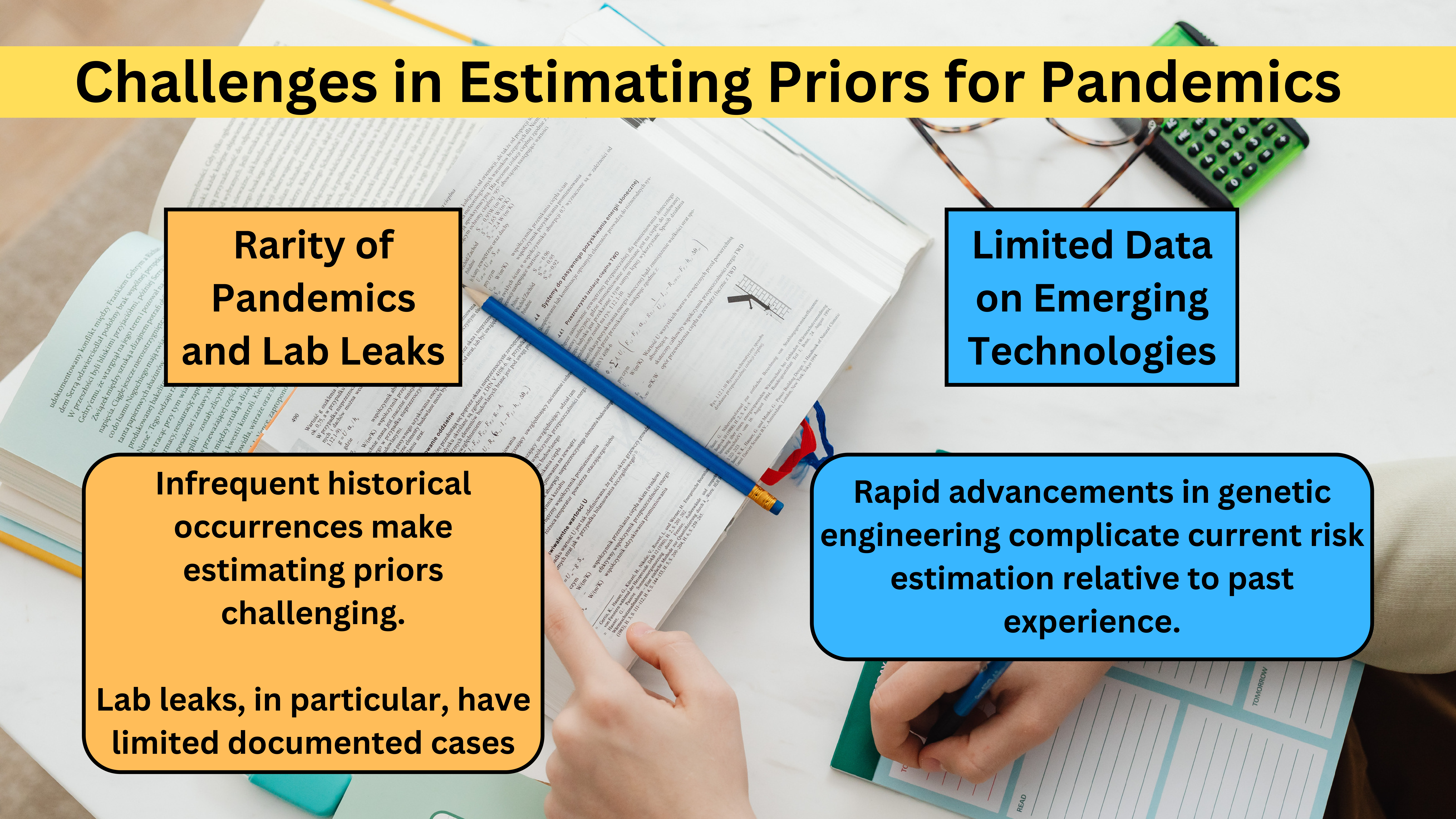
Estimating SARS-CoV-2 priors

Likelihood of Pandemic Occurring by Origin

- Nature
- Lab Leak

Historic data on pandemic origins provides a basis for estimating the initial likelihoods of each hypothesis.

Challenges in Estimating Priors for Pandemics



Rarity of Pandemics and Lab Leaks

Infrequent historical occurrences make estimating priors challenging.

Lab leaks, in particular, have limited documented cases

Limited Data on Emerging Technologies

Rapid advancements in genetic engineering complicate current risk estimation relative to past experience.

Prior: Confirmed & Suspected Lab Leaks

Confirmed Lab Leaks

1979 - Anthrax

Initially, the outbreak was blamed on the consumption of contaminated meat - Eventually being confirmed to have originated from a lab

2004 - SARS (leaked 4 times)

2014 - Anthrax

Suspected Lab Leaks

1977 - H1N1

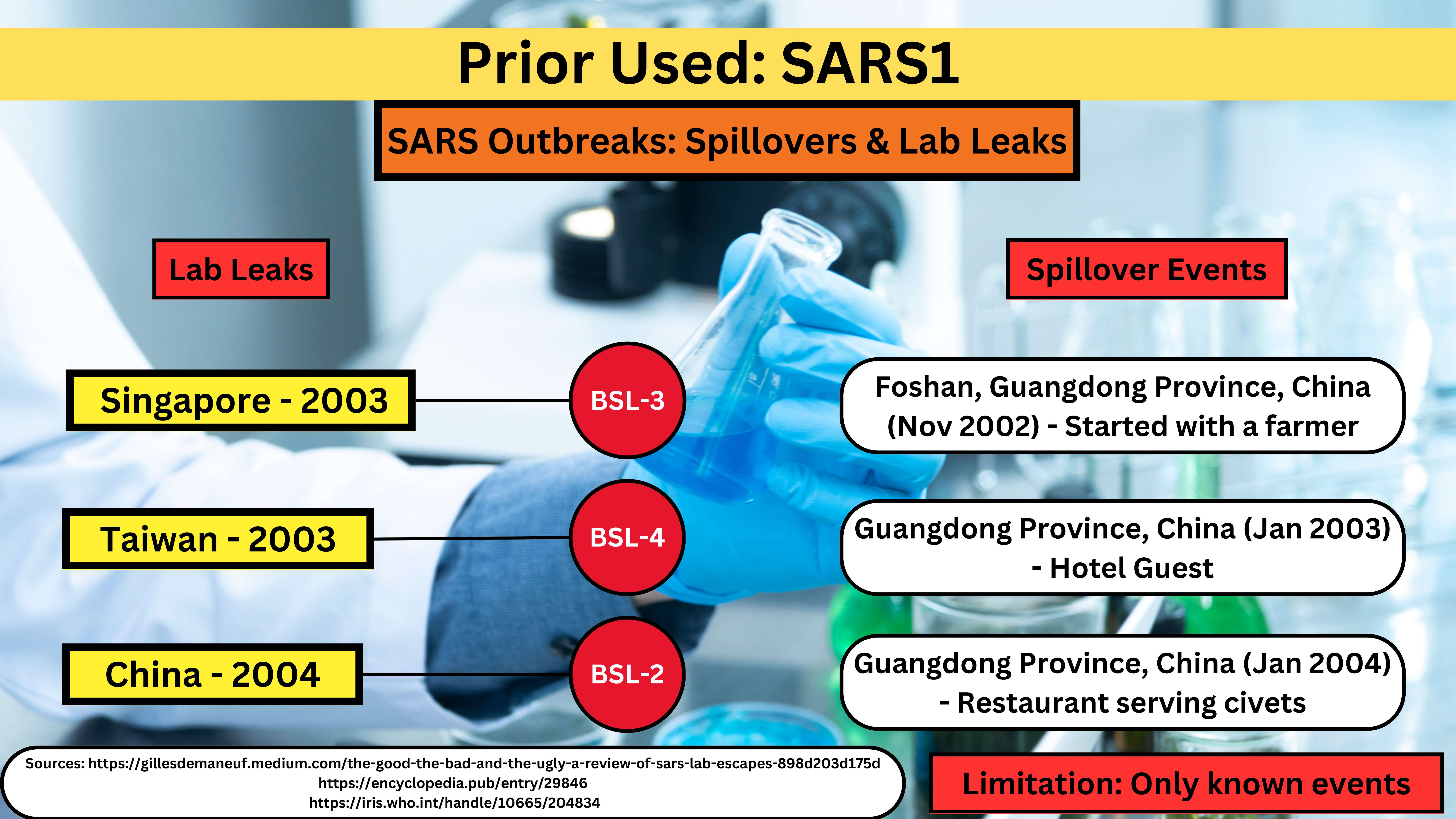
Suspected to be a Lab Leak due to similarity with H1N1 strain from 1946-1957

2021 - Zaire Ebolavirus

Suspected to be a Lab Leak due to similarities with strain from 2014

Prior Used: SARS1

SARS Outbreaks: Spillovers & Lab Leaks



Lab Leaks

Singapore - 2003 — BSL-3

Taiwan - 2003 — BSL-4

China - 2004 — BSL-2

Spillover Events

Foshan, Guangdong Province, China (Nov 2002) - Started with a farmer

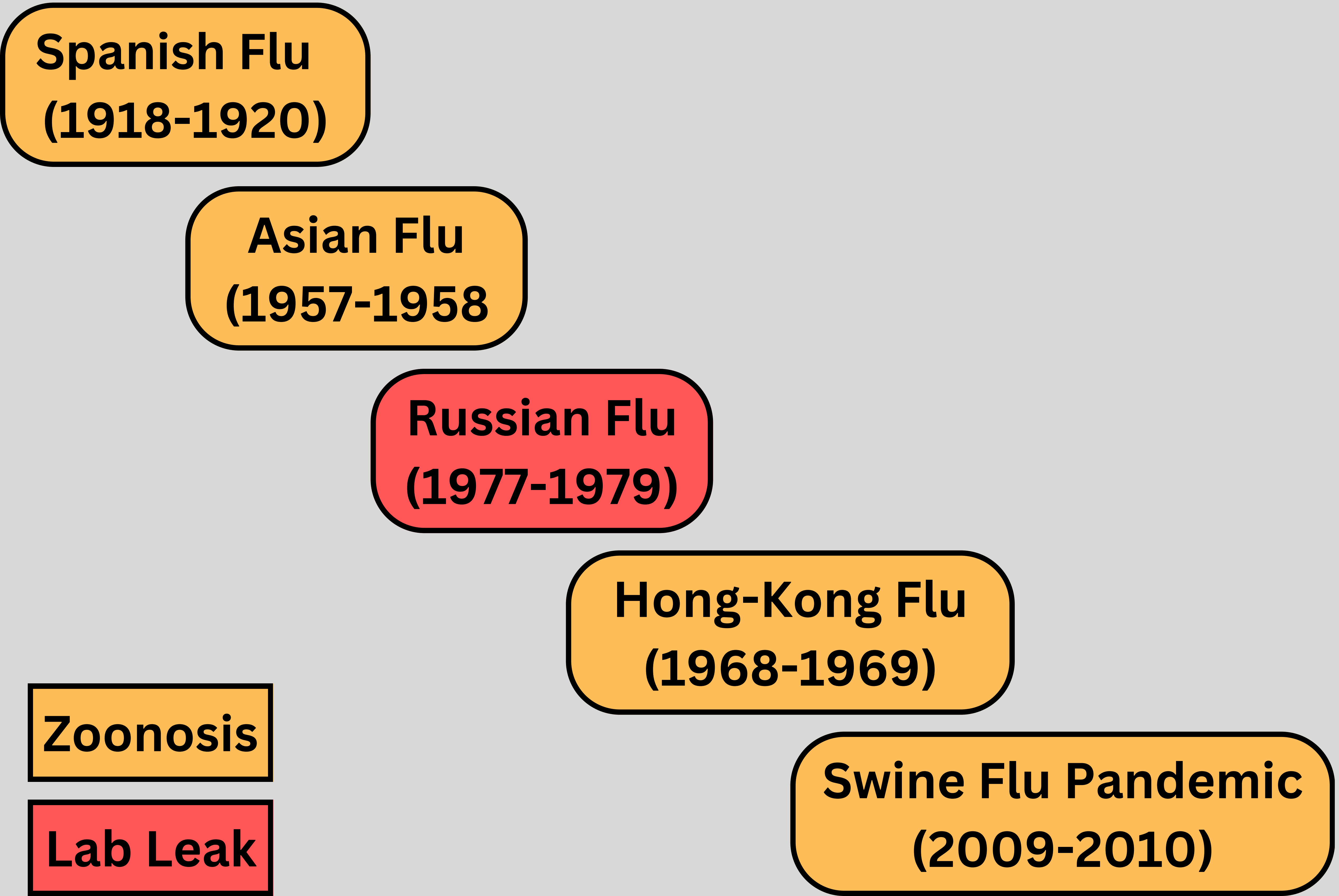
Guangdong Province, China (Jan 2003) - Hotel Guest

Guangdong Province, China (Jan 2004) - Restaurant serving civets

Sources: https://gillesdemaneuf.medium.com/the-good-the-bad-and-the-ugly-a-review-of-sars-lab-escapes-898d203d175d
https://encyclopedia.pub/entry/29846
https://iris.who.int/handle/10665/204834

Limitation: Only known events

Prior Used: Major Flu Pandemics



Spanish Flu
(1918-1920)

Asian Flu
(1957-1958

Russian Flu
(1977-1979)

Hong-Kong Flu
(1968-1969)

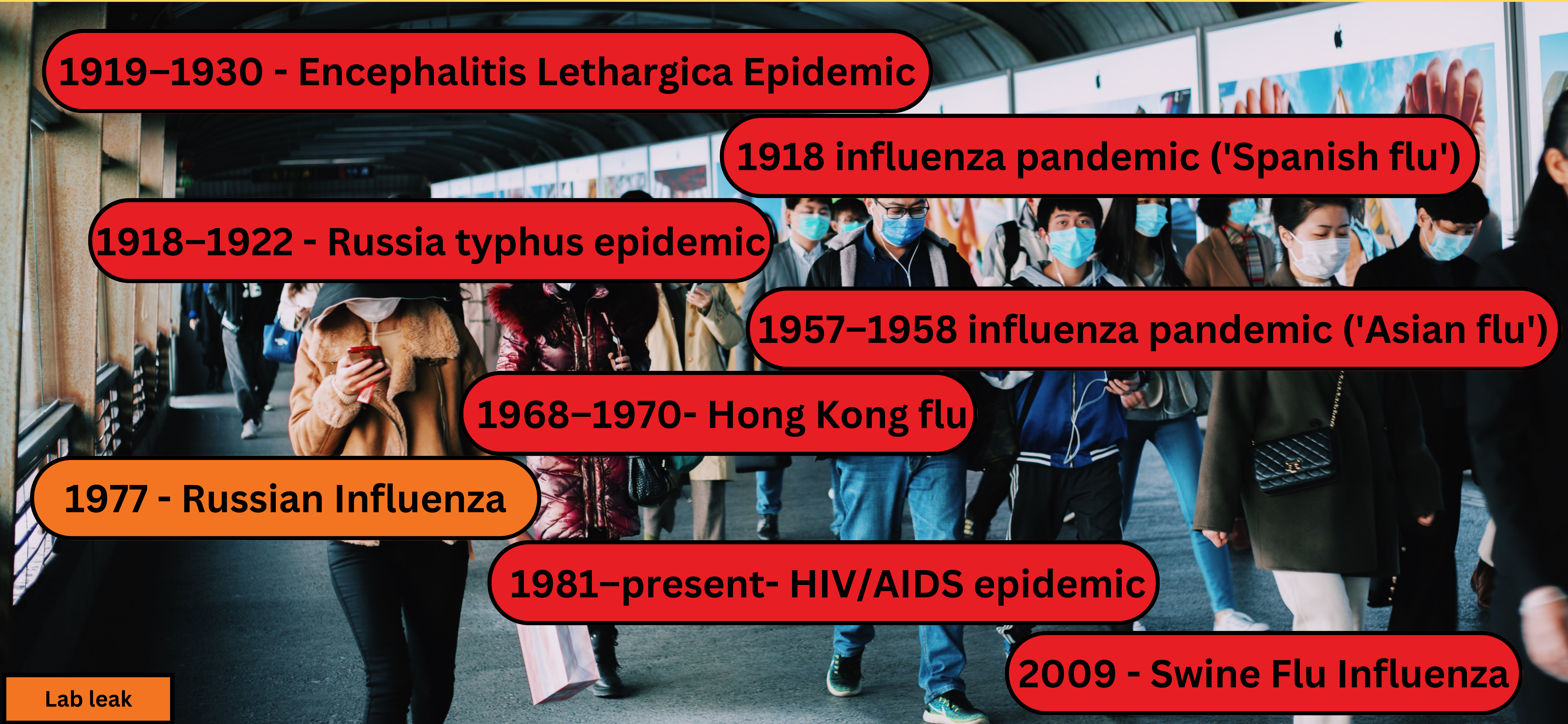
Swine Flu Pandemic
(2009-2010)

Zoonosis

Lab Leak

80% zoonotic
20% lab leaks.

Prior Used: “Major epidemics” (200K dead+)



- 1919–1930 - Encephalitis Lethargica Epidemic
- 1918 influenza pandemic ('Spanish flu')
- 1918–1922 - Russia typhus epidemic
- 1957–1958 influenza pandemic ('Asian flu')
- 1968–1970- Hong Kong flu
- 1977 - Russian Influenza
- 1981–present- HIV/AIDS epidemic
- 2009 - Swine Flu Influenza

Lab leak

Adjusting Priors for growth in Gain-Of-Function

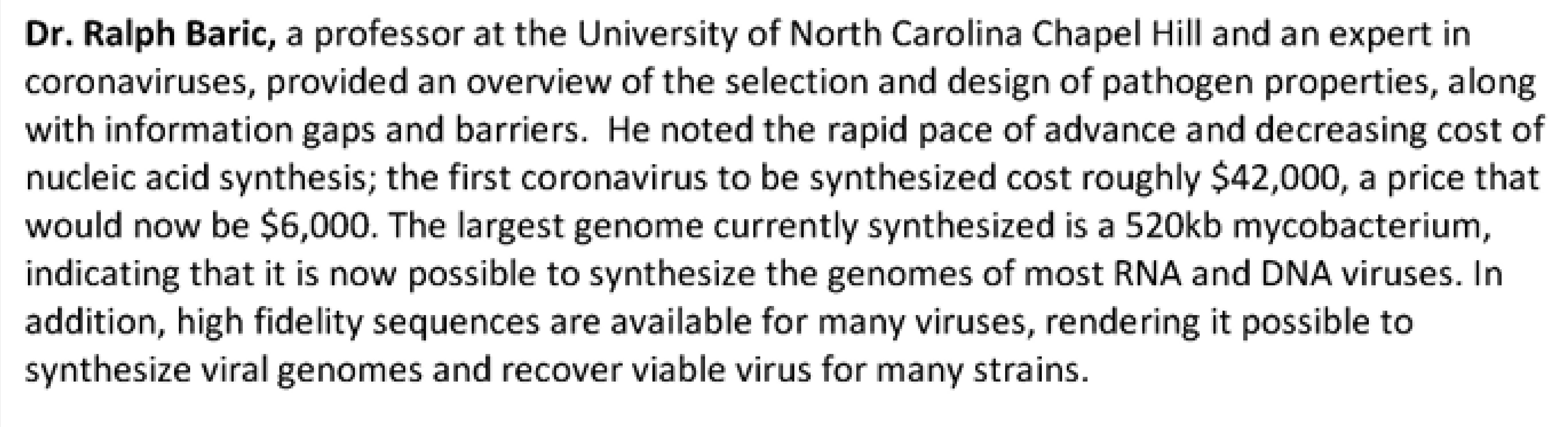
No precise measure of GoF work was found

The following two indicators are used as proxies

(1) Affordable genome editing tech advances

(2) Increase in BSL-4 labs

(1) Affordable genome editing tech advances

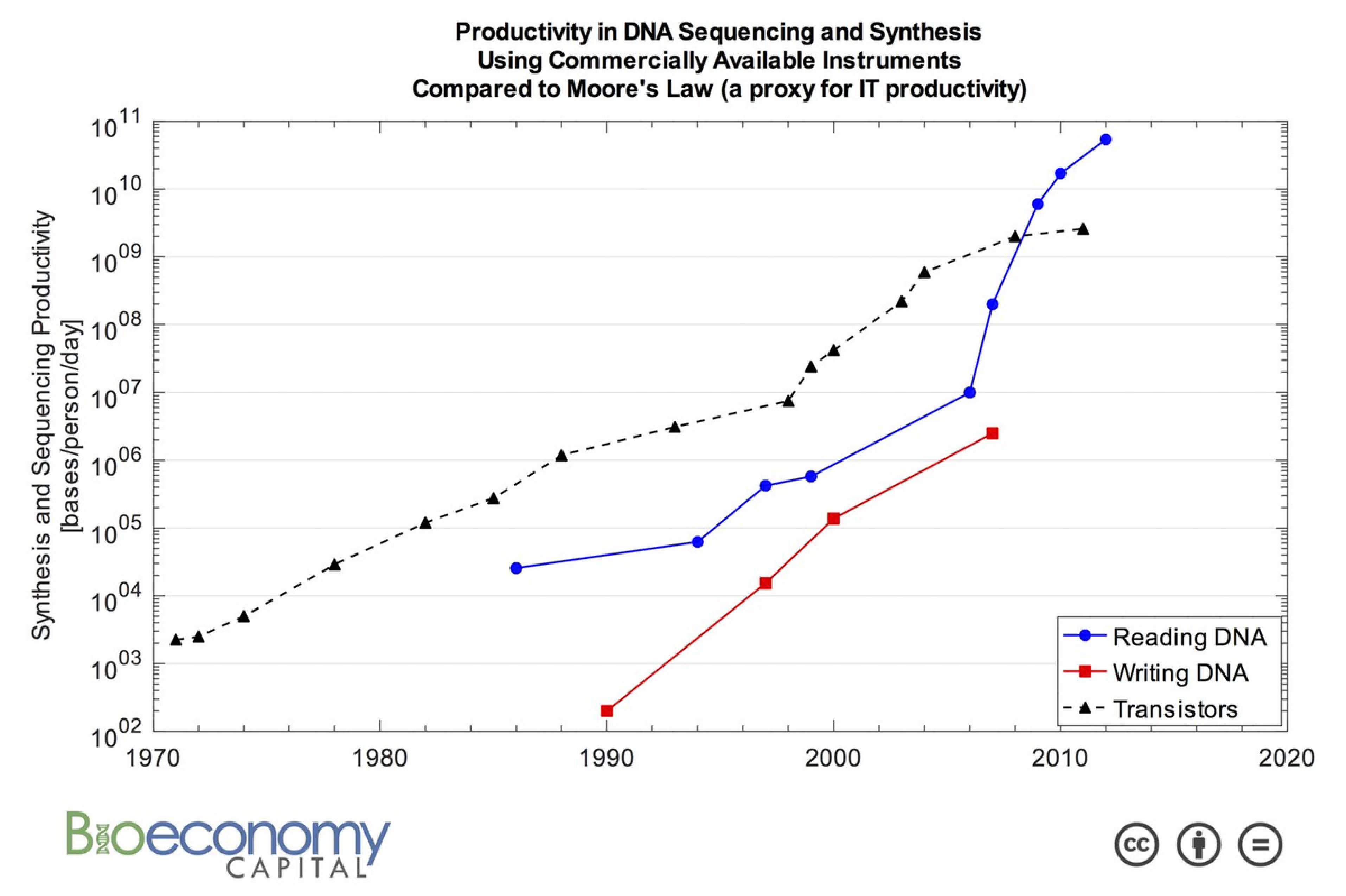


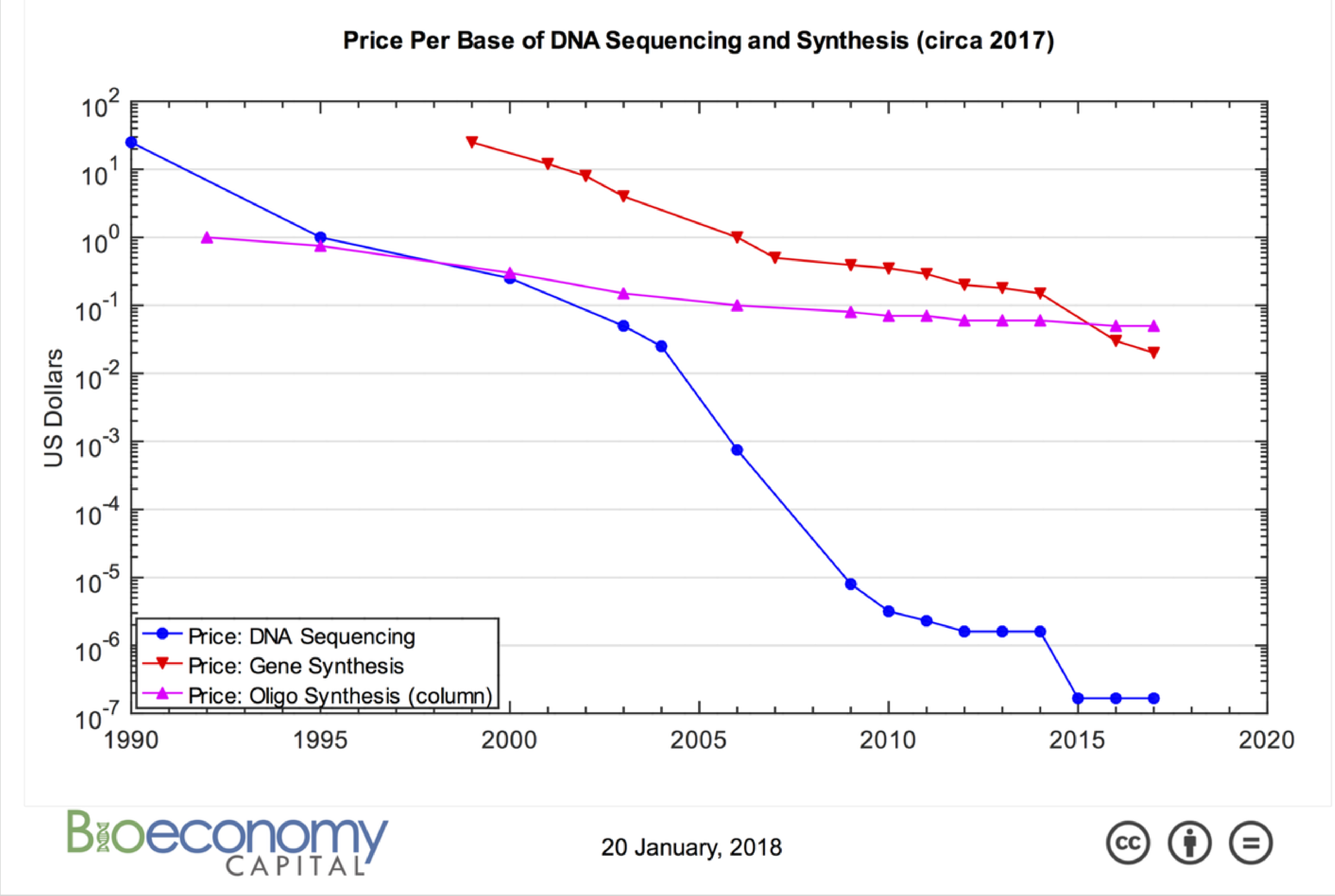
Dr. Ralph Baric, a professor at the University of North Carolina Chapel Hill and an expert in coronaviruses, provided an overview of the selection and design of pathogen properties, along with information gaps and barriers. He noted the rapid pace of advance and decreasing cost of nucleic acid synthesis; the first coronavirus to be synthesized cost roughly $42,000, a price that would now be $6,000. The largest genome currently synthesized is a 520kb mycobacterium, indicating that it is now possible to synthesize the genomes of most RNA and DNA viruses. In addition, high fidelity sequences are available for many viruses, rendering it possible to synthesize viral genomes and recover viable virus for many strains.

https://usrtk.org/wp-content/uploads/2022/04/US-China-dialogues-report.pdf
p. 10

Adjusting Priors for growth in Gain-Of-Function

(1) Affordable genome editing tech advances

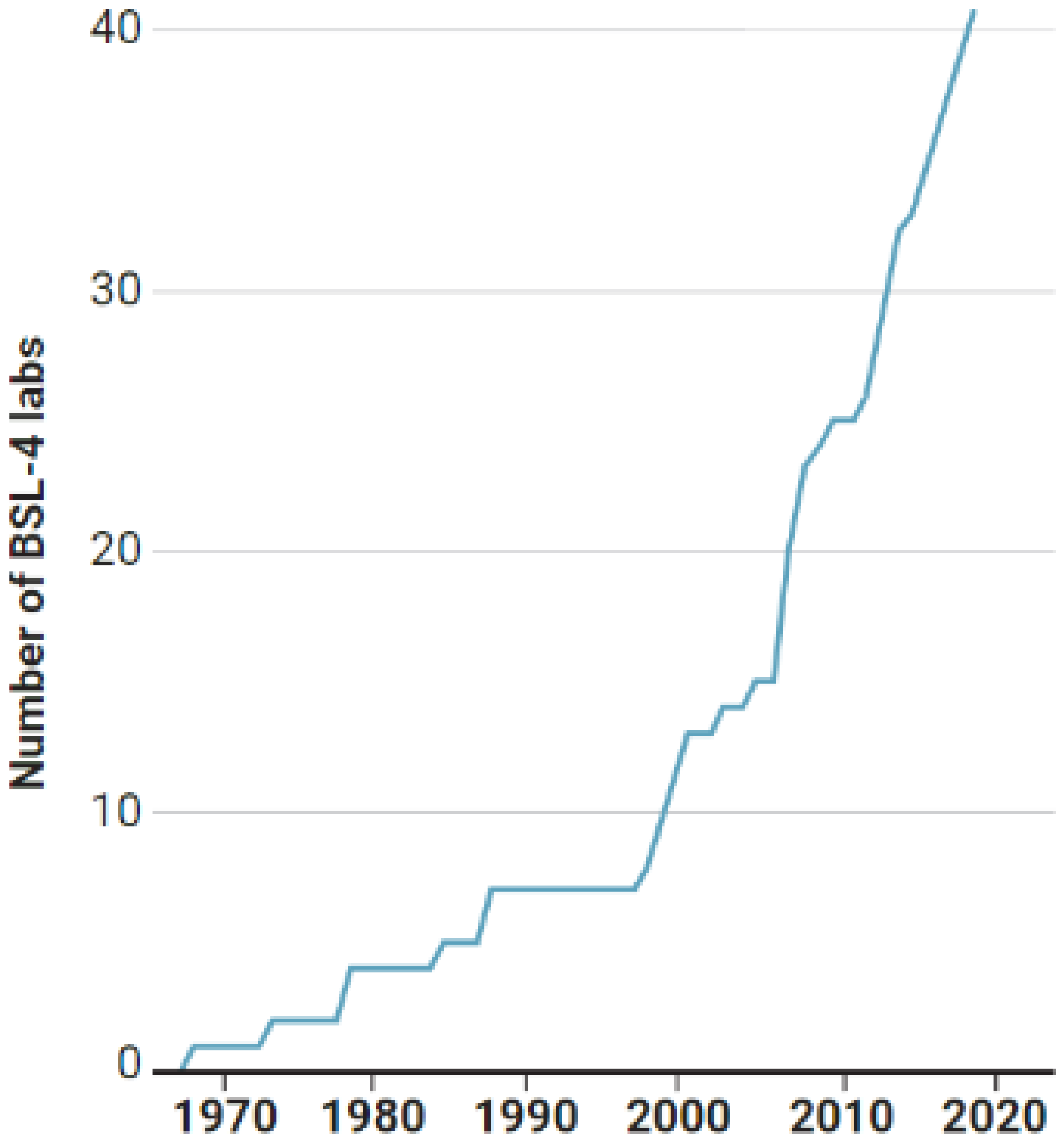

Productivity in DNA Sequencing and Synthesis
Using Commercially Available Instruments
Compared to Moore's Law (a proxy for IT productivity)


Price Per Base of DNA Sequencing and Synthesis (circa 2017)

20 January, 2018

Adjusting Priors for growth in Gain-Of-Function

(2) Increase in BSL-4 labs



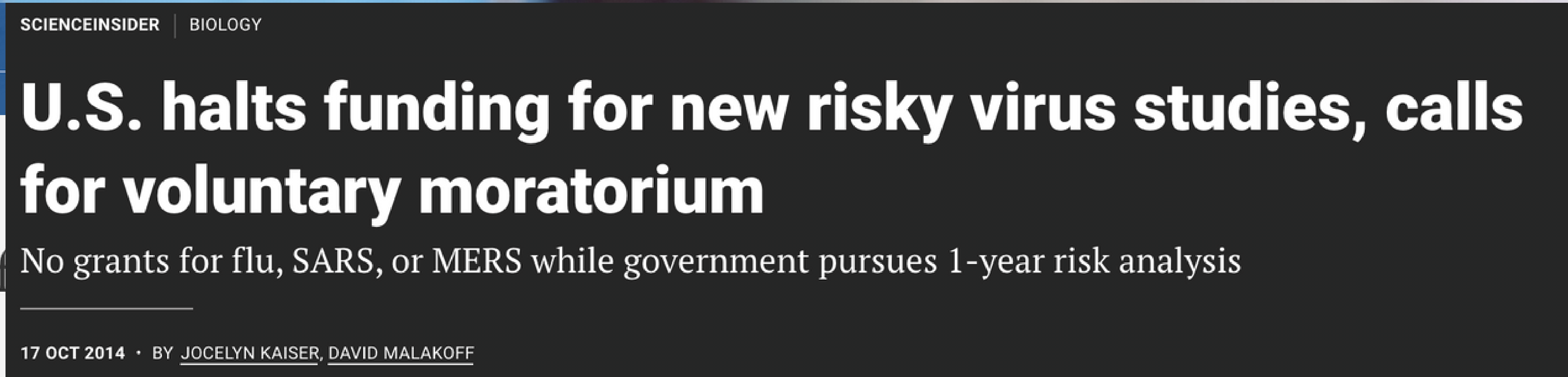
Growth industry

Europe has the most biosafety level-4 (BSL-4) labs, and three-quarters are in urban areas. (Ten existing labs without known start dates are not shown.)

These Concerns Have Resulted In Action Against GoF

National Institute of Health (NIH) placed a 3 year ban (2014 - 2017) on GOF research related to SARS, MERS and Influenza

Doing Diligence to Assess the Risks and Benefits of Li
Sciences Gain-of-Function Research



U.S. halts funding for new risky virus studies, calls for voluntary moratorium

No grants for flu, SARS, or MERS while government pursues 1-year risk analysis

17 OCT 2014 · BY JOCELYN KAISER, DAVID MALAKOFF

Prior: Humans Ability to Conduct Risk Assessments of New & Complex Technology

NASA estimated that the space shuttle programme would reach catastrophic failure once every 100,000 launches. In practice, there have been two instances in 136 attempts.

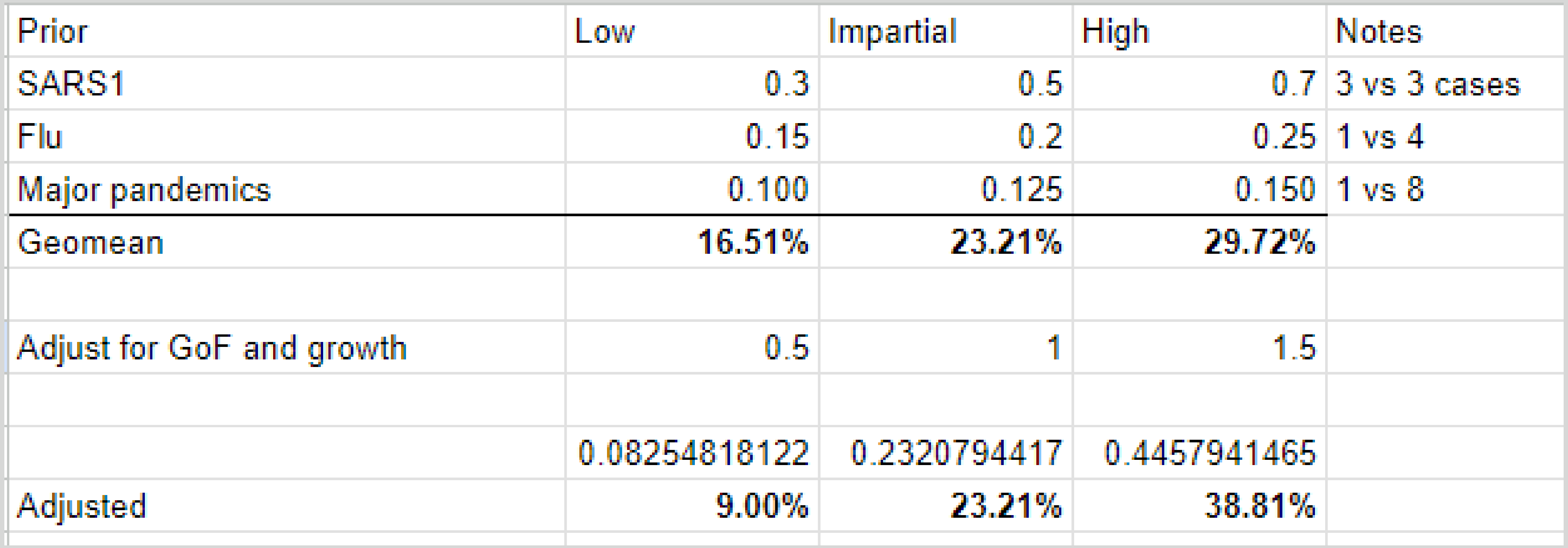
Likelihood of a catastrophic failure during a mission 1:100,000

Mission Count: 136

Failures: 2

Nuclear Power
While the risks of nuclear power are well known, there were still several major failures

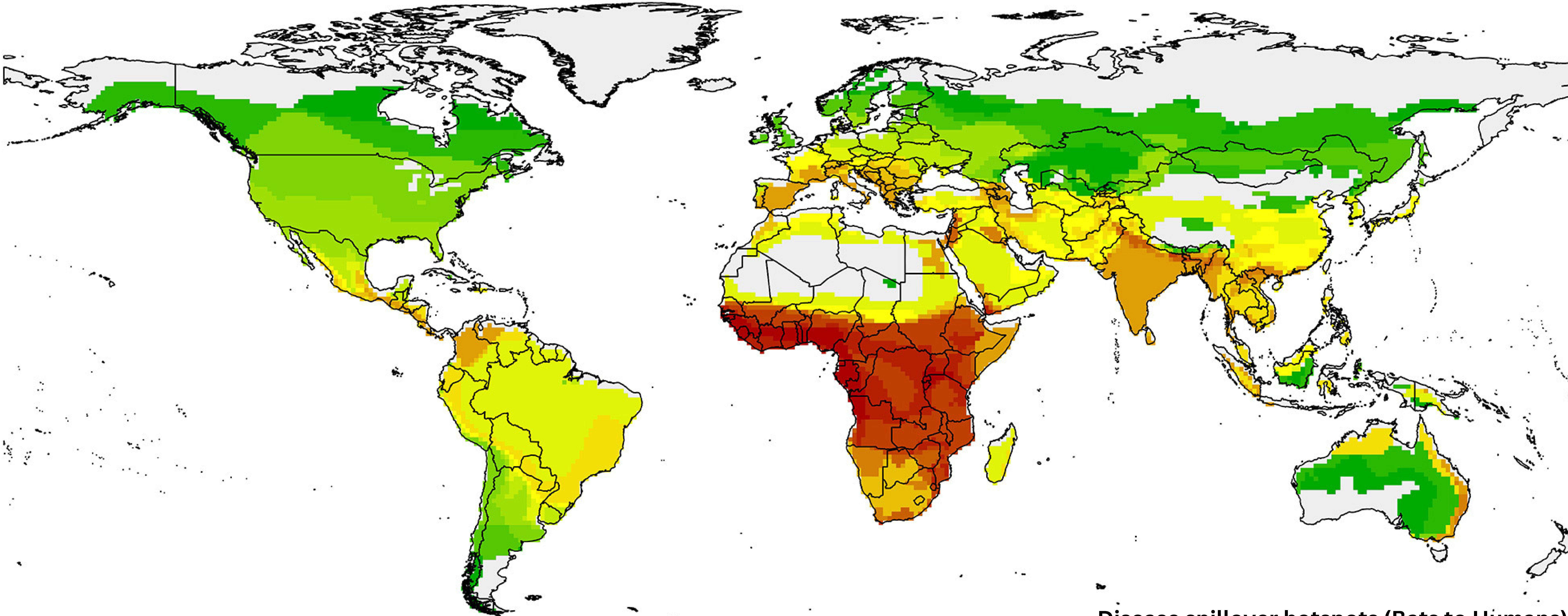
Prior Probabilities, After Adjustment



Prior	Low	Impartial	High	Notes
SARS1	0.3	0.5	0.7	3 vs 3 cases
Flu	0.15	0.2	0.25	1 vs 4
Major pandemics	0.100	0.125	0.150	1 vs 8
Geomean	**16.51%**	**23.21%**	**29.72%**	
Adjust for GoF and growth	0.5	1	1.5	
	0.08254818122	0.2320794417	0.4457941465	
Adjusted	**9.00%**	**23.21%**	**38.81%**	

Weighted:
23.5%

Location



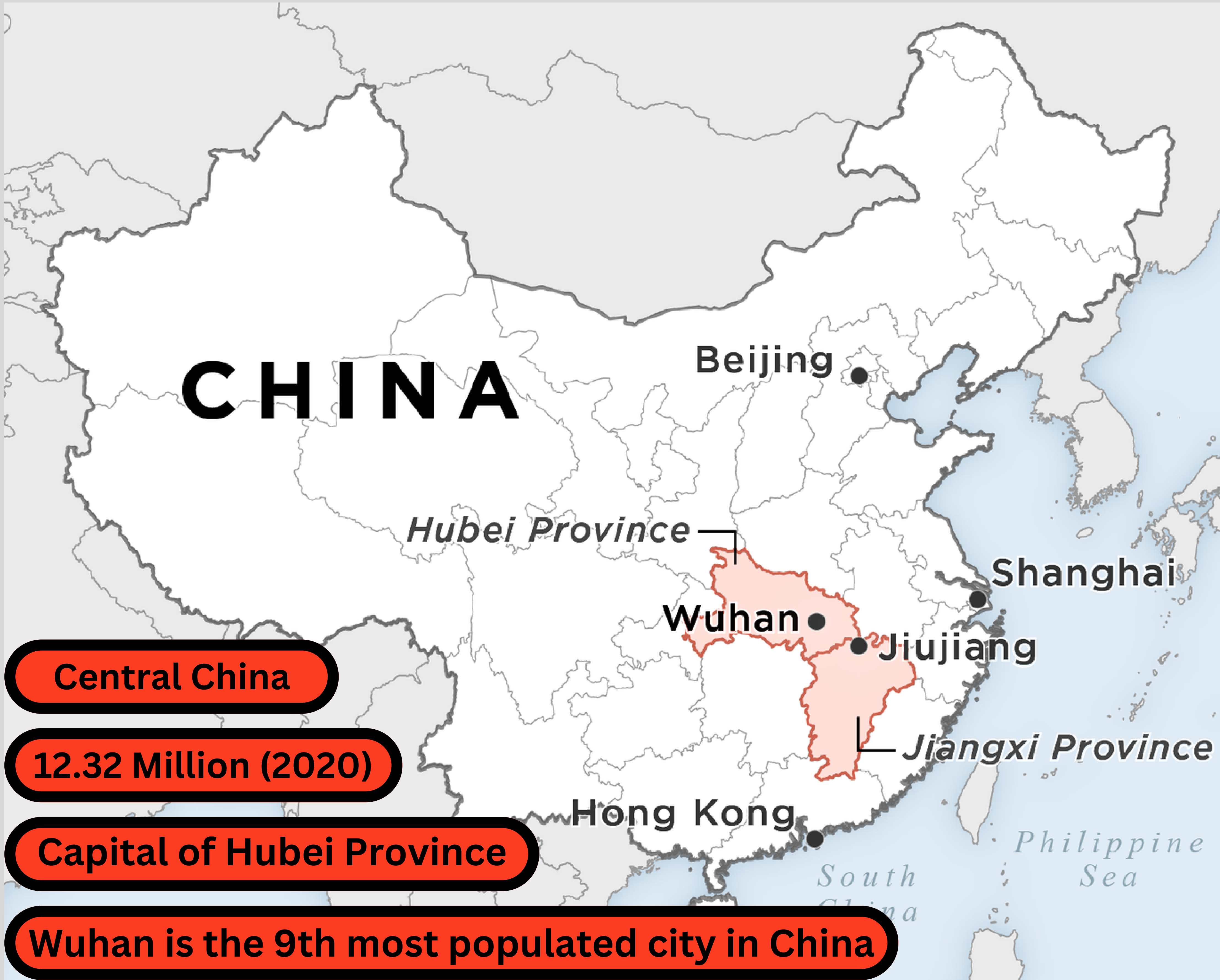
Disease spillover hotspots (Bats to Humans)

Wuhan, Hubei Province, China

How likely is Wuhan to be a zoonotic epicenter given its distance from bat populations in Southern China?

How unique is the Gain of Function research being done in the WIV in Wuhan?

To what extent does this work increase the likelihood of the Covid-19 Pandemic occuring?



Central China

12.32 Million (2020)

Capital of Hubei Province

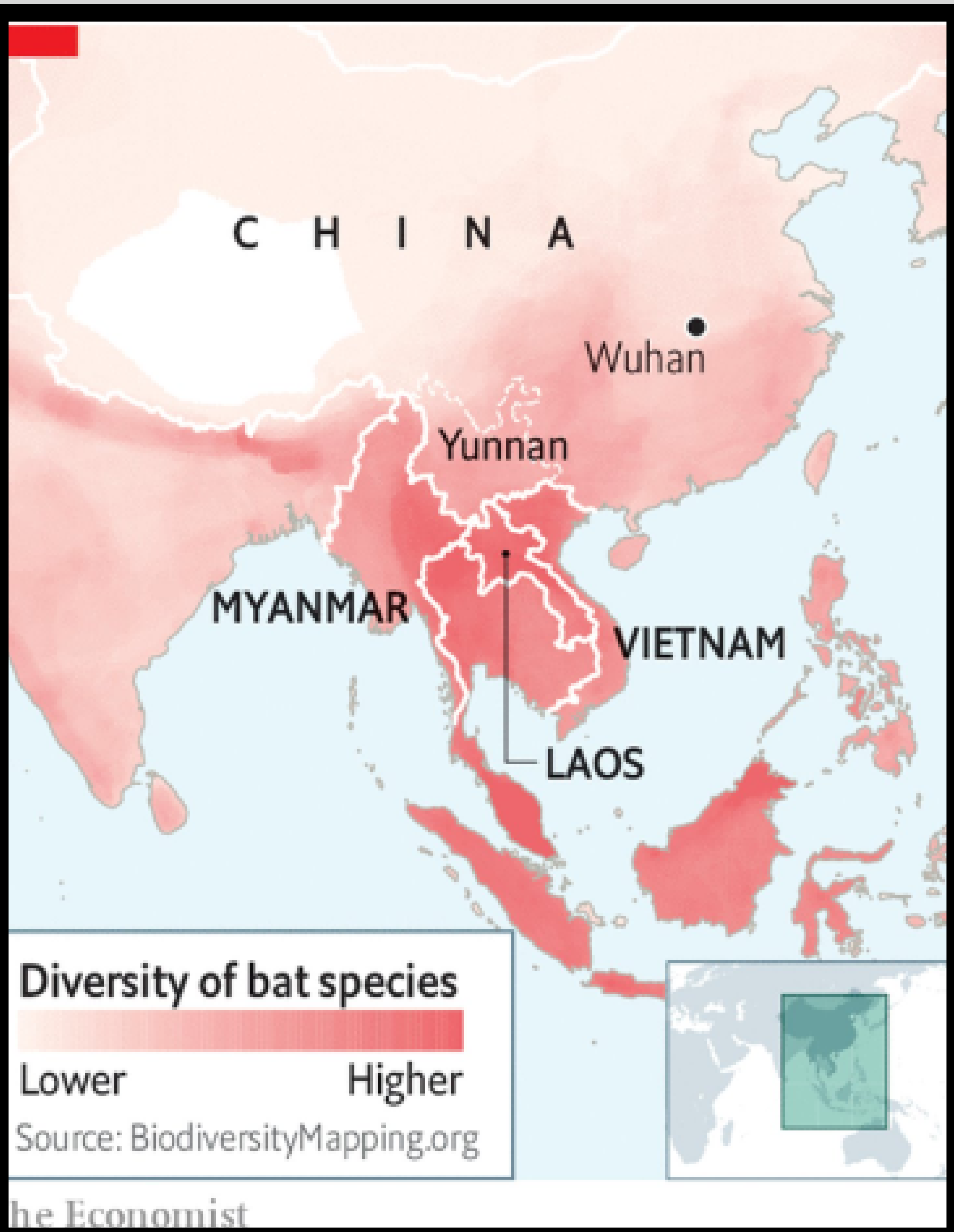
Wuhan is the 9th most populated city in China

Likelihood of Wuhan as the outbreak location

Under the zoonotic hypothesis

East Asia is home to a diverse distribution of bat species, which were the source for SARS in 2002, reaching humans through civets sold at a meat market in the Guangdong Province in southern China. The origin of another dangerous coronavirus (MERS) was in the middle east.

In order to account for the greater likelihood of a zoonotic outbreak in East Asia (the original SARS outbreak location, and where there are more wildlife-human interactions), we will measure the population of Wuhan relative only to urban areas in relevant East Asian countries.



Source: BiodiversityMapping.org

The Economist

The distribution is highest in southeast Asia, and fairly low in Wuhan

In 2020, Wuhan's population stood at 12.3 million / Total relevant East Asian urban population 1.66 billion. 2x for large cities.

Calc: 12.3m / 1.66bn * 2 = Wuhan's Share of east asia urban population = 1.48%.

The likelihood of Wuhan as the outbreak location is 1.48%, as Wuhan is no more likely for a bat coronavirus zoonosis than other large East Asian cities

Likelihood of Wuhan as the outbreak location

Under the lab leak hypothesis

WIV is located in Wuhan, and is the second largest lab for coronaviruses. They regularly collect coronavirsues from SE Asia and conduct GoF research.

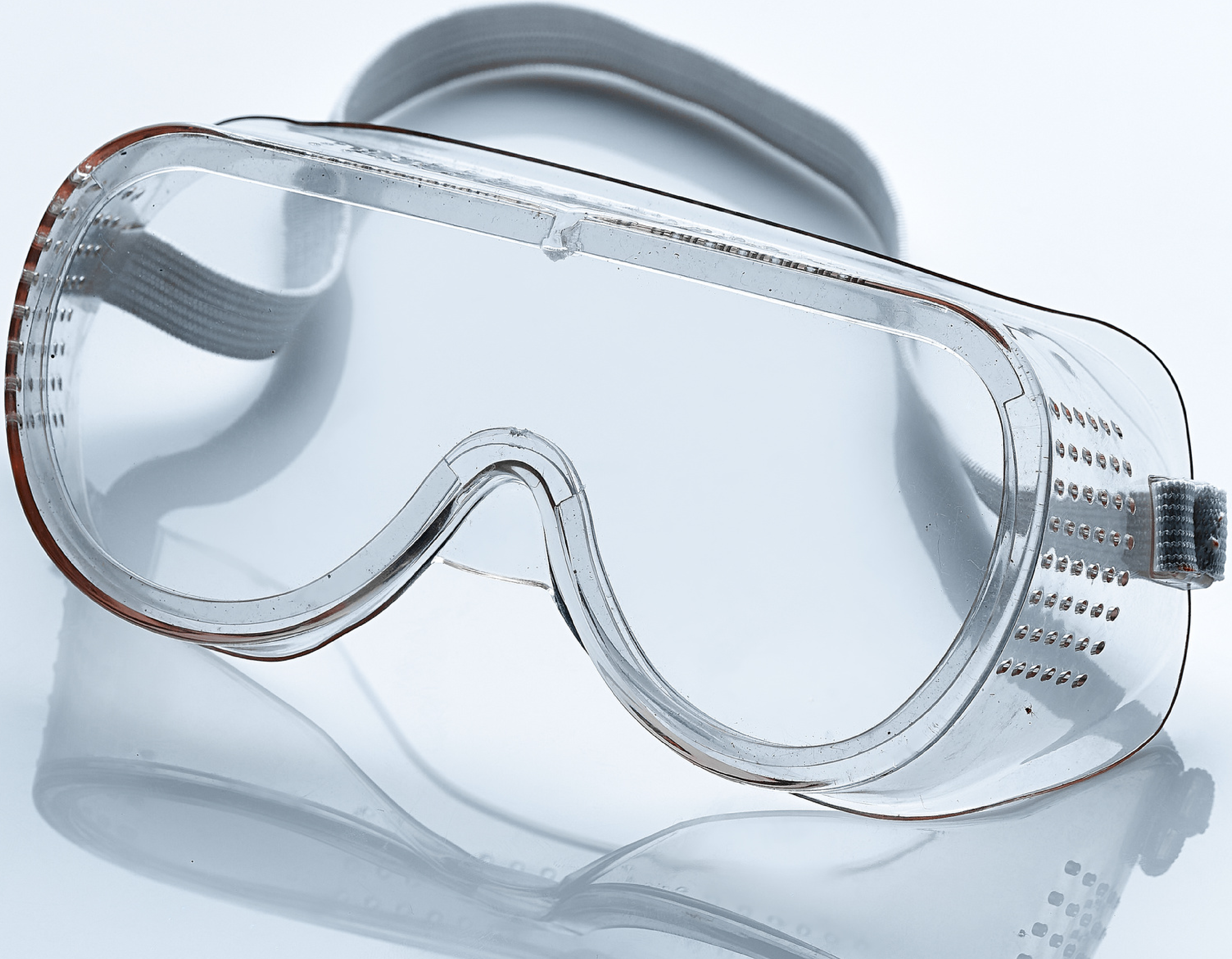
North Carolina lab is probably more likely, as the volume of GoF research they do on coronaviruses is greater.

WIV estimated to take 20% of all coronavirus GoF

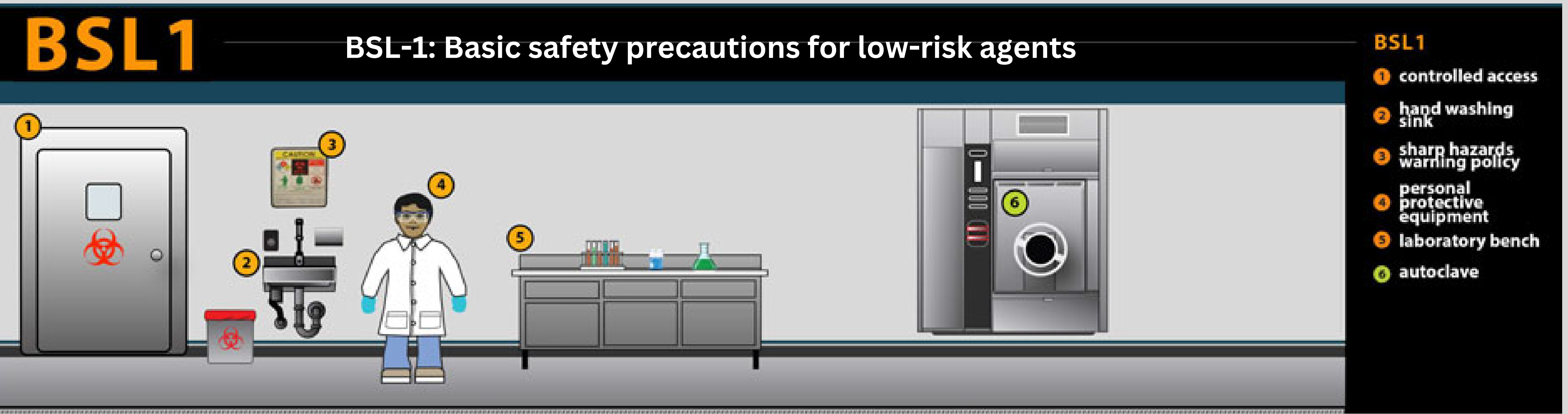
Lab Safety: Lack of Information

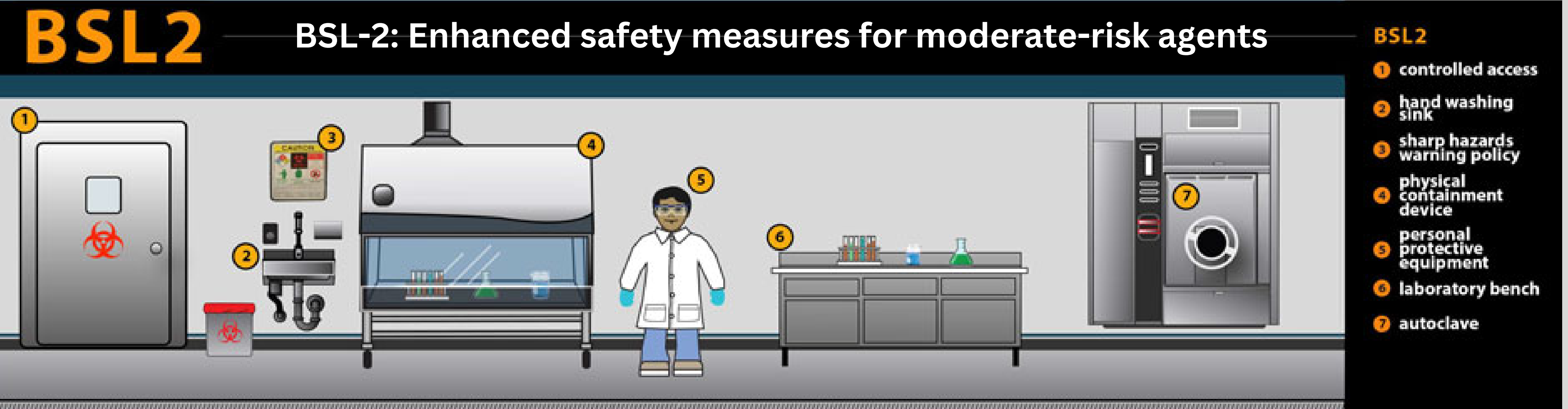
There have been numerous reports of safety issues and biocontamination problems at the Wuhan Institute of Virology (WIV) over the years.

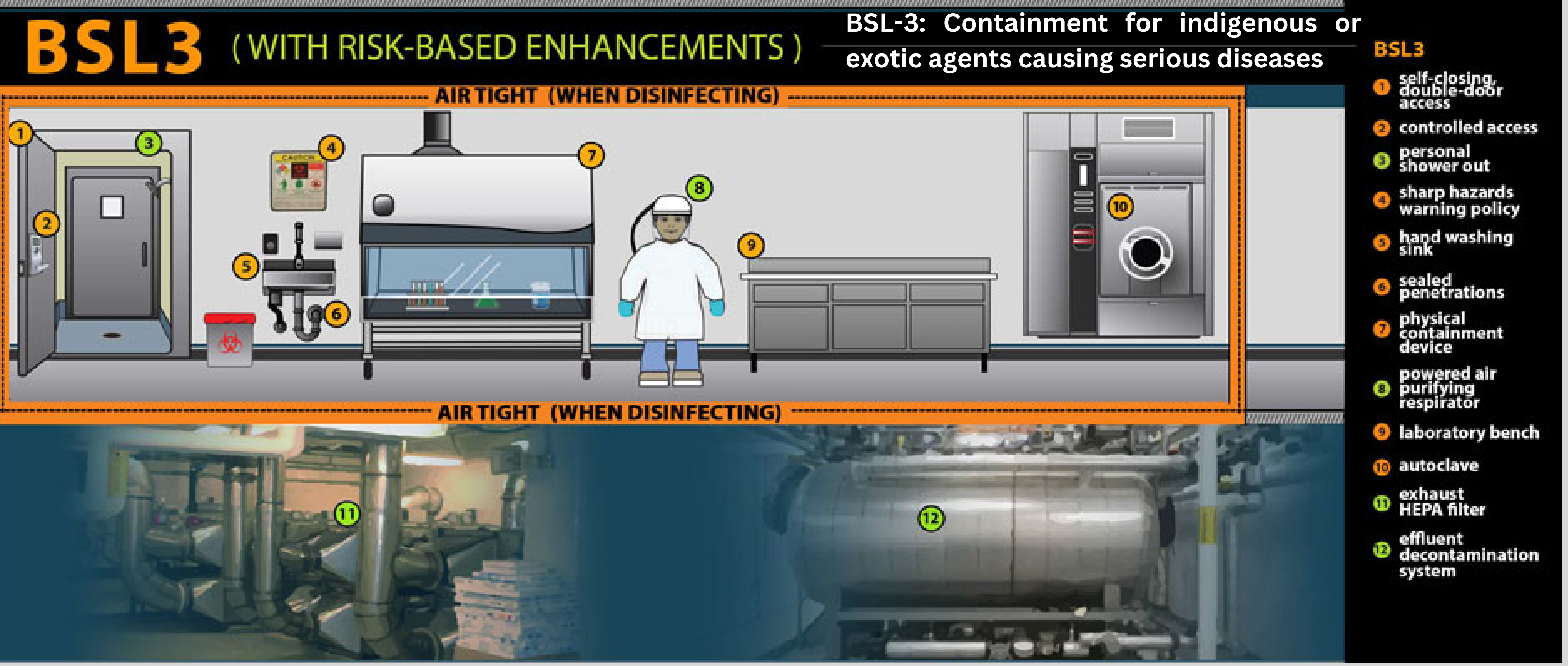
However, it’s hard to assess whether WIV is significantly worse in that aspect than other labs.



Biosafety Levels (BSL) & The Study of Dangerous Pathogens


BSL-1: Basic safety precautions for low-risk agents


BSL-2: Enhanced safety measures for moderate-risk agents


BSL-3: Containment for indigenous or exotic agents causing serious diseases

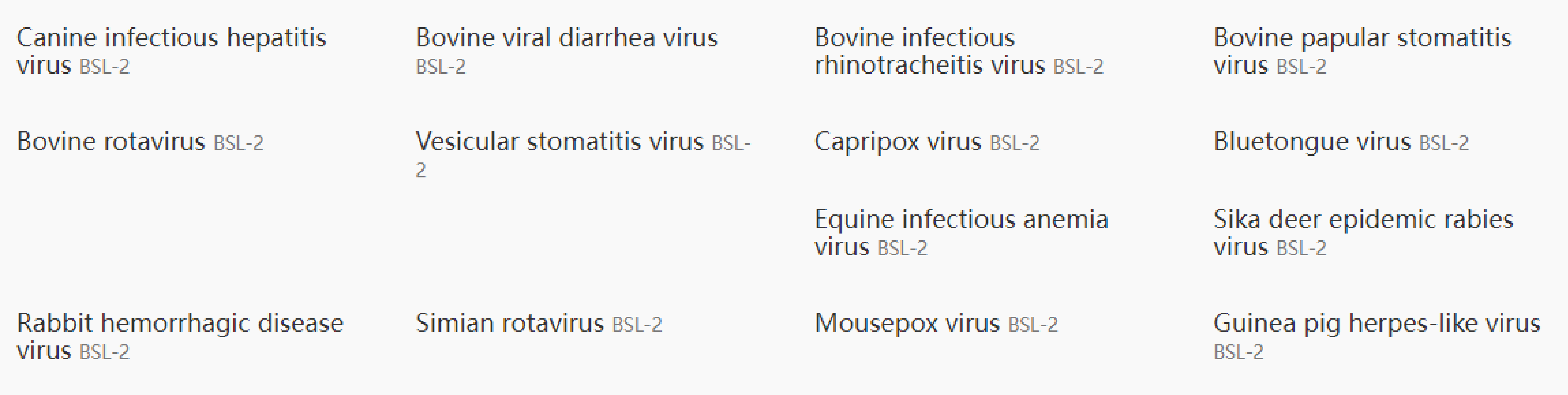
Potentially harmful pathogens like SARS and MERS usually require at least a BSL-3.

WIV had up to BSL-4.


BSL-4: Maximum containment for high-risk agents, often lethal without treatment

Designation of Bat Coronaviruses at WIV

On the official website of the Wuhan Institute of Virology in 2017, Bat coronaviruses are handled in BSL-2.



Canine infectious hepatitis virus BSL-2

Bovine rotavirus BSL-2

Rabbit hemorrhagic disease virus BSL-2

Rat coronavirus BSL-2

Grass carp hemorrhagic disease virus BSL-2

Bovine viral diarrhea virus BSL-2

Vesicular stomatitis virus BSL-2

Simian rotavirus BSL-2

Feline

BSL-2

Bovine infectious rhinotracheitis virus BSL-2

Capripox virus BSL-2

Equine infectious anemia virus BSL-2

Mousepox virus BSL-2

tis

Bovine papular stomatitis virus BSL-2

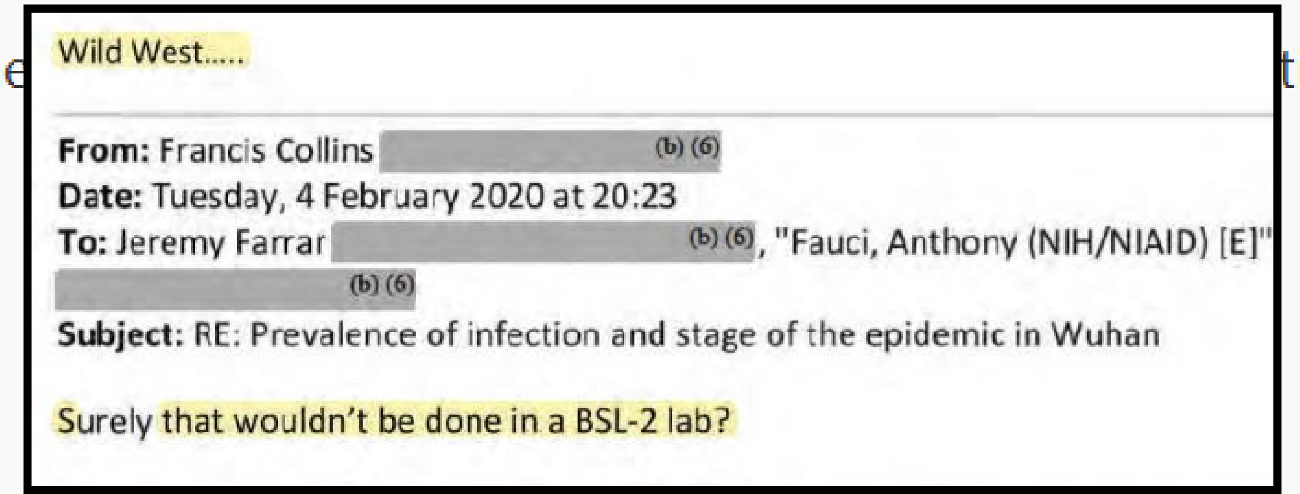
Bluetongue virus BSL-2

Sika deer epidemic rabies virus BSL-2

Guinea pig herpes-like virus BSL-2

Mink enteritis virus BSL-2

Bat coronavirus BSL-2



Wild West.....

From: Francis Collins [redacted] (b) (6)
Date: Tuesday, 4 February 2020 at 20:23
To: Jeremy Farrar [redacted] (b) (6), "Fauci, Anthony (NIH/NIAID) [E]" [redacted] (b) (6)
Subject: RE: Prevalence of infection and stage of the epidemic in Wuhan

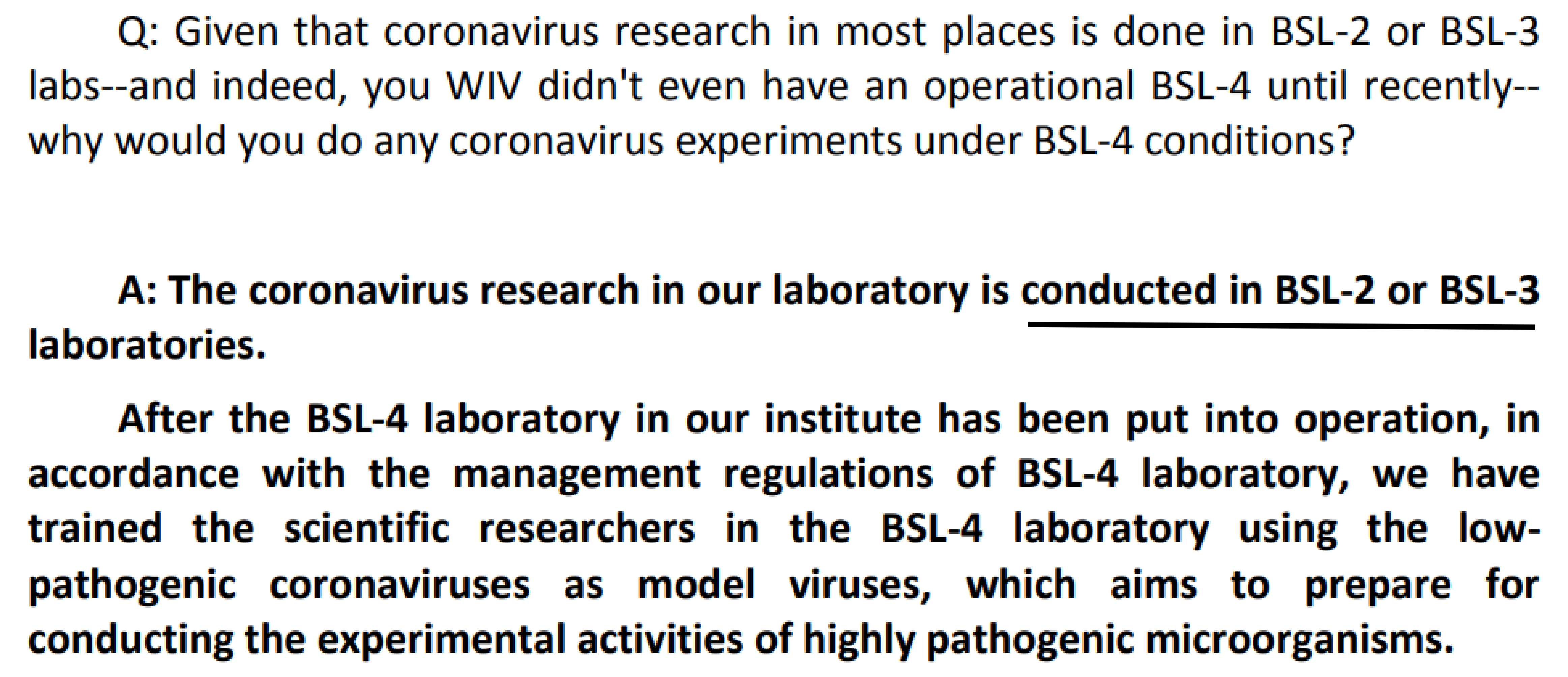
Surely that wouldn't be done in a BSL-2 lab?

https://web.archive.org/web/20171023053516/http://www.virus.org.cn/resource/

BSL-2 Research at Wuhan Institute of Virology

Much more troubling than the possible safety breaches, is that dangerous GoF research on bat coronaviruses was likely being conducted under BSL-2 conditions.

Improper Research Conditions of Coronaviruses at the WIV



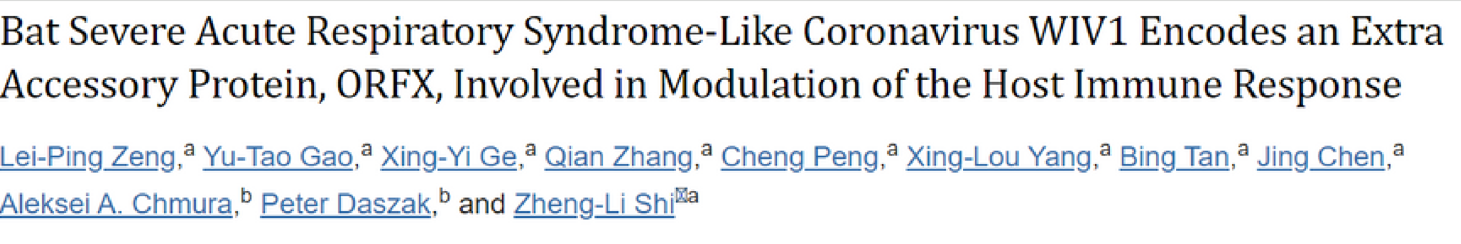
Q: Given that coronavirus research in most places is done in BSL-2 or BSL-3 labs--and indeed, you WIV didn't even have an operational BSL-4 until recently--why would you do any coronavirus experiments under BSL-4 conditions?

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.

https://www.science.org/pb-assets/PDF/News%20PDFs/Shi%20Zhengli%20Q&A-1630433861.pdf

Conducted under BSL-2 Conditions



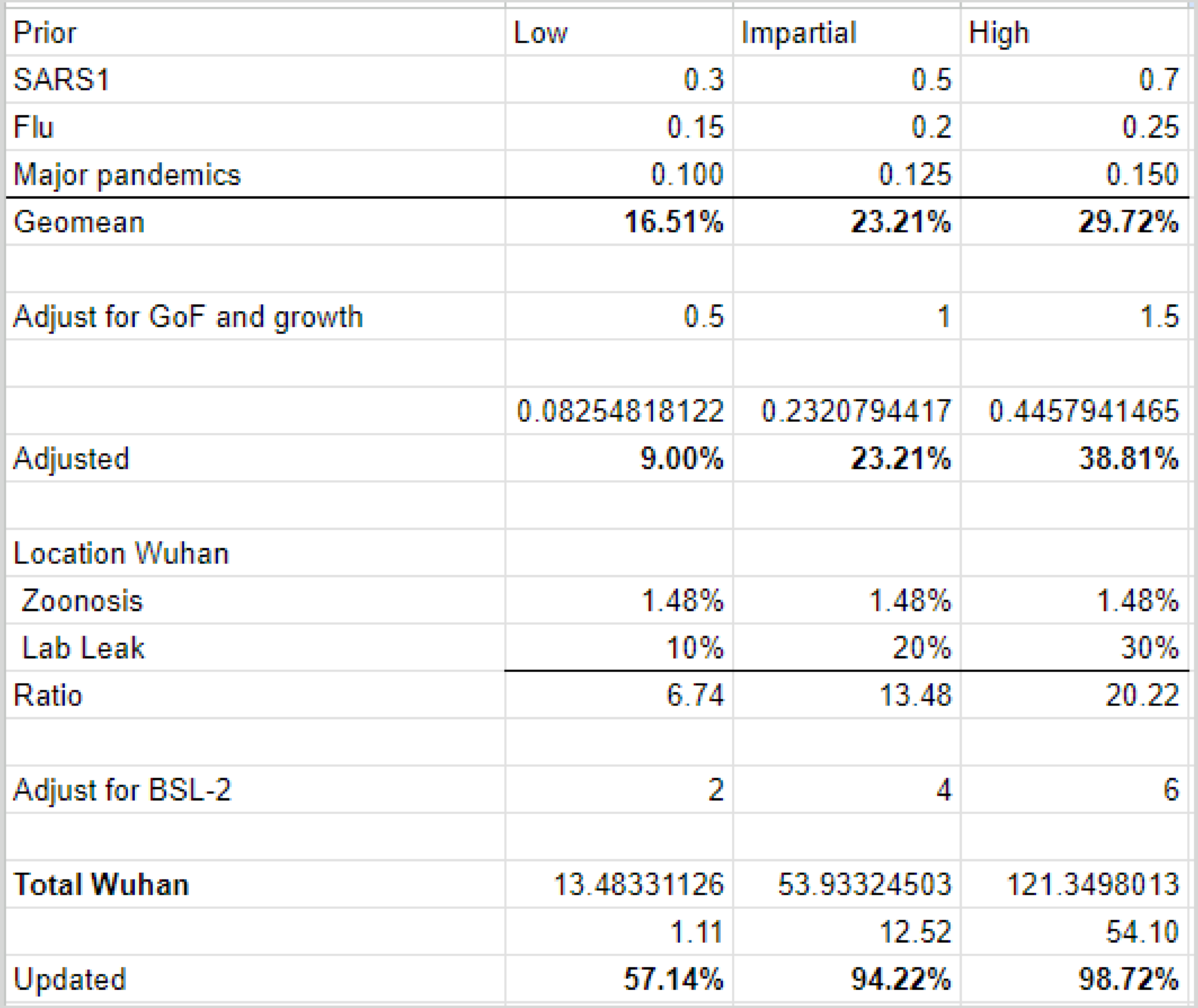
Bat Severe Acute Respiratory Syndrome-Like Coronavirus WIV1 Encodes an Extra Accessory Protein, ORFX, Involved in Modulation of the Host Immune Response

Lei-Ping Zeng,[a] Yu-Tao Gao,[a] Xing-Yi Ge,[a] Qian Zhang,[a] Cheng Peng,[a] Xing-Lou Yang,[a] Bing Tan,[a] Jing Chen,[a] Aleksei A. Chmura,[b] Peter Daszak,[b] and Zheng-Li Shi[a]

"In this study, we constructed a full-length cDNA clone of SL-CoV WIV1 (rWIV1), an ORFX deletion mutant (rWIV1-ΔX), and a green fluorescent protein (GFP)-expressing mutant (rWIV1-GFP-ΔX)."

"All experiments using live virus was conducted under biosafety level 2 (BSL2) conditions".

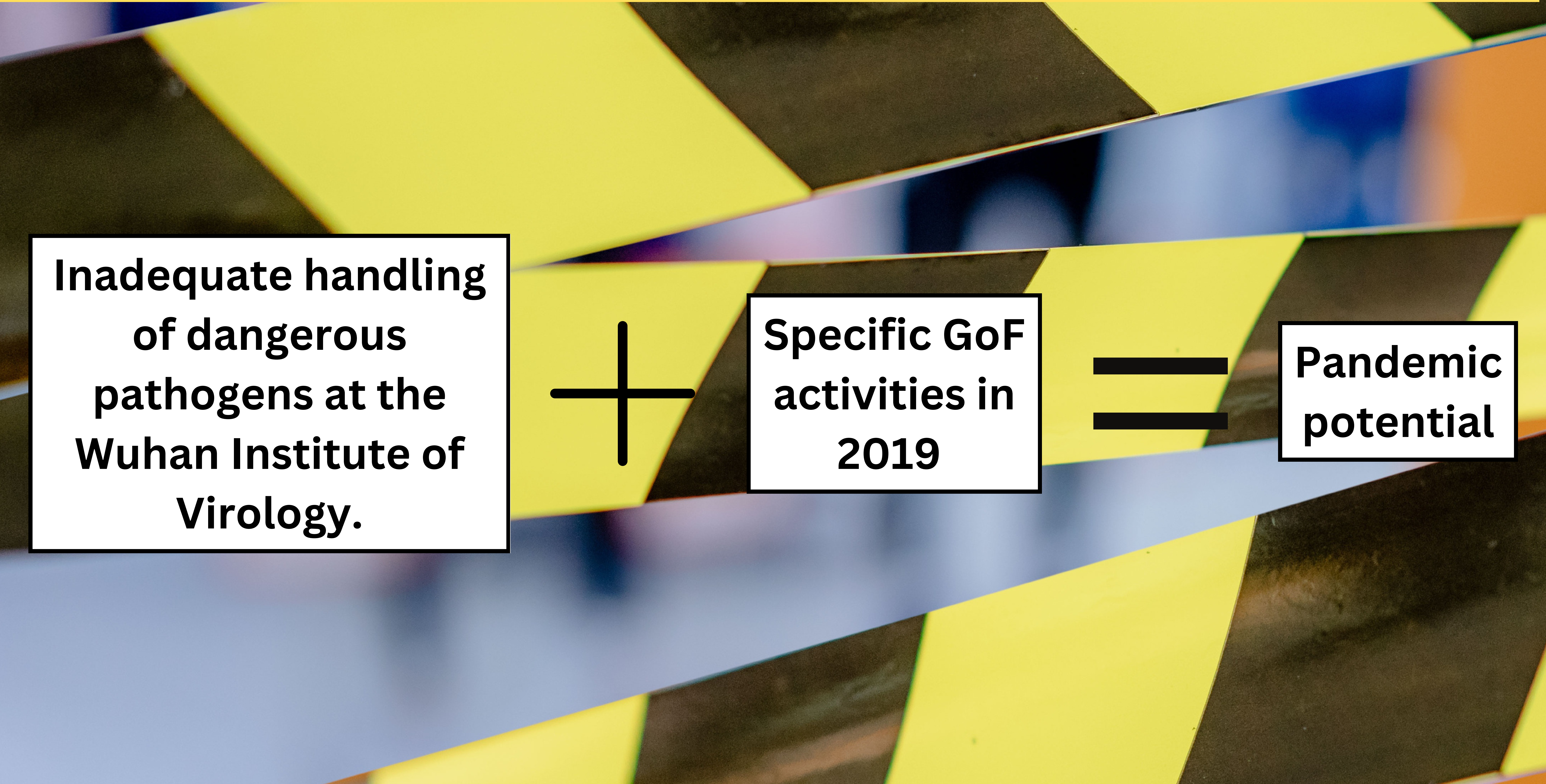
Summary of Probabilities



Prior	Low	Impartial	High
SARS1	0.3	0.5	0.7
Flu	0.15	0.2	0.25
Major pandemics	0.100	0.125	0.150
Geomean	**16.51%**	**23.21%**	**29.72%**
Adjust for GoF and growth	0.5	1	1.5
	0.08254818122	0.2320794417	0.4457941465
Adjusted	**9.00%**	**23.21%**	**38.81%**
Location Wuhan			
Zoonosis	1.48%	1.48%	1.48%
Lab Leak	10%	20%	30%
Ratio	6.74	13.48	20.22
Adjust for BSL-2	2	4	6
Total Wuhan	13.48331126	53.93324503	121.3498013
	1.11	12.52	54.10
Updated	**57.14%**	**94.22%**	**98.72%**

Weighted:
88%

Wuhan Institute of Virology - 2019 Research Focus



Inadequate handling of dangerous pathogens at the Wuhan Institute of Virology. + Specific GoF activities in 2019 = Pandemic potential

Furin Cleavage Sites were a focus of coronavirology in 2019

In 2019, virology saw a notable emphasis on understanding the furin cleavage site (FCS). This focus coincided with the period just before the potential virus leak, which also featured the presence of a furin cleavage site.

2019 Beijing paper that engineered a novel RRKR furin cleavage site in a chicken coronavirus (coauthored by Ian Lipkin — one of the Proximal Origin of SARS-CoV-2 coauthors)

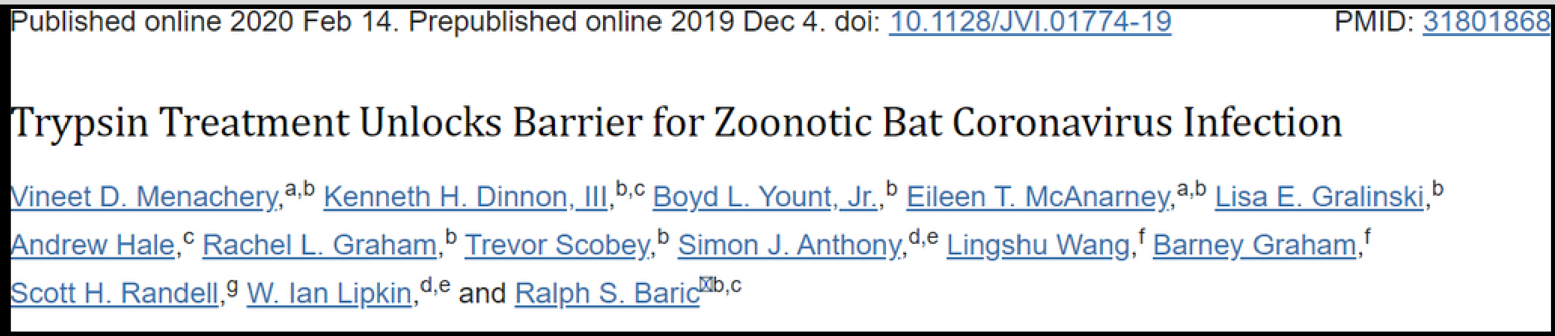

Published online 2019 Oct 22. doi: 10.3390/v11100972 PMID: 31652591

The S2 Subunit of QX-type Infectious Bronchitis Coronavirus Spike Protein Is an Essential Determinant of Neurotropism

Jinlong Cheng, Ye Zhao, Gang Xu, Keran Zhang, Wenfeng Jia, Yali Sun, Jing Zhao, Jia Xue, Yanxin Hu, and Guozhong Zhang*

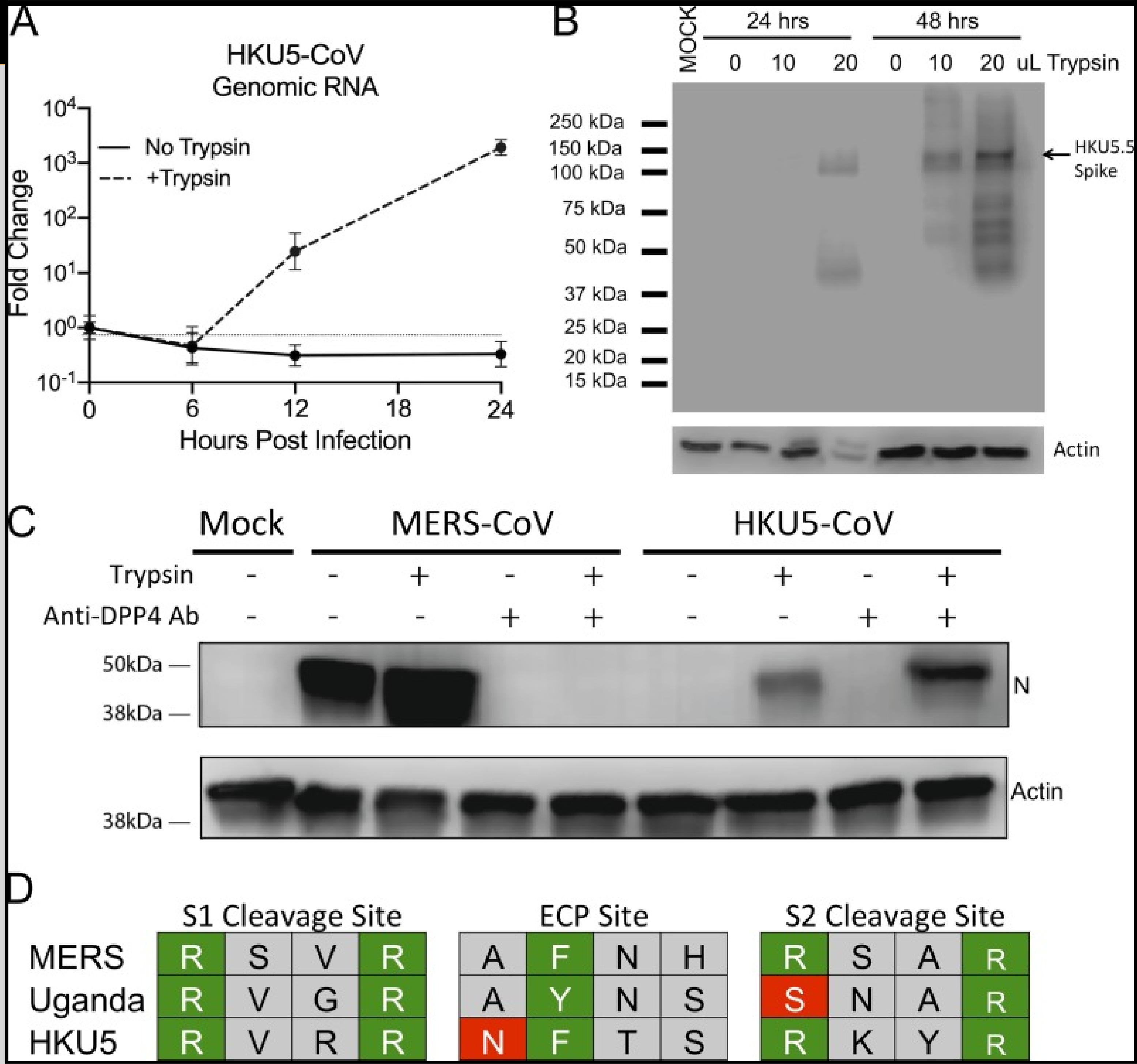
Ralph Baric speaking in China in early 2019 about engineering novel chimeric CoVs:

> *“Studies to alter pathogen properties of viruses can use several approaches, including selection pressure to drive evolution toward a phenotype as well as deliberate design. Potential opportunities might include building chimeric viruses with altered structures for the receptor for viral entry, or those that incorporate changes to other virulence determinants or that modulate host-pathogen interactions.”*


Published online 2020 Feb 14. Prepublished online 2019 Dec 4. doi: 10.1128/JVI.01774-19 PMID: 31801868

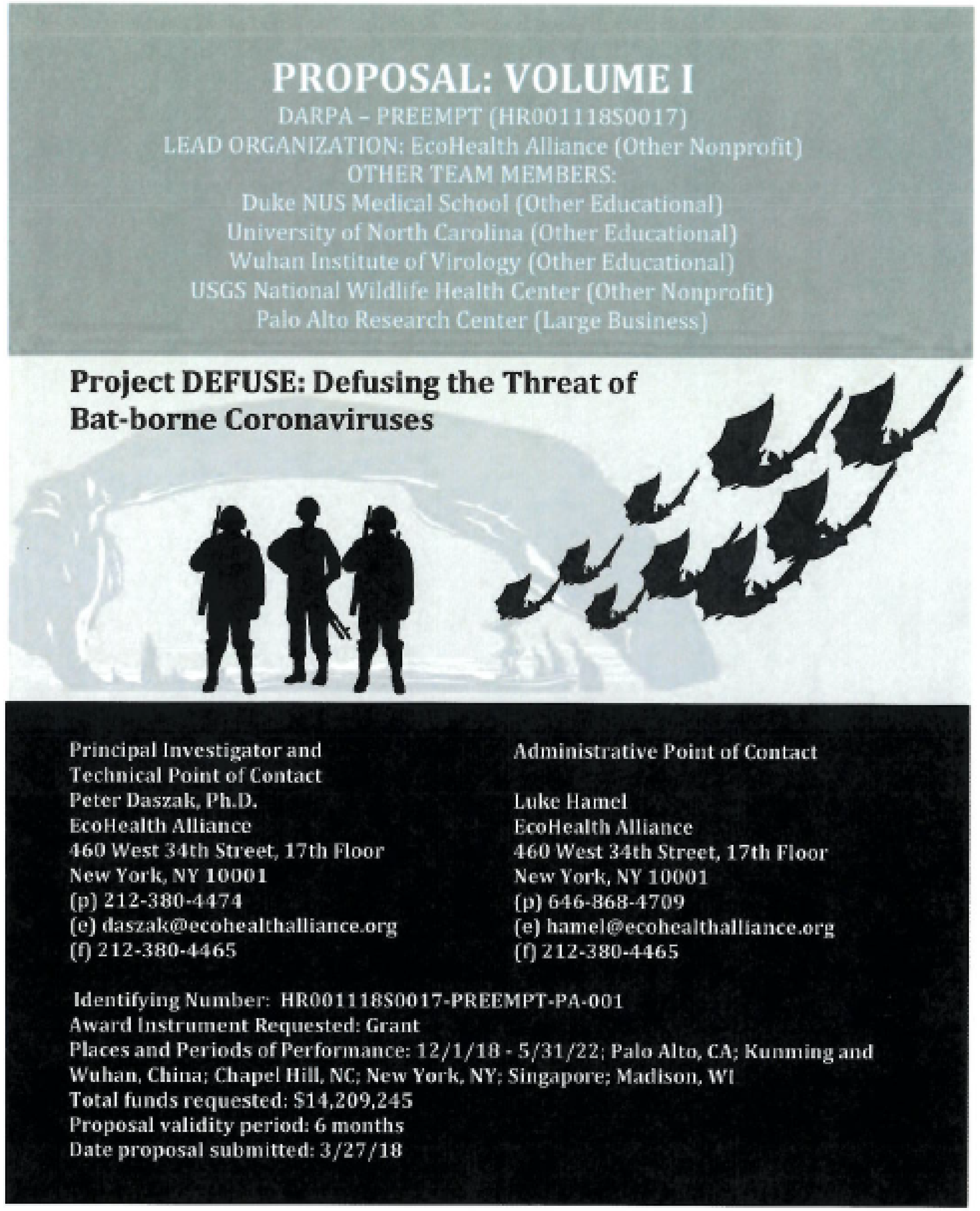
Trypsin Treatment Unlocks Barrier for Zoonotic Bat Coronavirus Infection

Vineet D. Menachery,[a,b] Kenneth H. Dinnon, III,[b,c] Boyd L. Yount, Jr.,[b] Eileen T. McAnarney,[a,b] Lisa E. Gralinski,[b] Andrew Hale,[c] Rachel L. Graham,[b] Trevor Scobey,[b] Simon J. Anthony,[d,e] Lingshu Wang,[f] Barney Graham,[f] Scott H. Randell,[g] W. Ian Lipkin,[d,e] and Ralph S. Baric[b,c]



	S1 Cleavage Site				ECP Site				S2 Cleavage Site			
MERS	R	S	V	R	A	F	N	H	R	S	A	R
Uganda	R	V	G	R	A	Y	N	S	S	N	A	R
HKU5	R	V	R	R	N	F	T	S	R	K	Y	R

DEFUSE Proposal



PROPOSAL: VOLUME I
DARPA – PREEMPT (HR001118S0017)
LEAD ORGANIZATION: EcoHealth Alliance (Other Nonprofit)
OTHER TEAM MEMBERS:
Duke NUS Medical School (Other Educational)
University of North Carolina (Other Educational)
Wuhan Institute of Virology (Other Educational)
USGS National Wildlife Health Center (Other Nonprofit)
Palo Alto Research Center (Large Business)

Project DEFUSE: Defusing the Threat of Bat-borne Coronaviruses

Principal Investigator and
Technical Point of Contact
Peter Daszak, Ph.D.
EcoHealth Alliance
460 West 34th Street, 17th Floor
New York, NY 10001
(p) 212-380-4474
(e) daszak@ecohealthalliance.org
(f) 212-380-4465

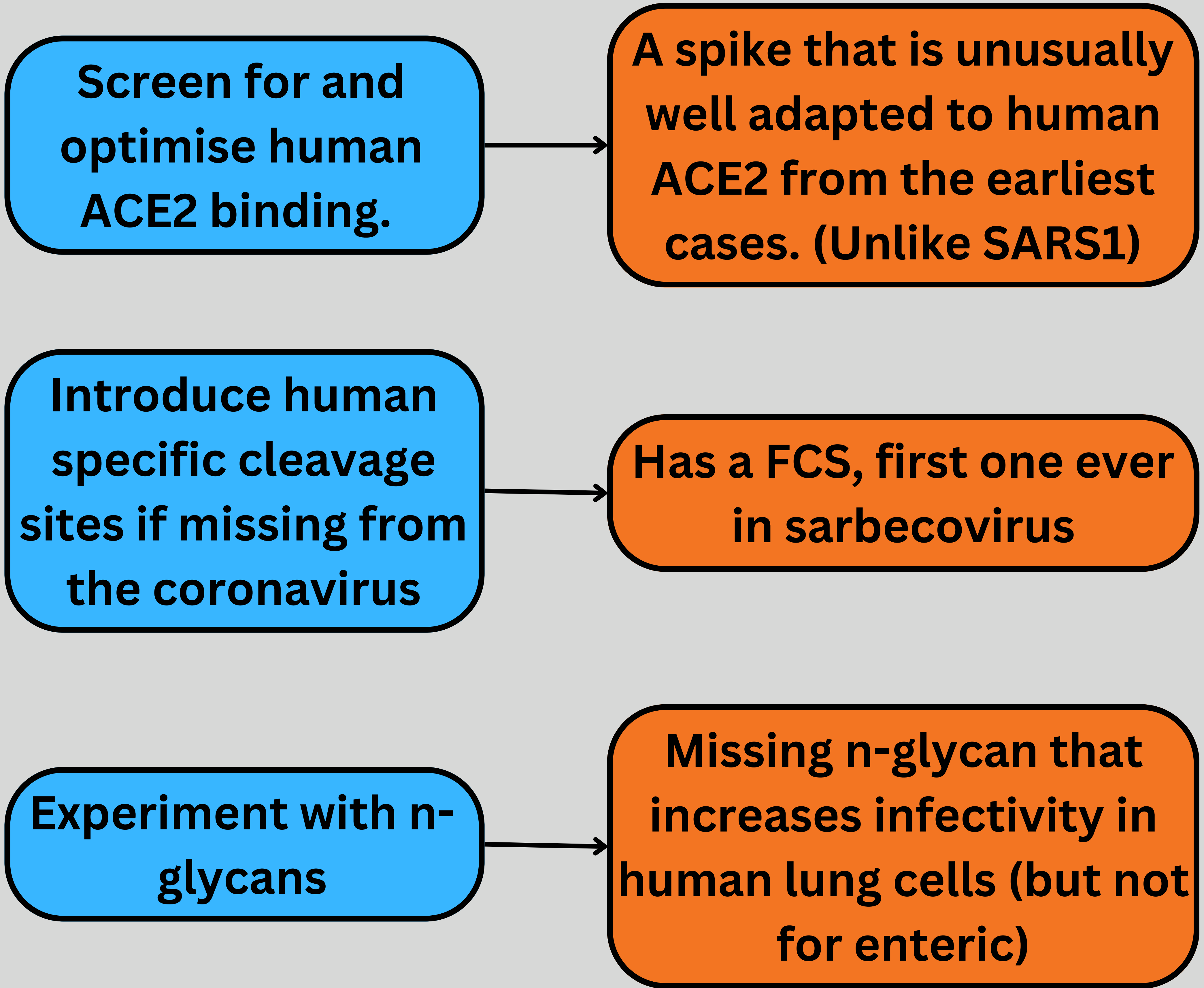
Administrative Point of Contact

Luke Hamel
EcoHealth Alliance
460 West 34th Street, 17th Floor
New York, NY 10001
(p) 646-868-4709
(e) hamel@ecohealthalliance.org
(f) 212-380-4465

Identifying Number: HR001118S0017-PREEMPT-PA-001
Award Instrument Requested: Grant
Places and Periods of Performance: 12/1/18 - 5/31/22; Palo Alto, CA; Kunming and Wuhan, China; Chapel Hill, NC; New York, NY; Singapore; Madison, WI
Total funds requested: $14,209,245
Proposal validity period: 6 months
Date proposal submitted: 3/27/18

The specific genetics of SARS-CoV-2, and their influence on the probabalistic analysis will be discussed in 2nd session.

Components of the DEFUSE proposal are also found in SARS-COV-2.



Screen for and optimise human ACE2 binding.

A spike that is unusually well adapted to human ACE2 from the earliest cases. (Unlike SARS1)

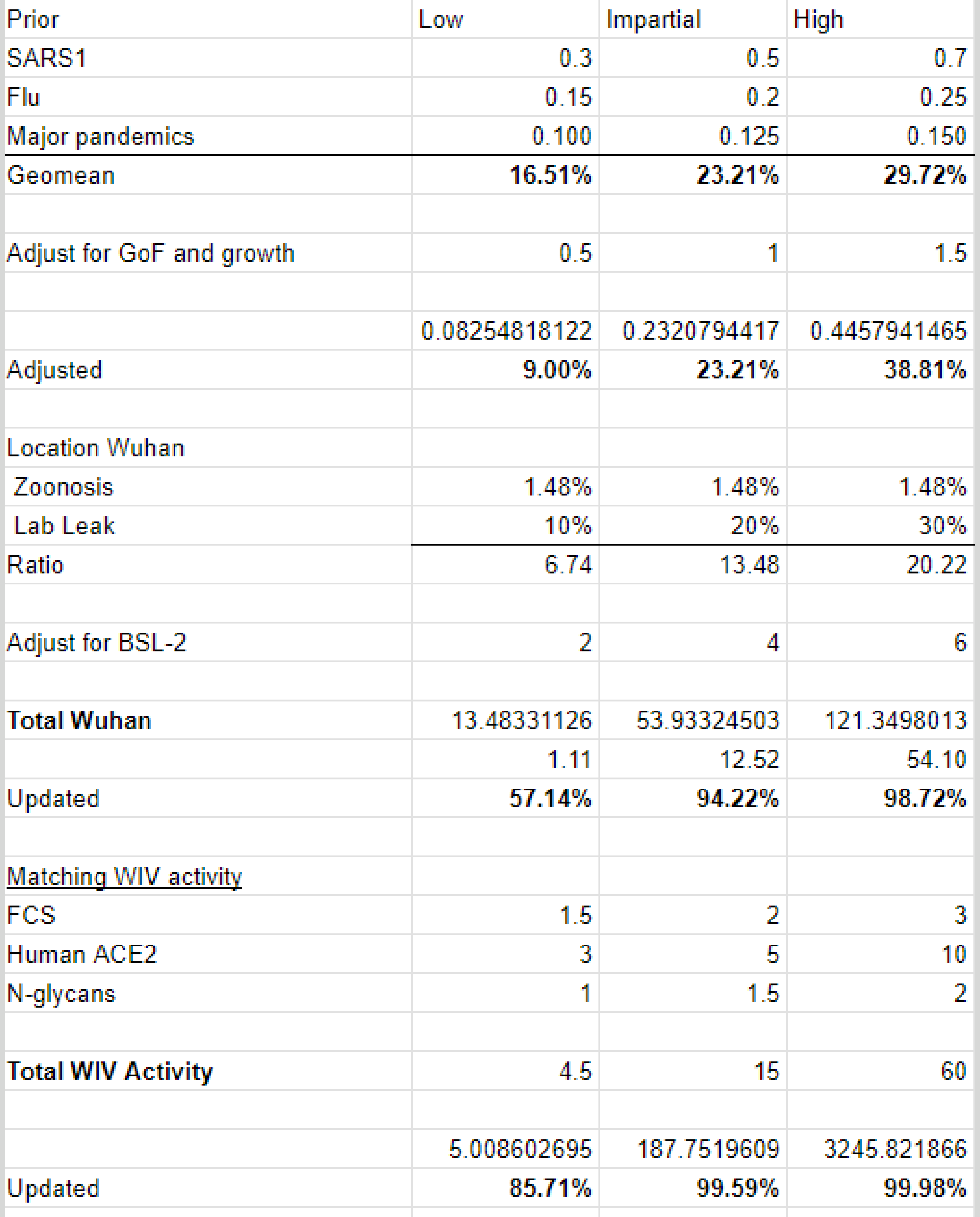
Introduce human specific cleavage sites if missing from the coronavirus

Has a FCS, first one ever in sarbecovirus

Experiment with n-glycans

Missing n-glycan that increases infectivity in human lung cells (but not for enteric)

Summary of Probabilities



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	1.11	12.52	54.10
Updated	**57.14%**	**94.22%**	**98.72%**
Matching WIV activity			
FCS	1.5	2	3
Human ACE2	3	5	10
N-glycans	1	1.5	2
Total WIV Activity	4.5	15	60
	5.008602695	187.7519609	3245.821866
Updated	**85.71%**	**99.59%**	**99.98%**

Best explanations under Zoonosis:

- **FCS - This is what enabled the jump**
- **ACE2 and N-glycans - Coincidence and cryptic transmission**

Weighted: 96.9%

Alternative Calculation / Sanity Check

Estimating directly the rate of emergence, rather than the ratio between the hypotheses.
Definition: Probability per year of a bat coronavirus pandemic starting in Wuhan.

Zoonosis

- We have SARS and MERS which were not infectious enough to cause a pandemic and HKU-1 which wasn't lethal enough.
- So a generous estimate is once every twenty years, or 5% a year.
- 1.5% for it to happen in Wuhan

Total: 0.075% per year

In a lab leak the following need to occur:

- Despite DEFUSE rejection, WIV started a similar project: 40%
- This involves screening for human ACE2 match. Given BANAL-52 is identical to SARS2 in that aspect, and WIV had 180 unpublished viruses, it's likely they would find a good match: 50%
- They would then optimize it for human infection (e.g. adding an FCS).
- Given that this work was done in BSL-2 a lab worker infection is quite likely: 15% per year
- Given infectivity, this would start a pandemic in Wuhan: 40%

Total: 1.2% per year

Final Result 94% Lab Leak

Location: Huanan Seafood Market

How likely was the Huanan market to be the first location noticed?

Probability under: Zoonosis Hypothesis

Probability under: Lab Leak Hypothesis

The Zoonosis Case

The case for zoonosis in the market rests on the following claims:

The market is one of very few places in Wuhan with live wild life.

The market is only the 1600th most visited place in Wuhan, making this a very strong coincidence.

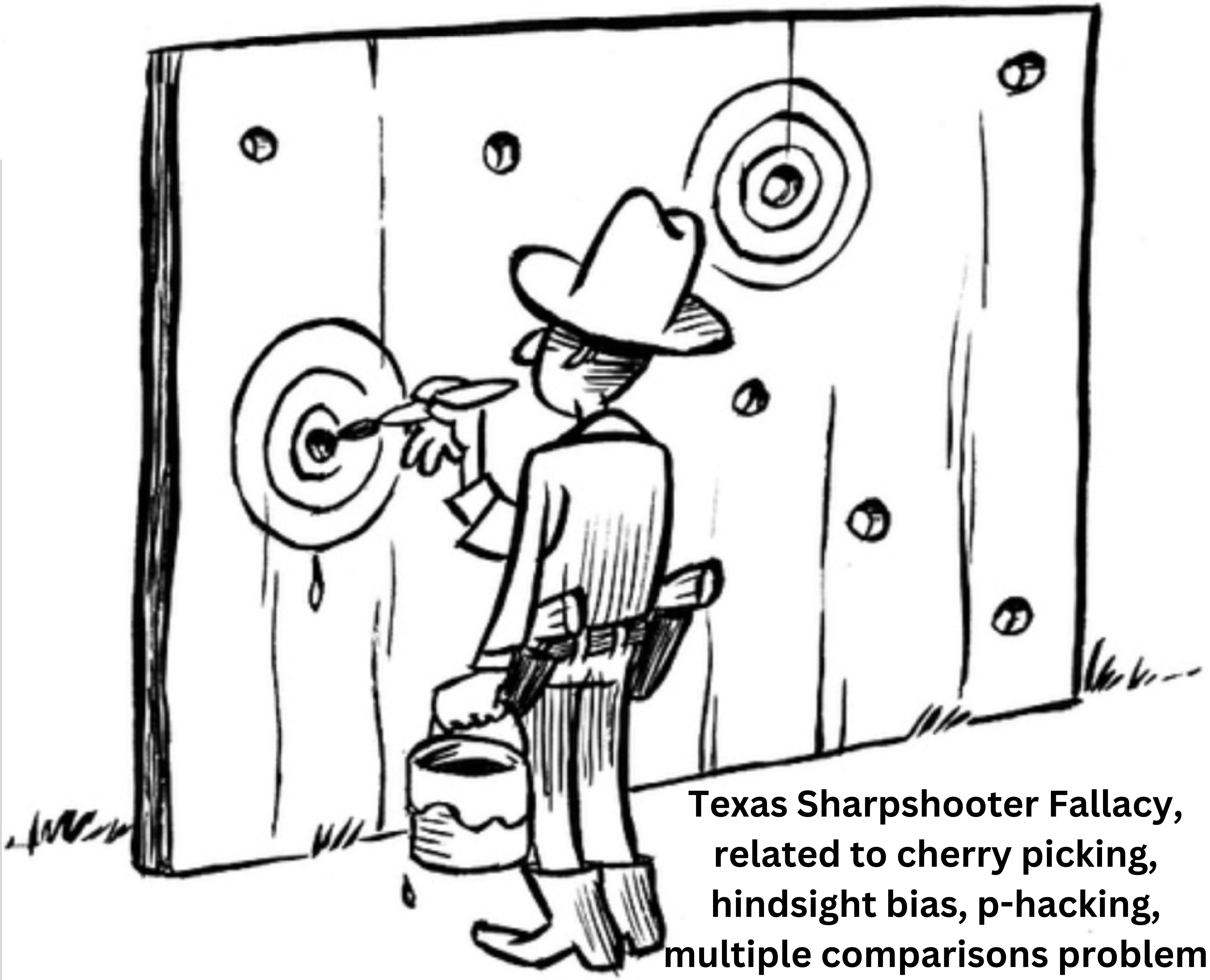
One market environmental sample contained both raccoon dog DNA and SARS2.

The positive environmental samples from the market appear to be near wild life stalls.

Retrospective Study Risk

The Issue with Retrospective Studies on Large Datasets

- "If you torture the data long enough, it will eventually confess to anything."(Ronald Coase)
- In extensive data analysis, patterns can emerge due to the sheer volume of data.
- To claim significance, it's crucial to account for the scale of the search and the size of the search space.



Texas Sharpshooter Fallacy, related to cherry picking, hindsight bias, p-hacking, multiple comparisons problem

Junk Science - Examples

Dreyfus Affair - Handwriting

Exposed by Henri Poincaré

Tair Rada Case - Shoe Print/Jeans

The handwriting evidence in the Dreyfus affair, like the shoeprint in the Tair Rada case was based on finding a few matches from a large search space, and claiming together they form a strong match.
Both accused were later exonerated.

Motivations to Find Patterns

This problem becomes much worse when researchers are particularly motivated to find patterns in support of a certain conclusion. In private discussions, the researchers saw a lab leak as plausible while dismissing it in public. These emails reveal a deliberate intent to manipulate public discourse of COVID origins, driven not by scientific considerations but by political factors. They are therefore especially susceptible to the sharpshooter fallacy, finding false patterns in data.

The emails among the authors of Proximal Origins exposed their biases in favor of zoonosis and willingness to manipulate public discourse.

4 of these authors are in the market study.

The proximal origin of SARS-CoV-2

Kristian G. Andersen, Andrew Rambaut, W. Ian Lipkin, Edward C. Holmes & Robert F. Garry

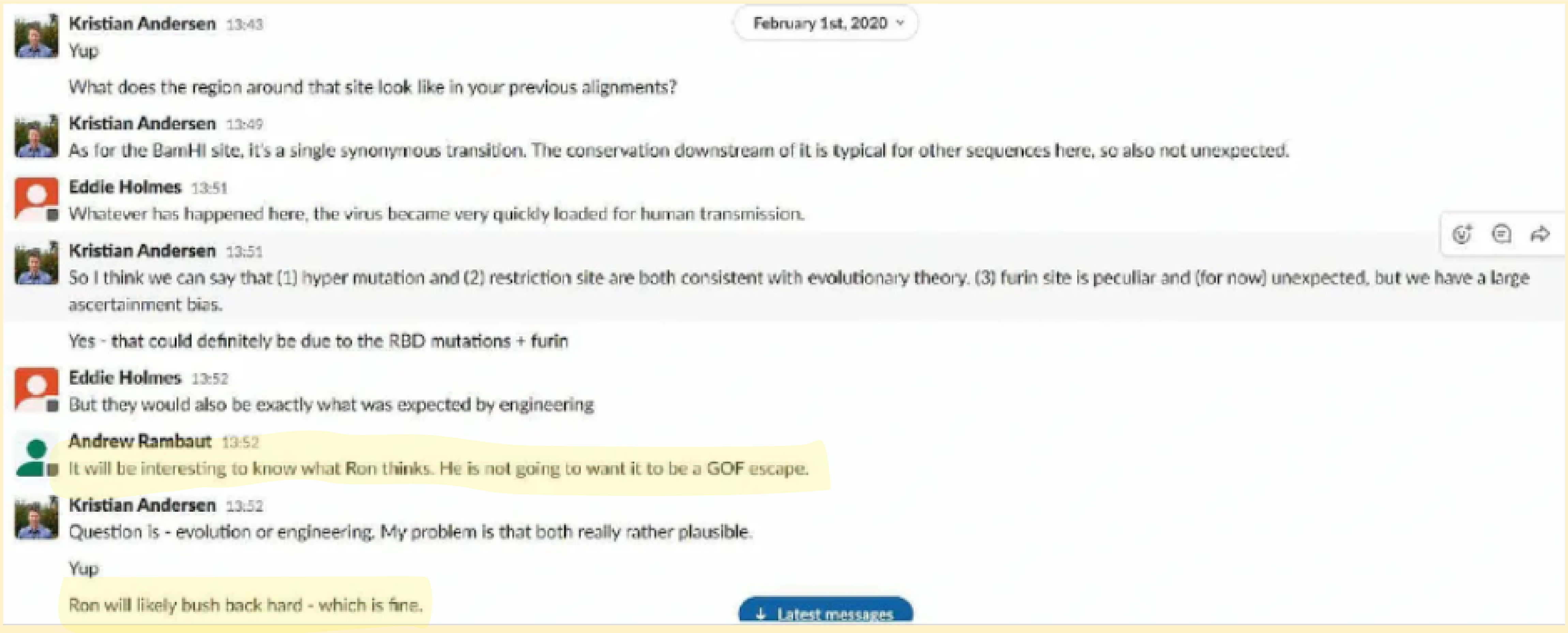
Nature Medicine **26**, 450–452 (2020) | Cite this article

The Huanan Seafood Wholesale Market in Wuhan was the early epicenter of the COVID-19 pandemic

MICHAEL WOROBEY, JOSHUA I. LEVY, LORENA MALPICA SERRANO, ALEXANDER CRITS-CHRISTOPH, JONATHAN E. PEKAR, STEPHEN A. GOLDSTEIN, ANGELA L. RASMUSSEN, MORITZ U. G. KRAEMER, CHRIS NEWMAN, MARION P. G. KOOPMANS, MARC A. SUCHARD, JOEL O. WERTHEIM, PHILIPPE LEMEY, DAVID L. ROBERTSON, ROBERT F. GARRY, EDWARD C. HOLMES, ANDREW RAMBAUT, AND KRISTIAN G. ANDERSEN

Authors Info & Affiliations

Motivations to Find Patterns



February 1st, 2020

Kristian Andersen 13:43
Yup

What does the region around that site look like in your previous alignments?

Kristian Andersen 13:49
As for the BamHI site, it's a single synonymous transition. The conservation downstream of it is typical for other sequences here, so also not unexpected.

Eddie Holmes 13:51
Whatever has happened here, the virus became very quickly loaded for human transmission.

Kristian Andersen 13:51
So I think we can say that (1) hyper mutation and (2) restriction site are both consistent with evolutionary theory. (3) furin site is peculiar and (for now) unexpected, but we have a large ascertainment bias.

Yes - that could definitely be due to the RBD mutations + furin

Eddie Holmes 13:52
But they would also be exactly what was expected by engineering

Andrew Rambaut 13:52
It will be interesting to know what Ron thinks. He is not going to want it to be a GOF escape.

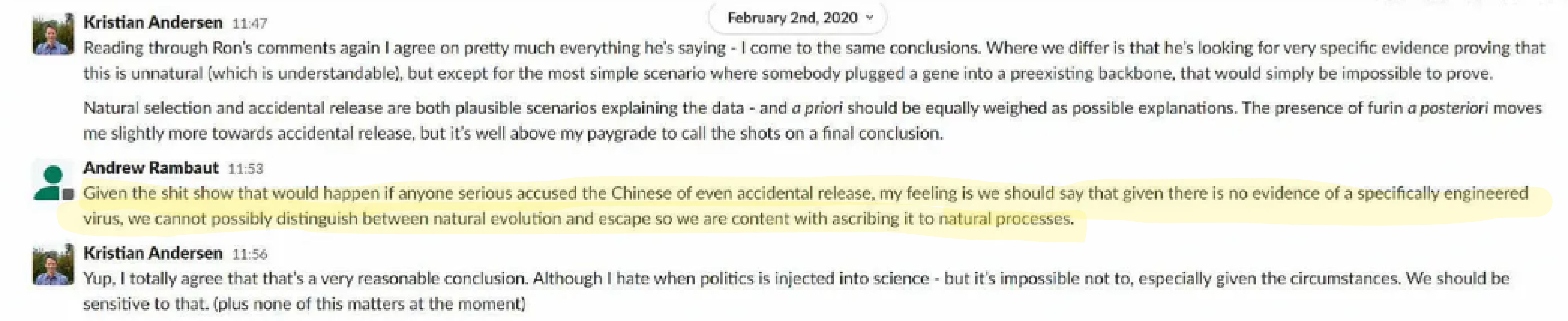
Kristian Andersen 13:52
Question is - evolution or engineering. My problem is that both really rather plausible.

Yup

Ron will likely bush back hard - which is fine.

These messages unmistakably demonstrate the researchers' awareness of their colleagues' biases for specific outcomes, as highlighted in the quote about Ron. However, it's important to note that Ron is not included in the HSM paper.

February 2, 2020, Rambaut discussed omitting the likely possibility of a lab leak to avoid a political "shit show". Andersen said, "I totally agree." Additionally, Andrew fears the Chinese reaction to being accusing of even an "accidental release".



February 2nd, 2020

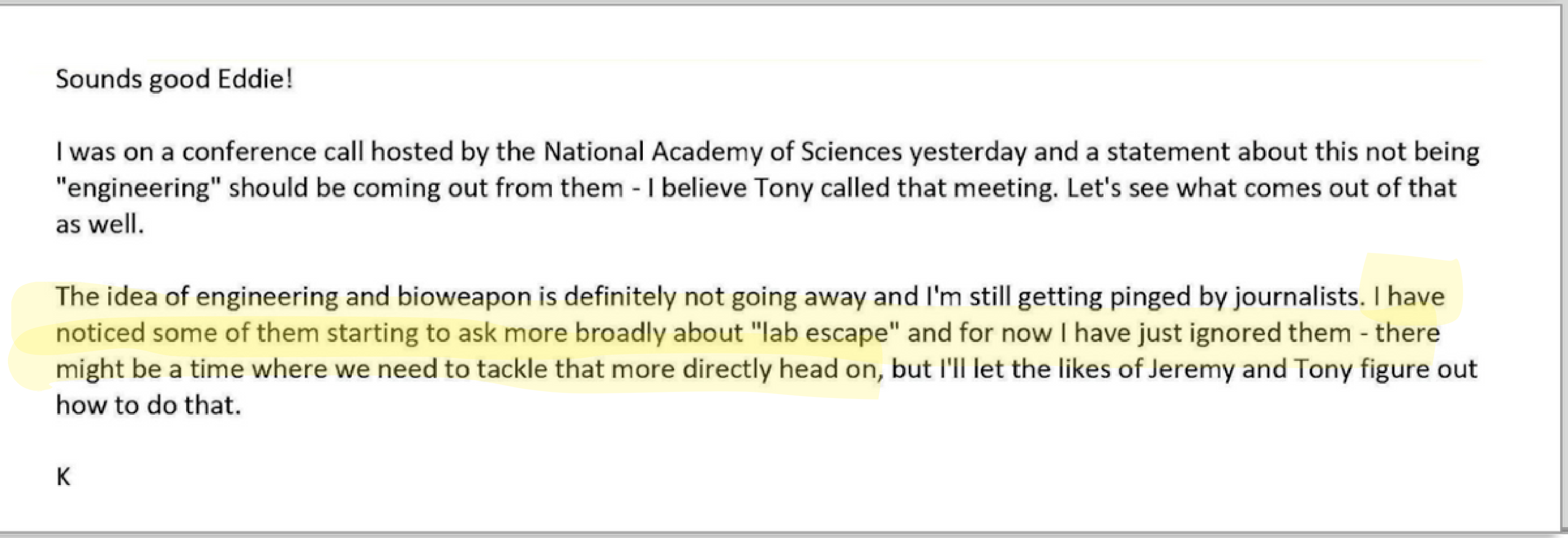
Kristian Andersen 11:47
Reading through Ron's comments again I agree on pretty much everything he's saying - I come to the same conclusions. Where we differ is that he's looking for very specific evidence proving that this is unnatural (which is understandable), but except for the most simple scenario where somebody plugged a gene into a preexisting backbone, that would simply be impossible to prove.

Natural selection and accidental release are both plausible scenarios explaining the data - and *a priori* should be equally weighed as possible explanations. The presence of furin *a posteriori* moves me slightly more towards accidental release, but it's well above my paygrade to call the shots on a final conclusion.

Andrew Rambaut 11:53
Given the shit show that would happen if anyone serious accused the Chinese of even accidental release, my feeling is we should say that given there is no evidence of a specifically engineered virus, we cannot possibly distinguish between natural evolution and escape so we are content with ascribing it to natural processes.

Kristian Andersen 11:56
Yup, I totally agree that that's a very reasonable conclusion. Although I hate when politics is injected into science - but it's impossible not to, especially given the circumstances. We should be sensitive to that. (plus none of this matters at the moment)

Motivations to Find Patterns



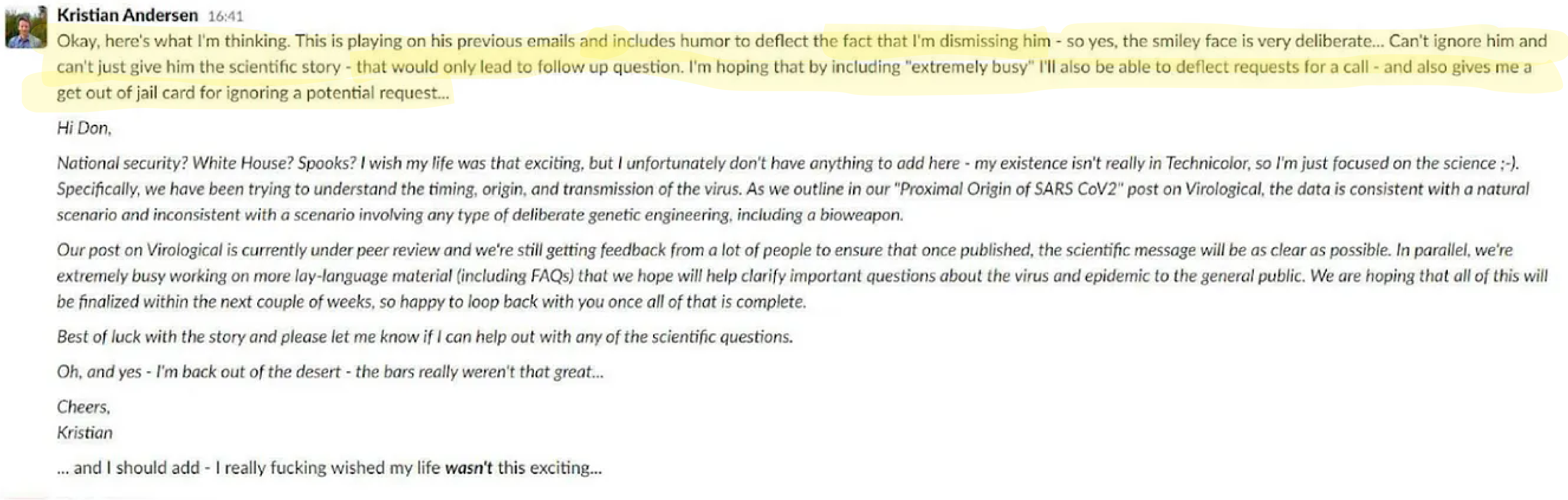
Sounds good Eddie!

I was on a conference call hosted by the National Academy of Sciences yesterday and a statement about this not being "engineering" should be coming out from them - I believe Tony called that meeting. Let's see what comes out of that as well.

The idea of engineering and bioweapon is definitely not going away and I'm still getting pinged by journalists. I have noticed some of them starting to ask more broadly about "lab escape" and for now I have just ignored them - there might be a time where we need to tackle that more directly head on, but I'll let the likes of Jeremy and Tony figure out how to do that.

K

The emails revealed efforts to deflect questions about the possibility of COVID-19 originating from a lab, using strategies that appear more political than scientific.



Kristian Andersen 16:41

Okay, here's what I'm thinking. This is playing on his previous emails and includes humor to deflect the fact that I'm dismissing him - so yes, the smiley face is very deliberate... Can't ignore him and can't just give him the scientific story - that would only lead to follow up question. I'm hoping that by including "extremely busy" I'll also be able to deflect requests for a call - and also gives me a get out of jail card for ignoring a potential request...

Hi Don,

National security? White House? Spooks? I wish my life was that exciting, but I unfortunately don't have anything to add here - my existence isn't really in Technicolor, so I'm just focused on the science ;-). Specifically, we have been trying to understand the timing, origin, and transmission of the virus. As we outline in our "Proximal Origin of SARS CoV2" post on Virological, the data is consistent with a natural scenario and inconsistent with a scenario involving any type of deliberate genetic engineering, including a bioweapon.

Our post on Virological is currently under peer review and we're still getting feedback from a lot of people to ensure that once published, the scientific message will be as clear as possible. In parallel, we're extremely busy working on more lay-language material (including FAQs) that we hope will help clarify important questions about the virus and epidemic to the general public. We are hoping that all of this will be finalized within the next couple of weeks, so happy to loop back with you once all of that is complete.

Best of luck with the story and please let me know if I can help out with any of the scientific questions.

Oh, and yes - I'm back out of the desert - the bars really weren't that great...

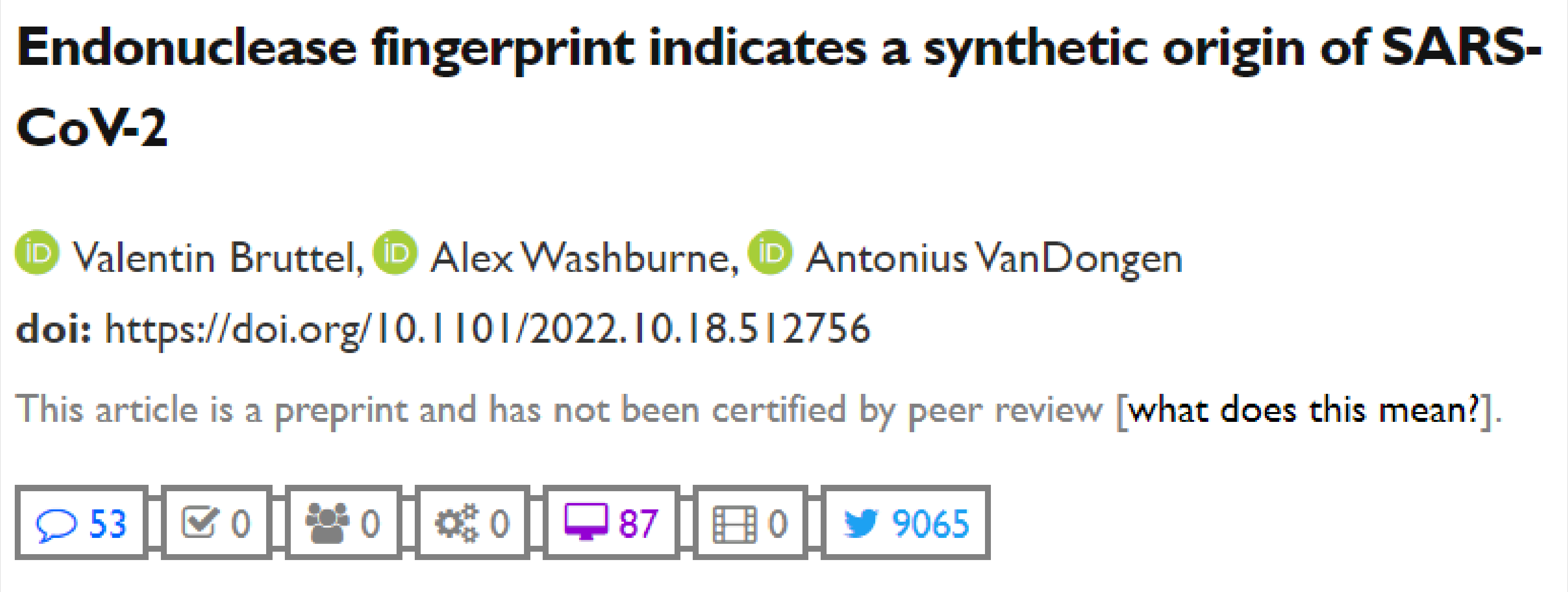
Cheers,
Kristian

... and I should add - I really fucking wished my life **wasn't** this exciting...

Retrospective Study Risk

In a robust probabilistic analysis, we should be extremely careful when incorporating studies relying on retrospective pattern matching in large datasets. The Huanan Market study in its current form should be ignored.

We of course apply this standard to all hypotheses. In Bruttel et al, researchers found patterns supporting genetic manipulation at a P-value of 1 in 10,000,000.
While we generally agree with the study, we couldn't incorporate it due to these limitations.



Endonuclease fingerprint indicates a synthetic origin of SARS-CoV-2

Valentin Bruttel, Alex Washburne, Antonius VanDongen

doi: https://doi.org/10.1101/2022.10.18.512756

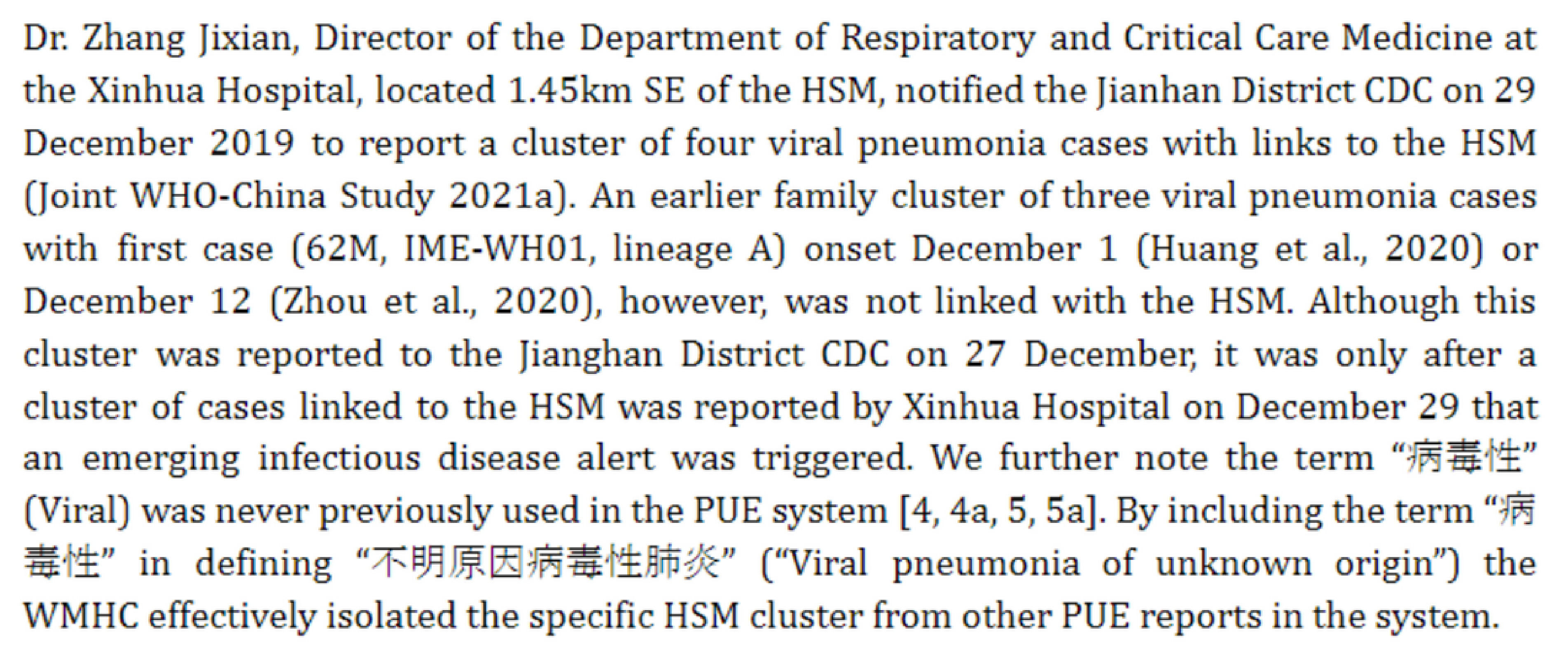
This article is a preprint and has not been certified by peer review [what does this mean?].

It is very difficult to identify the source of the biases in such studies.
Luckily, the market study has already been thoroughly analyzed by others.

Bias in Early Cases

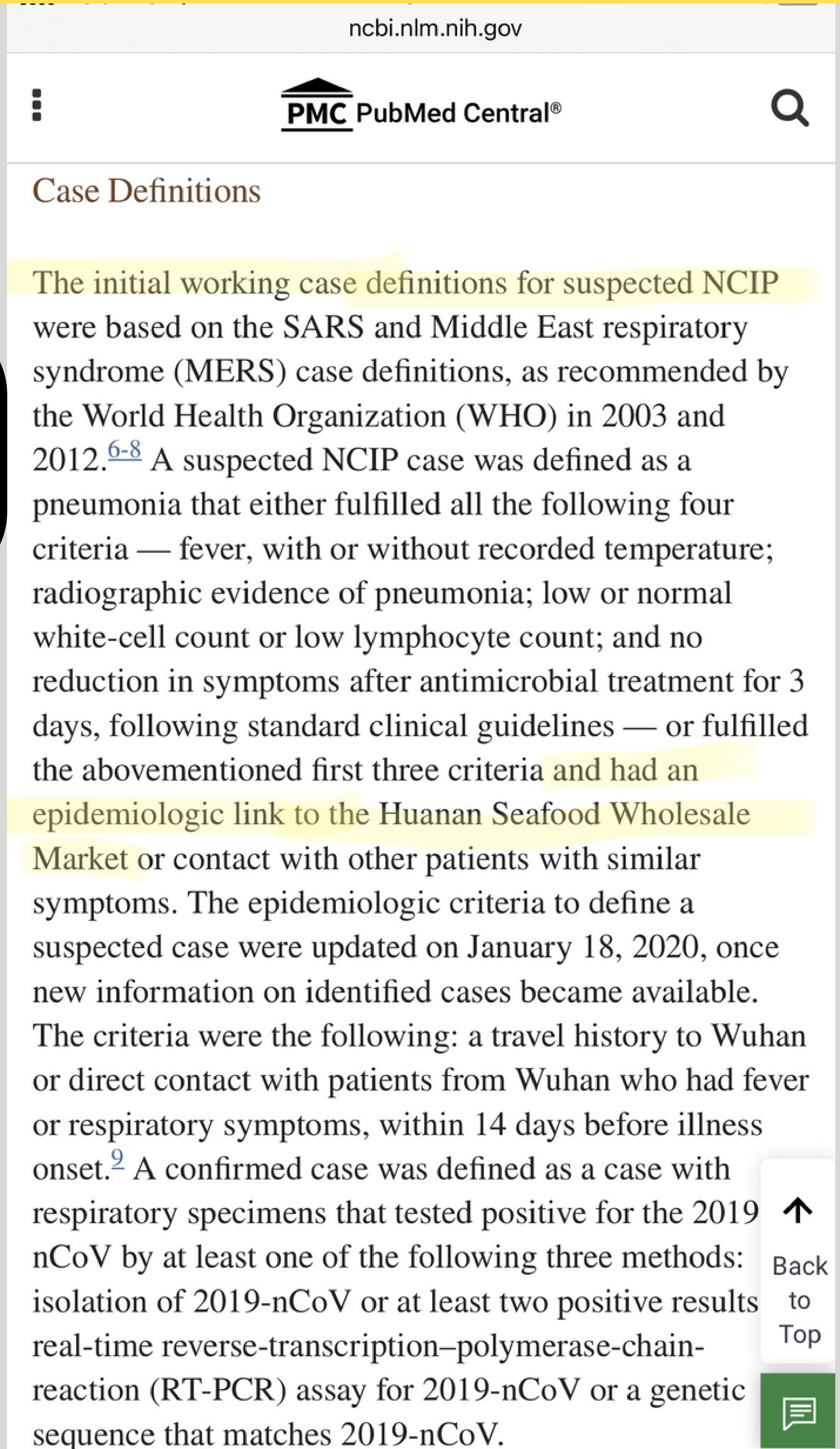
Early in the pandemic, diagnoses were partially given based on whether a patient had a connection to the Huanan Seafood Market.

Until January 18th, 2020 a connection to the market was a requirement for a Covid-19 diagnosis because it was thought to be the source. This led to a selection bias wherein only those connected to the seafood market were diagnosed with covid-19, which further fueled speculation that Huanan was the epicenter and the likely spillover location.



Dr. Zhang Jixian, Director of the Department of Respiratory and Critical Care Medicine at the Xinhua Hospital, located 1.45km SE of the HSM, notified the Jianhan District CDC on 29 December 2019 to report a cluster of four viral pneumonia cases with links to the HSM (Joint WHO-China Study 2021a). An earlier family cluster of three viral pneumonia cases with first case (62M, IME-WH01, lineage A) onset December 1 (Huang et al., 2020) or December 12 (Zhou et al., 2020), however, was not linked with the HSM. Although this cluster was reported to the Jianghan District CDC on 27 December, it was only after a cluster of cases linked to the HSM was reported by Xinhua Hospital on December 29 that an emerging infectious disease alert was triggered. We further note the term “病毒性” (Viral) was never previously used in the PUE system [4, 4a, 5, 5a]. By including the term “病毒性” in defining “不明原因病毒性肺炎” (“Viral pneumonia of unknown origin”) the WMHC effectively isolated the specific HSM cluster from other PUE reports in the system.

Due to SARS experience, healthcare workers were more inclined to report new diseases with connection to a market.

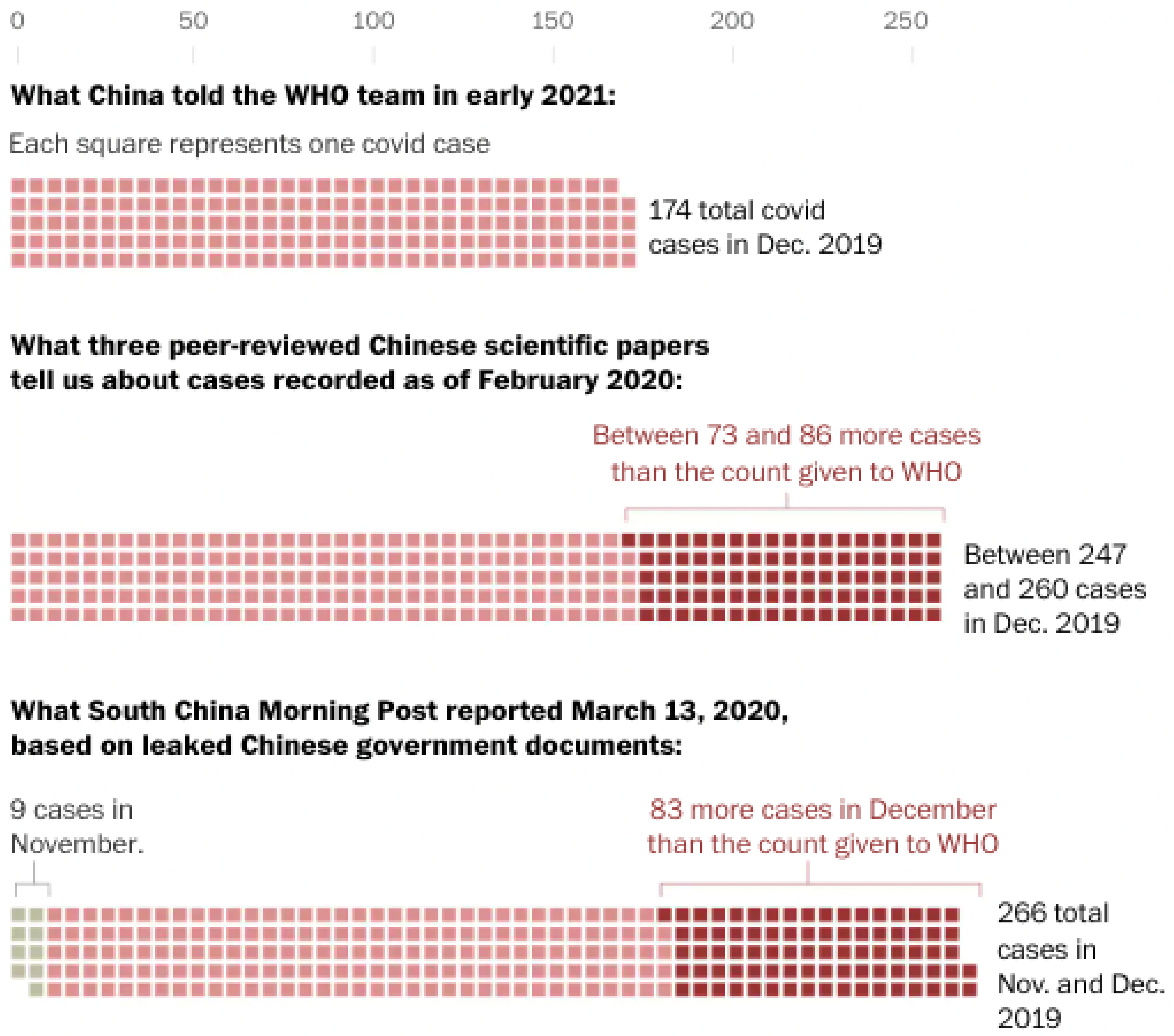


Case Definitions

The initial working case definitions for suspected NCIP were based on the SARS and Middle East respiratory syndrome (MERS) case definitions, as recommended by the World Health Organization (WHO) in 2003 and 2012.[6-8] A suspected NCIP case was defined as a pneumonia that either fulfilled all the following four criteria — fever, with or without recorded temperature; radiographic evidence of pneumonia; low or normal white-cell count or low lymphocyte count; and no reduction in symptoms after antimicrobial treatment for 3 days, following standard clinical guidelines — or fulfilled the abovementioned first three criteria and had an epidemiologic link to the Huanan Seafood Wholesale Market or contact with other patients with similar symptoms. The epidemiologic criteria to define a suspected case were updated on January 18, 2020, once new information on identified cases became available. The criteria were the following: a travel history to Wuhan or direct contact with patients from Wuhan who had fever or respiratory symptoms, within 14 days before illness onset.[9] A confirmed case was defined as a case with respiratory specimens that tested positive for the 2019-nCoV by at least one of the following three methods: isolation of 2019-nCoV or at least two positive results real-time reverse-transcription–polymerase-chain-reaction (RT-PCR) assay for 2019-nCoV or a genetic sequence that matches 2019-nCoV.

Evidence of Bias

Furthermore, there seem to be around 90 December cases missing. There is no way to know why this happened and what biases it introduces. Any claims based on this data are of low confidence.

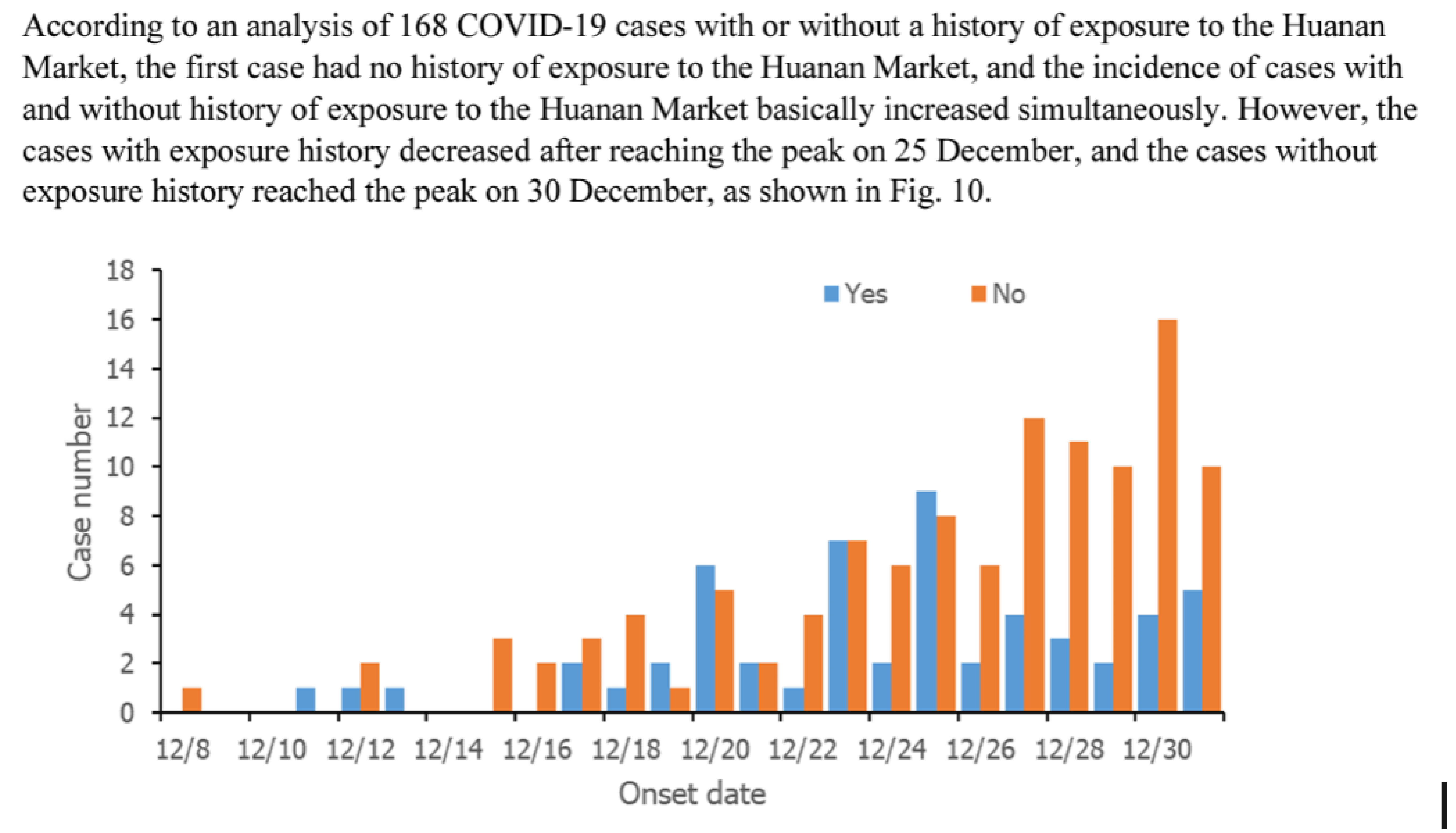


The Wuhan early cases — more questions than answers

An accurate account of 2019 covid cases could help establish the origin of the pandemic. But the tallies for that time differ substantially. A serious investigation is needed.

Sources: World Health Organization; Cao Wuchun, et al., International Journal of Environmental Research and Public Health, 2020; Yu Chuanhua, et al., Global Health Research and Policy, 2021; Josephine Ma, South China Morning Post, March 13, 2020; An Pan, Li Liu, Chaolong Wang, et al., JAMA, April 10, 2020; Gilles Demaneuf, DRASTIC.

Early Cases not Connected to Market



According to an analysis of 168 COVID-19 cases with or without a history of exposure to the Huanan Market, the first case had no history of exposure to the Huanan Market, and the incidence of cases with and without history of exposure to the Huanan Market basically increased simultaneously. However, the cases with exposure history decreased after reaching the peak on 25 December, and the cases without exposure history reached the peak on 30 December, as shown in Fig. 10.

Rates with and without connection to HSM "increased simultaneously". If HSM is G0 a likelier distribution would be mostly HSM-related patients at first and only then the rest of Wuhan catching up - but HSM and Wuhan are neck and neck.

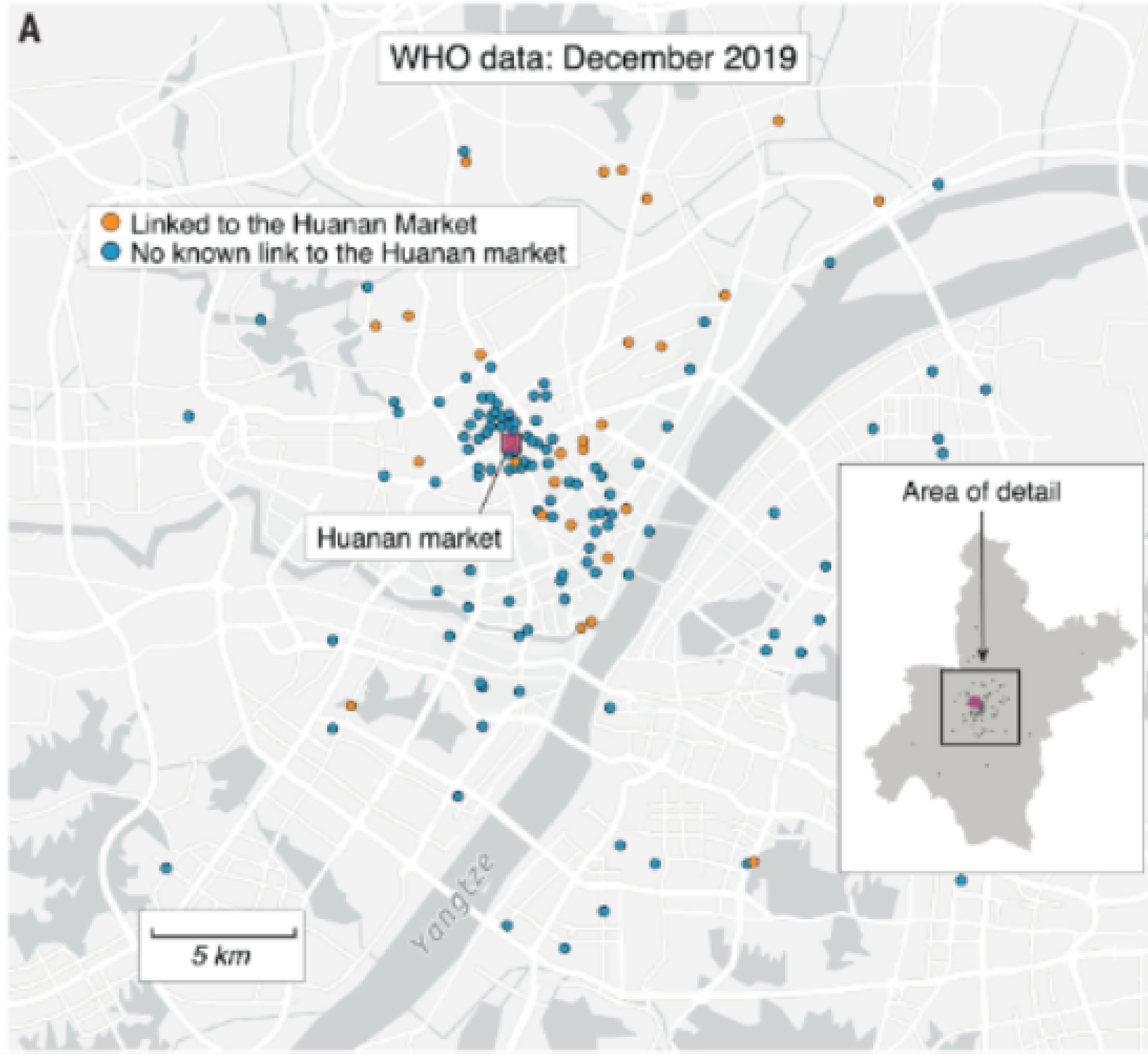
https://www.who.int/publications/i/item/who-convened-global-study-of-origins-of-sars-cov-2-china-part

Early Cases not Connected to Market

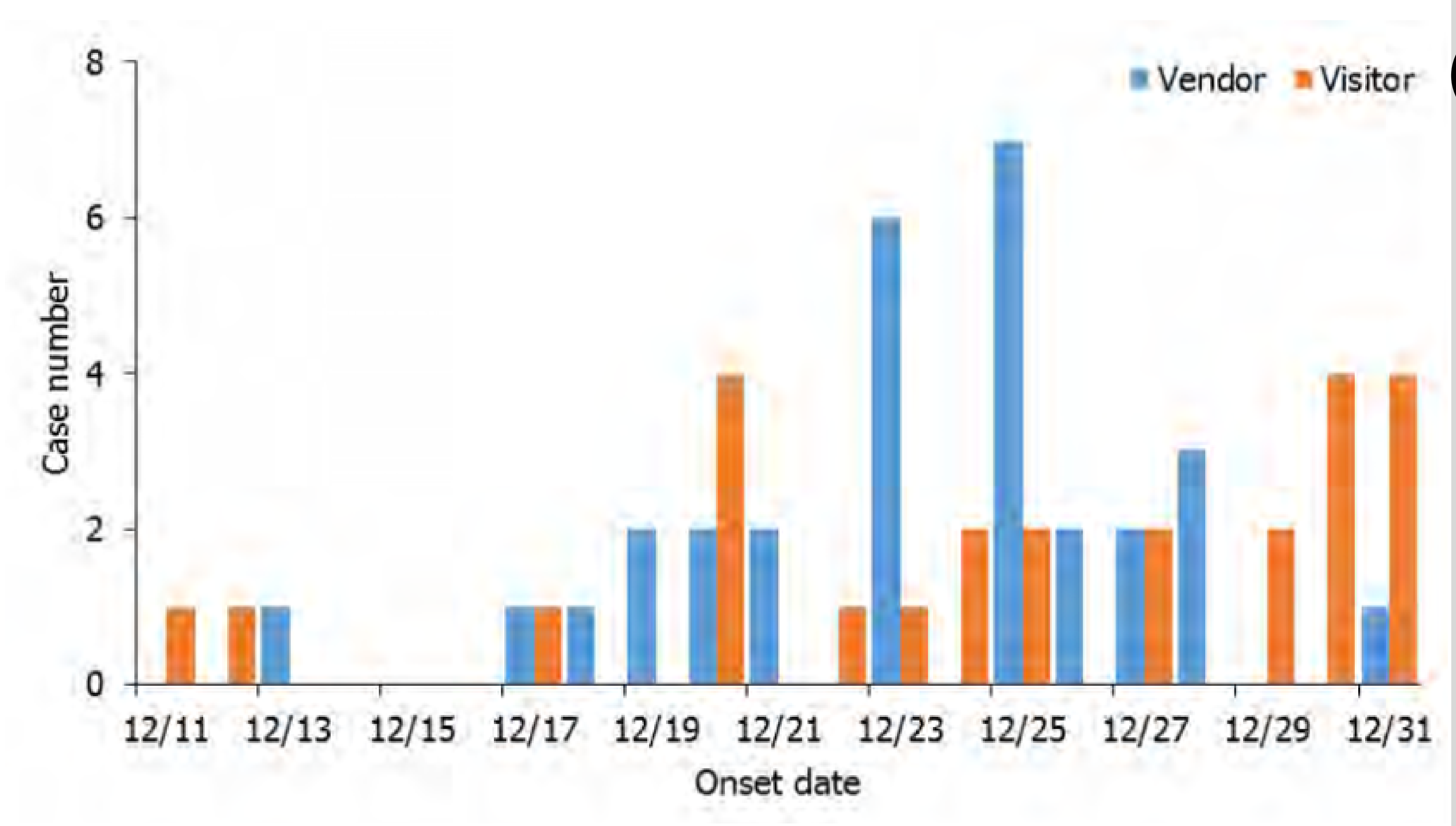
A large portion of the early cases were not linked to the Huanan market

In general, early cases are unreliable, as there was no published effort to contact trace or find the earliest cases.
This in itself is evidence for a lab leak.

https://www.science.org/doi/10.1126/science.abp8715#



Earliest Patients are Visitors



https://www.who.int/publications/i/item/who-convened-global-study-of-origins-of-sars-cov-2-china-part

“both of the first two cases were visitors (11 and 12 December); the first vendor case appeared on 13 December”.

Given that the first cases were only a day apart, they could feasibly have been infected at the same time due to the length of the incubation period. However, if the market were the source, we would expect a significant majority of the first cases to be vendors.

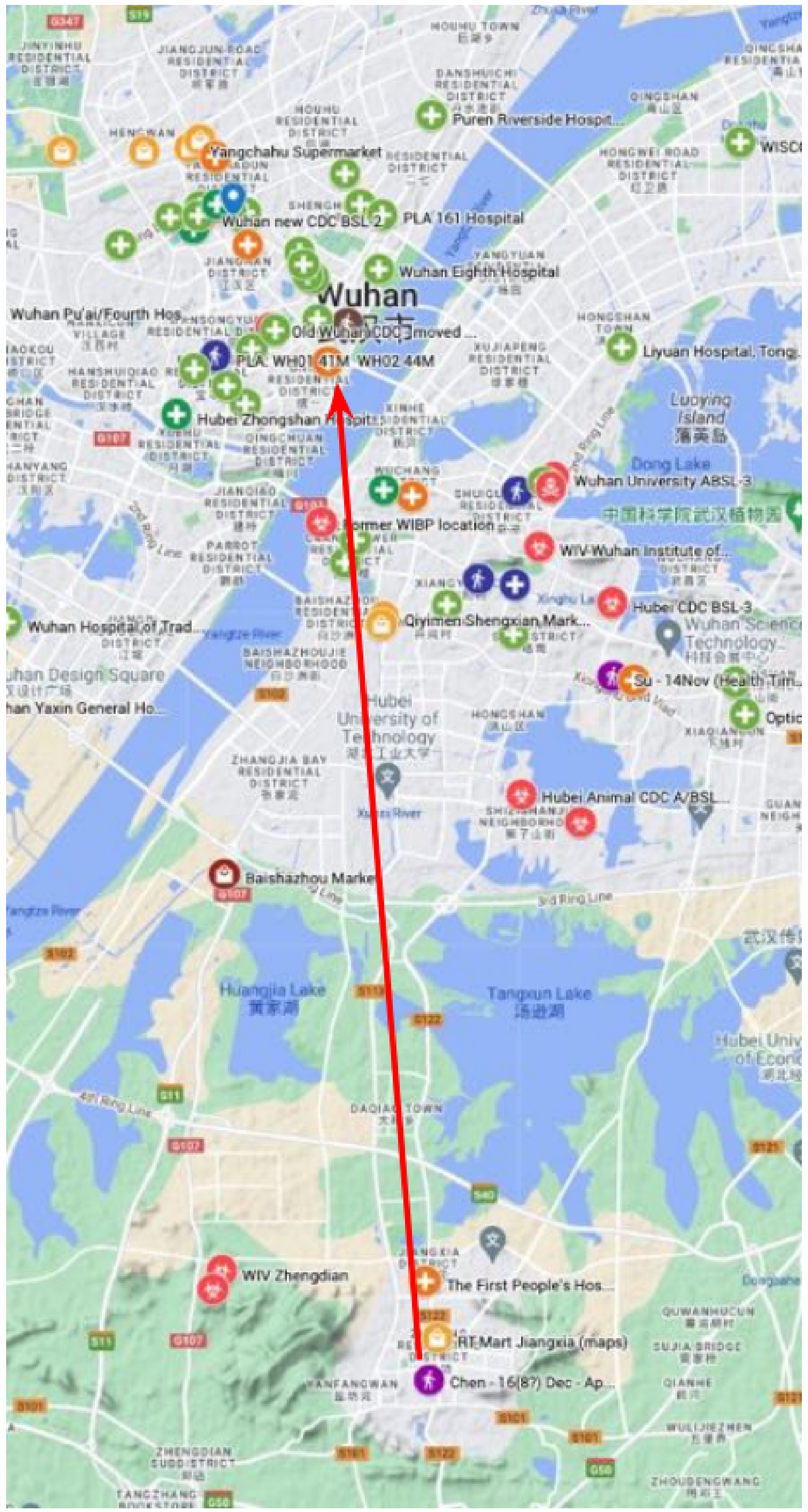
Bias: Case of Mr. Chen

A good indication of selection bias is the case of Mr Chen:

- Fever 16 December
- Did not go to any wet market, lived and worked exclusively locally in rural Jiangxia (30km south)
- Was diagnosed only because a relative worked in the ER of Wuhan Central Hospital, across the river.

This implies widespread infection early December.

https://www.washingtonpost.com/documents/a5102da1-9b47-4e11-b615-9f59b7d3a3c3.pdf?itid=lk_inline_manual_17 (Page 96-97)

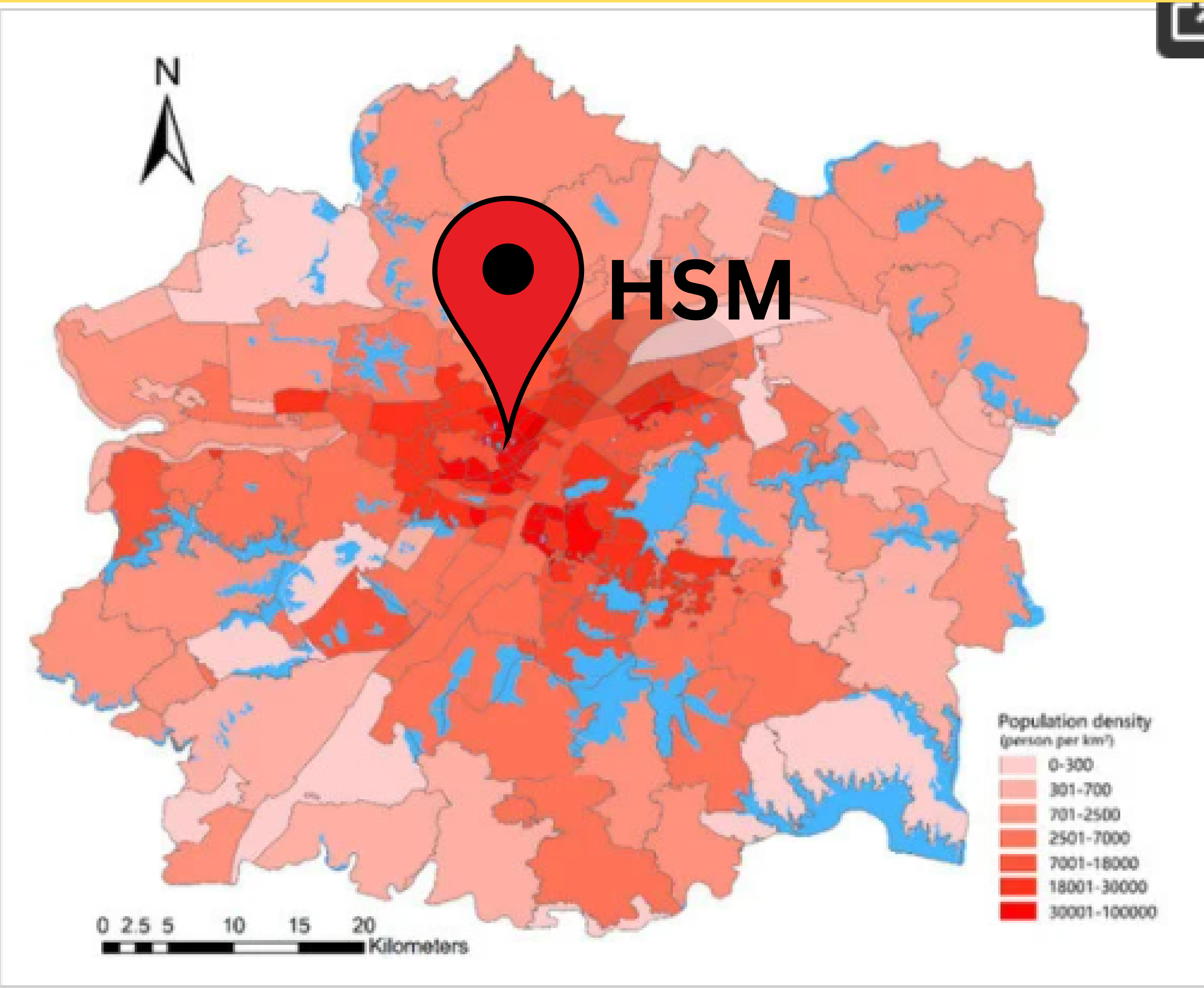


Bias: Using Check-in Data

The claim that the market was not a likely location (absent wild life) due to its low-traffic was based primarily on social check-In data.

Social check-ins are popular among younger crowds, at trendy locations. The median age of those infected at the market was 56, and a seafood market is not a place people would check-in to. In reality, Huanan market is fairly busy with 10,000 visitors a day.

"Many of the early cases were associated with the Huanan market, **but a similar number of cases were associated with other markets** and some were not associated with any markets. Transmission within the wider community in December could account for cases not associated with the Huanan market which, together with the presence of early cases not associated with that market, could **suggest that the Huanan market was not the original source of the outbreak.** [...]**No firm conclusion therefore about the role of the Huanan market in the origin of the outbreak, or how the infection was introduced into the market, can currently be drawn."** page 7 of the WHO report source: https://www.who.int/publications/i/item/who-convened-global-study-of-origins-of-sars-cov-2-china-part

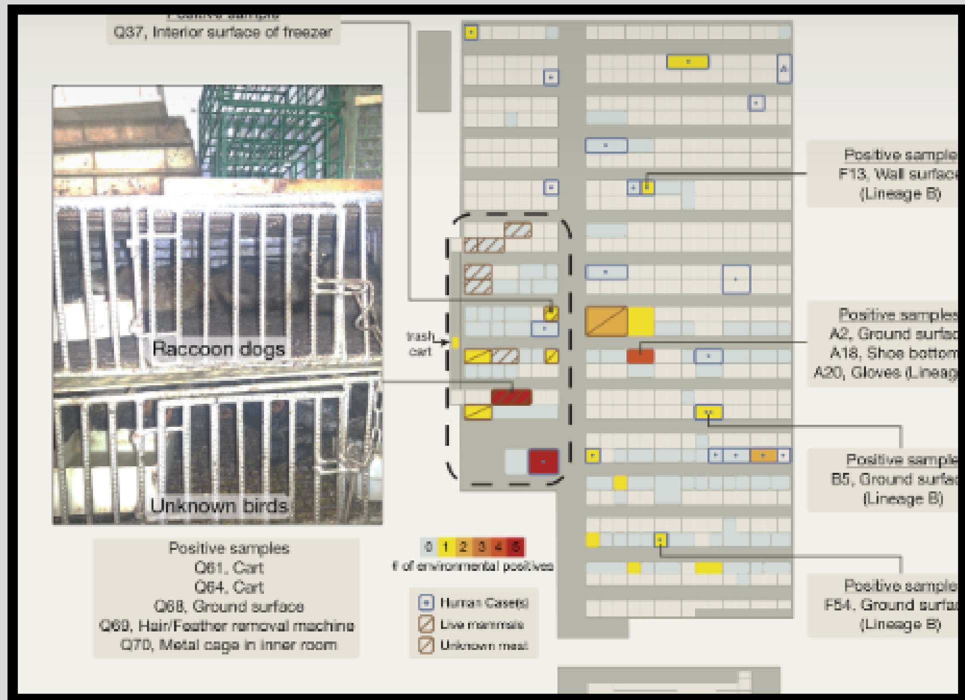


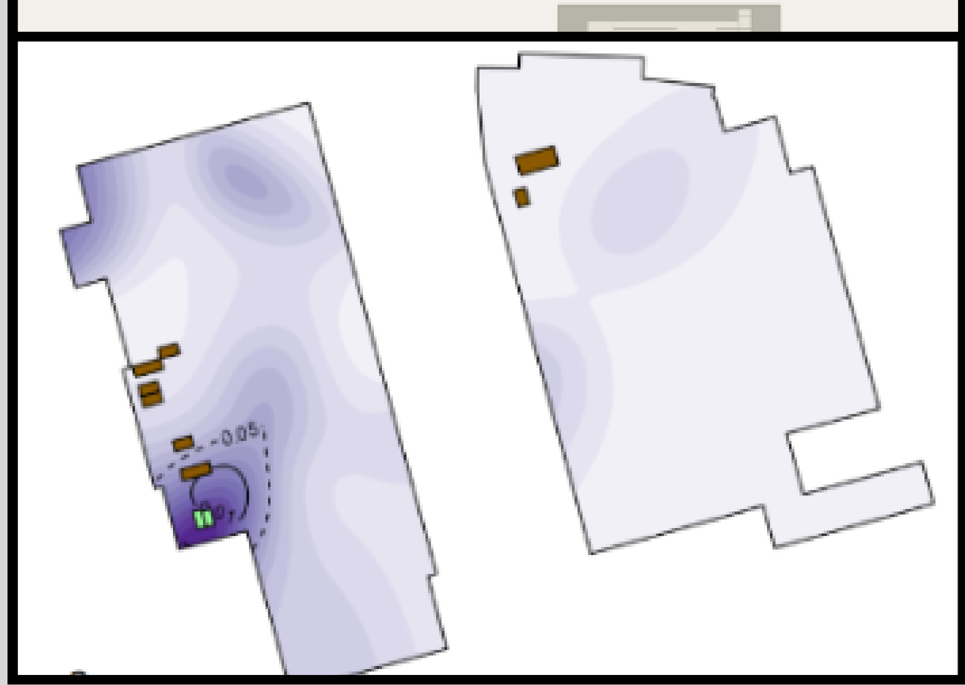
Bias: Environmental Samples

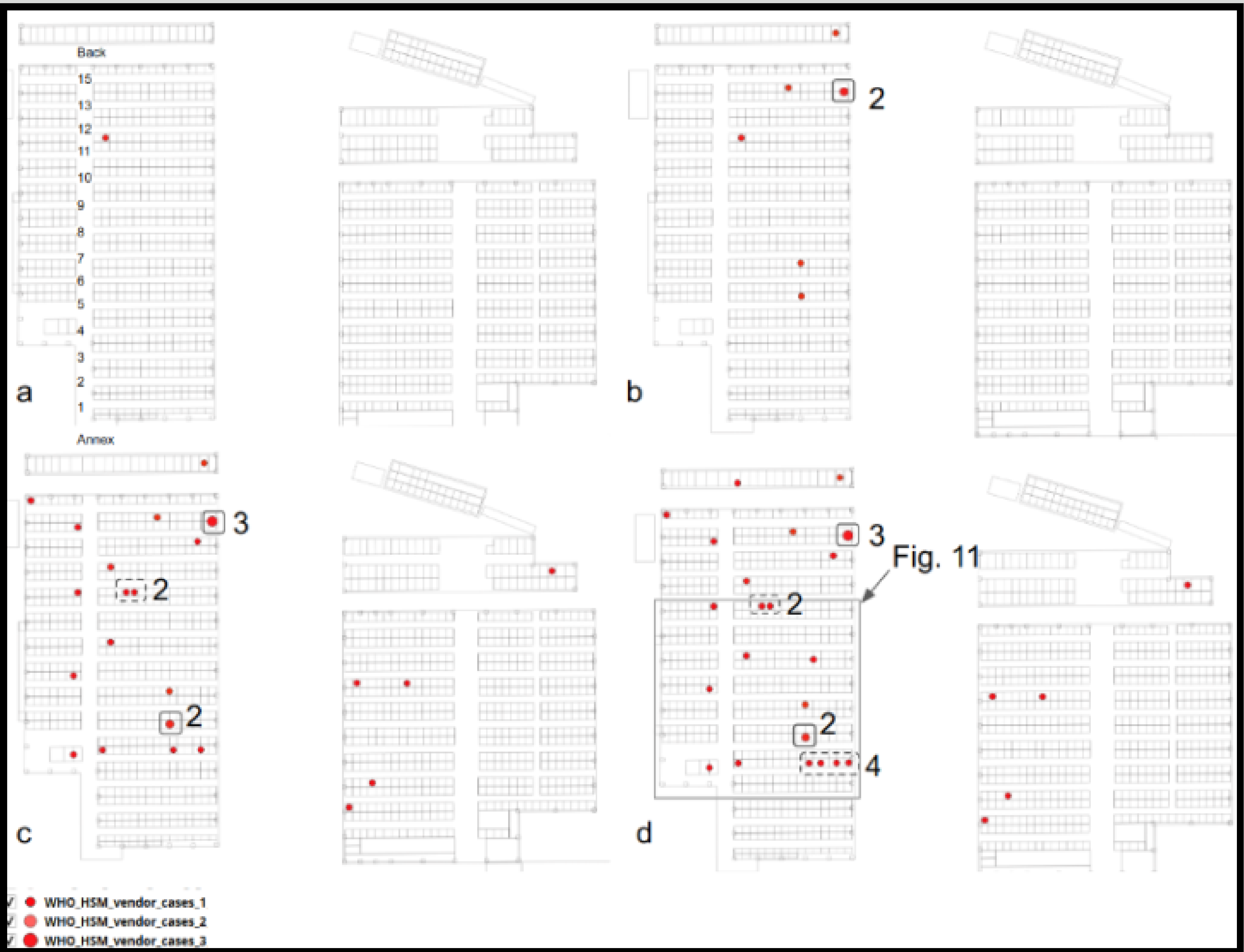
Environmental samples from the market show a number of areas with a stronger rate of positive samples in the south-west corner of the market place that also had live animal stalls, specifically racoon dogs.

Unlike environmental samples, cases are evenly distributed across the market

Initially, positive samples were shown to be close to wildlife stalls. However, the sample was biased, as those areas were oversampled so, naturally, they produced more positive samples.



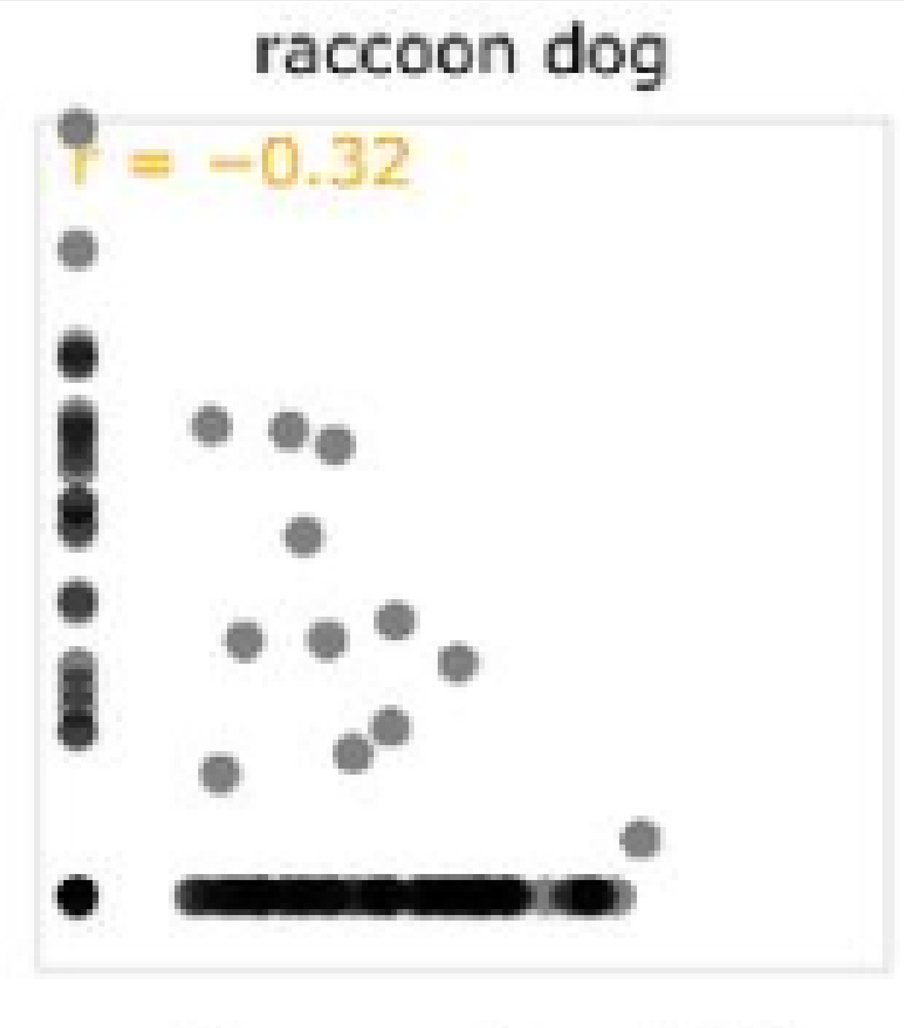




Once corrected, the positive samples better match the toilets and a Mahjong room, ideal for airborne virus transmission like SARS-CoV-2.

https://www.science.org/doi/10.1126/science.abp8715#

Mistake: Cherry-Picking Raccoon Dog Sample



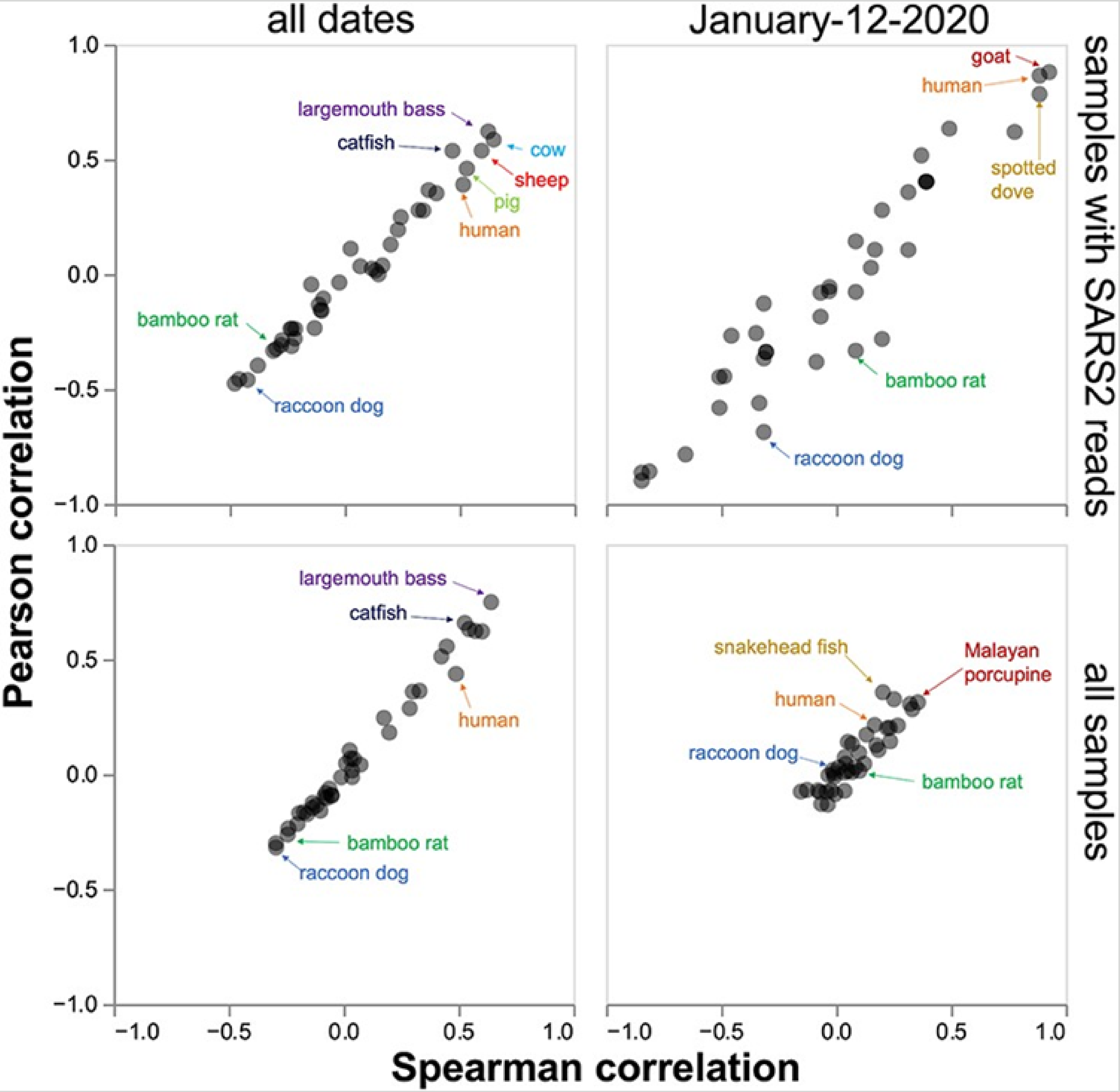
An environmental sample from a raccoon dog cage (not the animal itself) was positive for SARS2, indicating that raccoon dogs could potentially be the intermediate host for the virus.

There was only one SARS2 RNA read, and raccoon dog mtDNA was in fact negatively correlated with SARS2 RNA

https://www.biorxiv.org/content/10.1101/2023.04.25.538336v2

https://www.npr.org/sections/goatsandsoda/2022/03/03/1083751272/striking-new-evidence-points-to-seafood-market-in-wuhan-as-pandemic-origin-point

Wildlife Inversely Correlated with SARS2



Positive environmental samples around raccoon dog stalls were in fact lower than other animals. This negates the hypothesis that raccoon dogs were the intermediary species.

Note that in any case, infected raccoon dogs in the market isn't strong evidence for zoonosis. If they are as susceptible to SARS-CoV-2 as claimed, they could have contracted it from humans. Strong evidence would be them being infected by an earlier strain phylogenetically.

JOURNAL ARTICLE

Association between SARS-CoV-2 and metagenomic content of samples from the Huanan Seafood Market

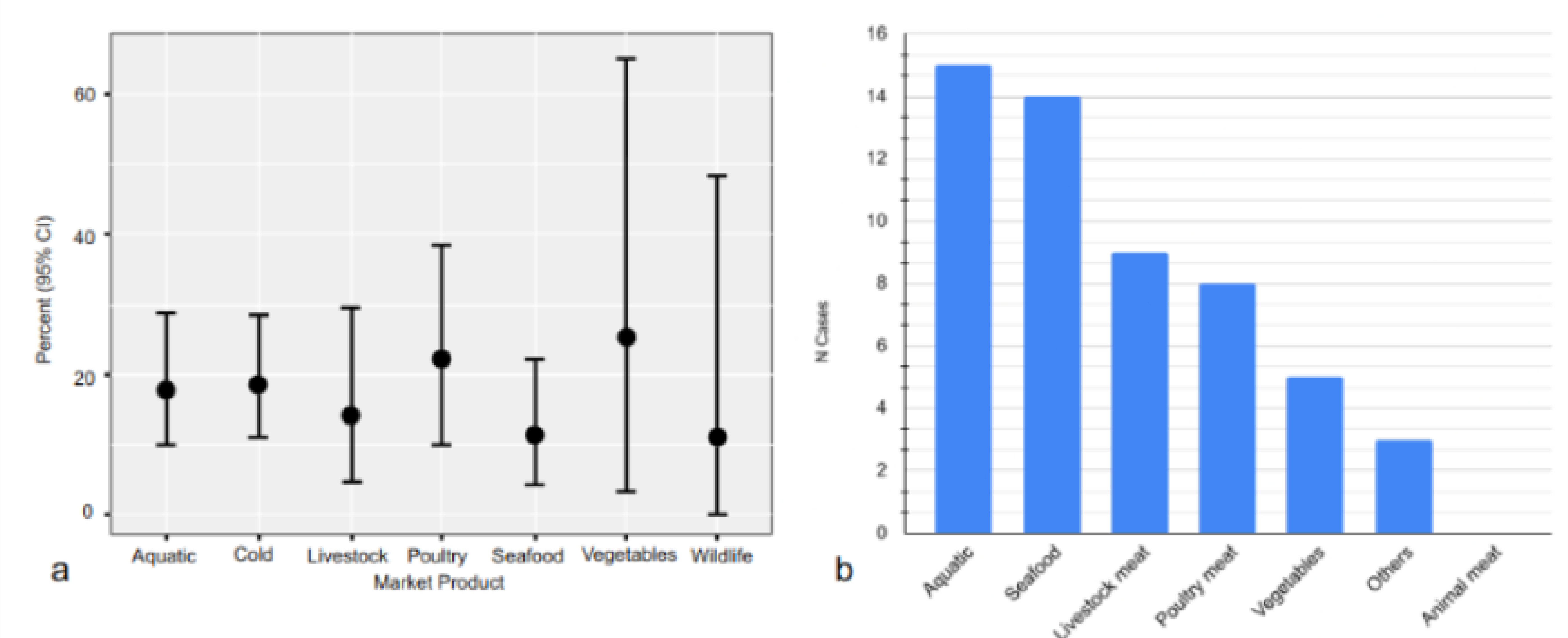
Jesse D Bloom ✉ Author Notes

Virus Evolution, Volume 9, Issue 2, 2023, vead050,
https://doi.org/10.1093/ve/vead050

Published: 24 August 2023 **Article history** ▾

Stalls also not Correlated

Positive environmental samples are not positively correlated with wildlife stalls in particular.



Market Strains not Ancestral

Two Lineages of SARS-CoV-2 observed: Lineage A & Lineage B

Lineage A is ancestral to Lineage B. This is a contested claim, and we will explain why there is strong evidence for this in session 2.

All the market cases were lineage B, not the earlier lineage A .

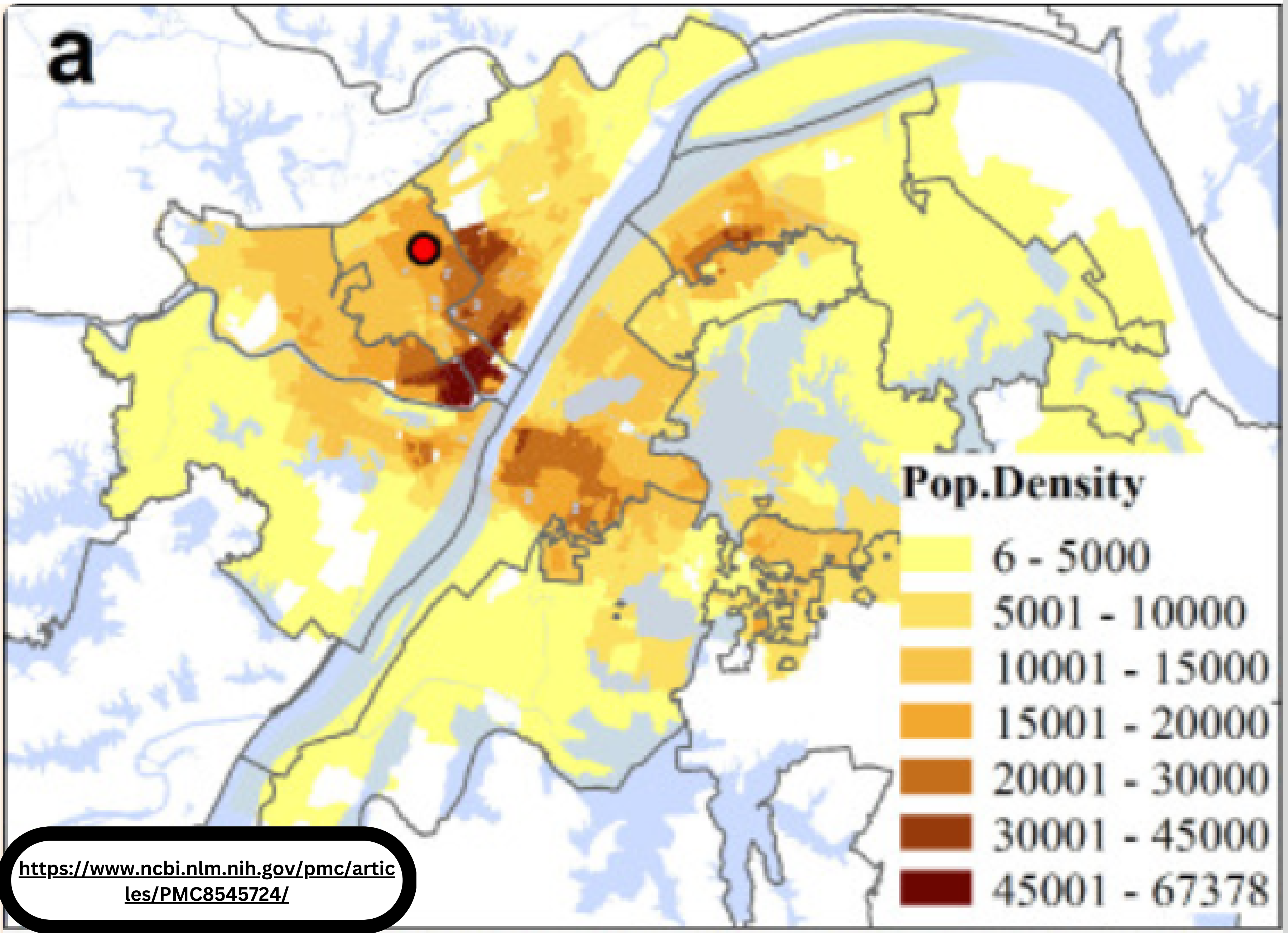
Early appearance of two distinct genomic lineages of SARS-CoV-2 in different Wuhan wildlife markets suggests SARS-CoV-2 has a natural origin

SARS-CoV-2 coronavirus

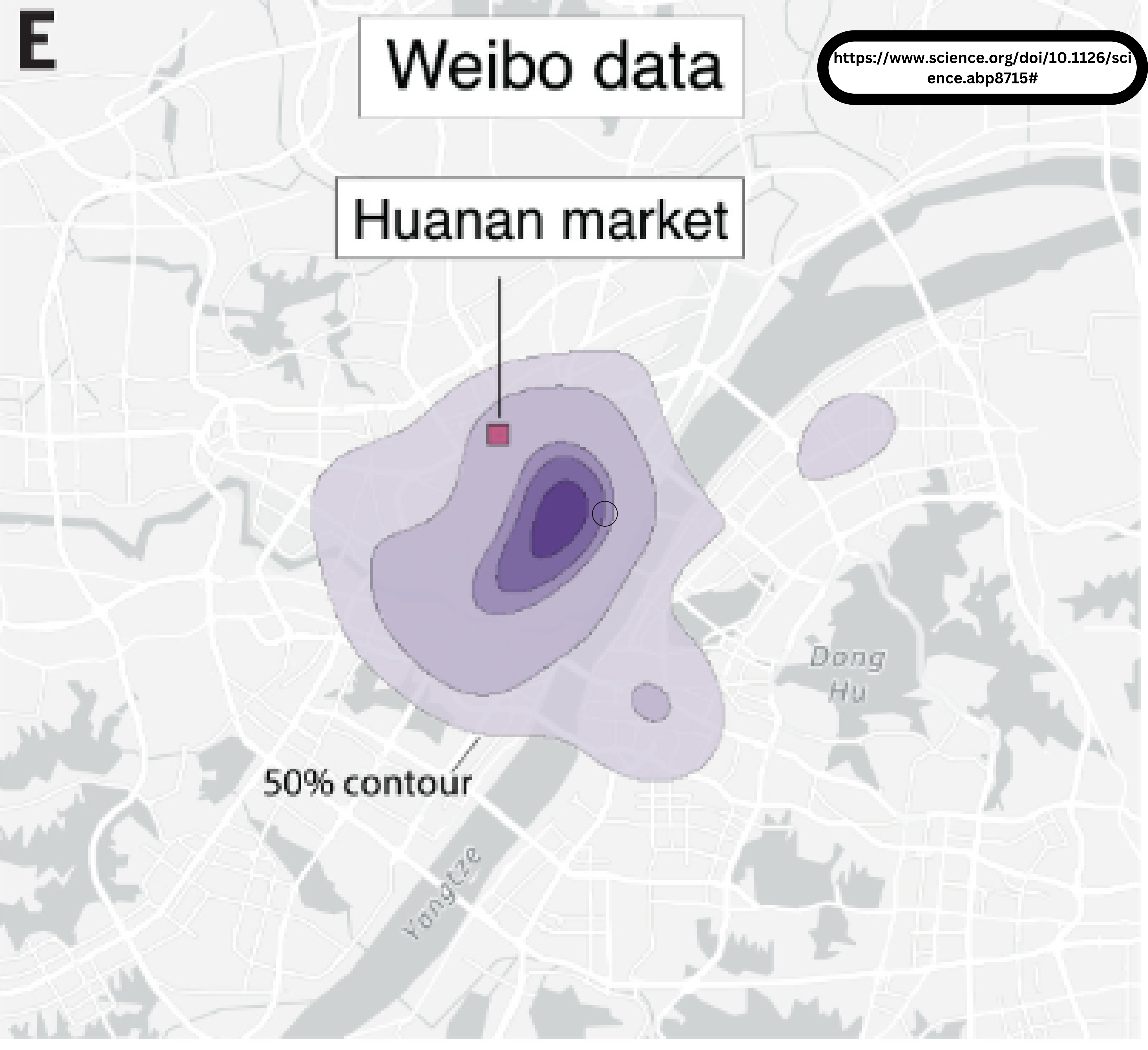
https://virological.org/t/early-appearance-of-two-distinct-genomic-lineages-of-sars-cov-2-in-different-wuhan-wildlife-markets-suggests-sars-cov-2-has-a-natural-origin/691

Unbiased Cases not Centered on HSM

When looking at the spread of reported cases on the Weibo social media platform, we can see they are not centered around the Huanan market, but instead correlate with population density.

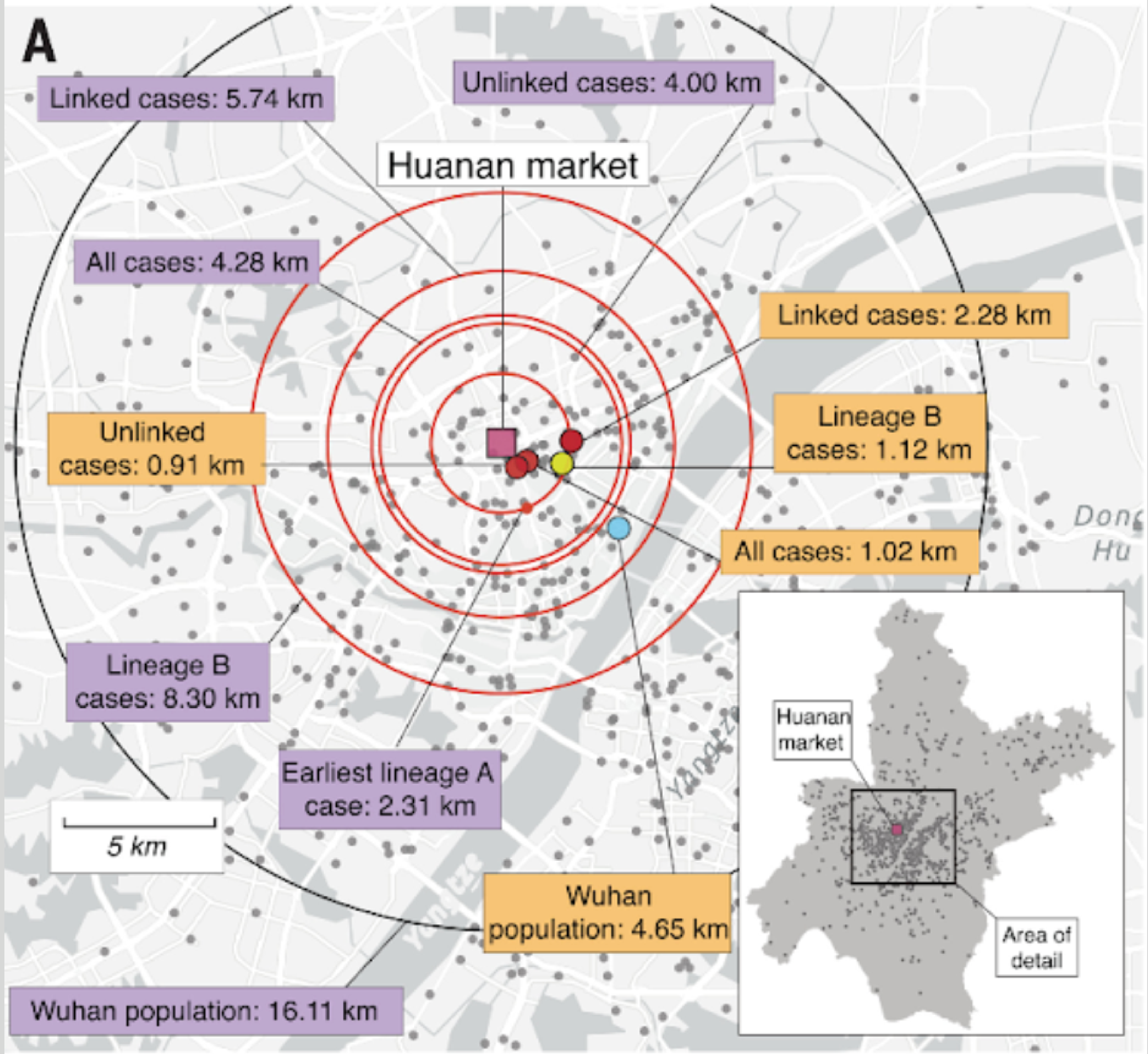


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8545724/



https://www.science.org/doi/10.1126/science.abp8715#

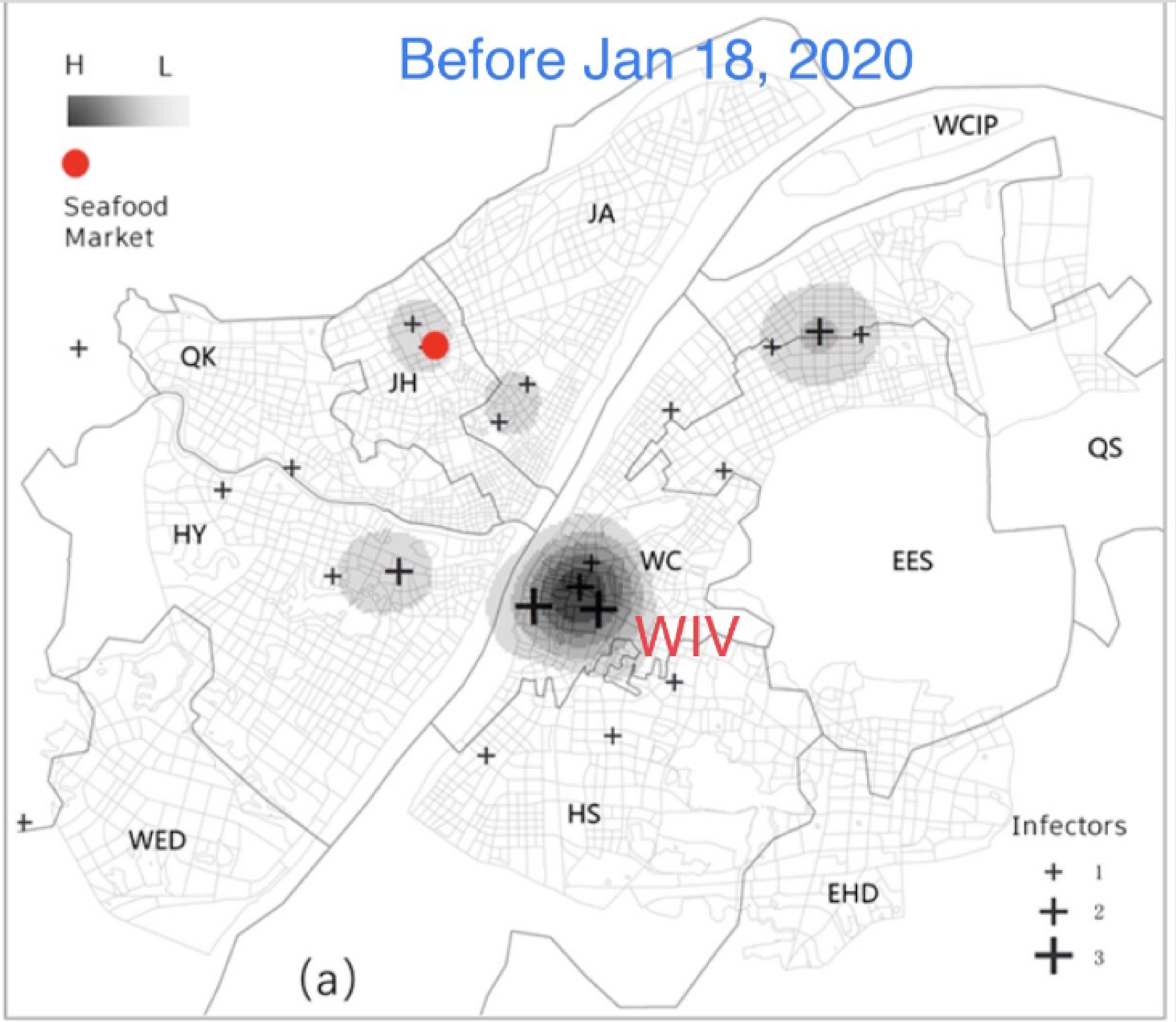
Unbiased Cases not Centered on HSM



Interesting to note the study did not show the population center in the Weibo data...

DOI: 10.1126/science.abp871

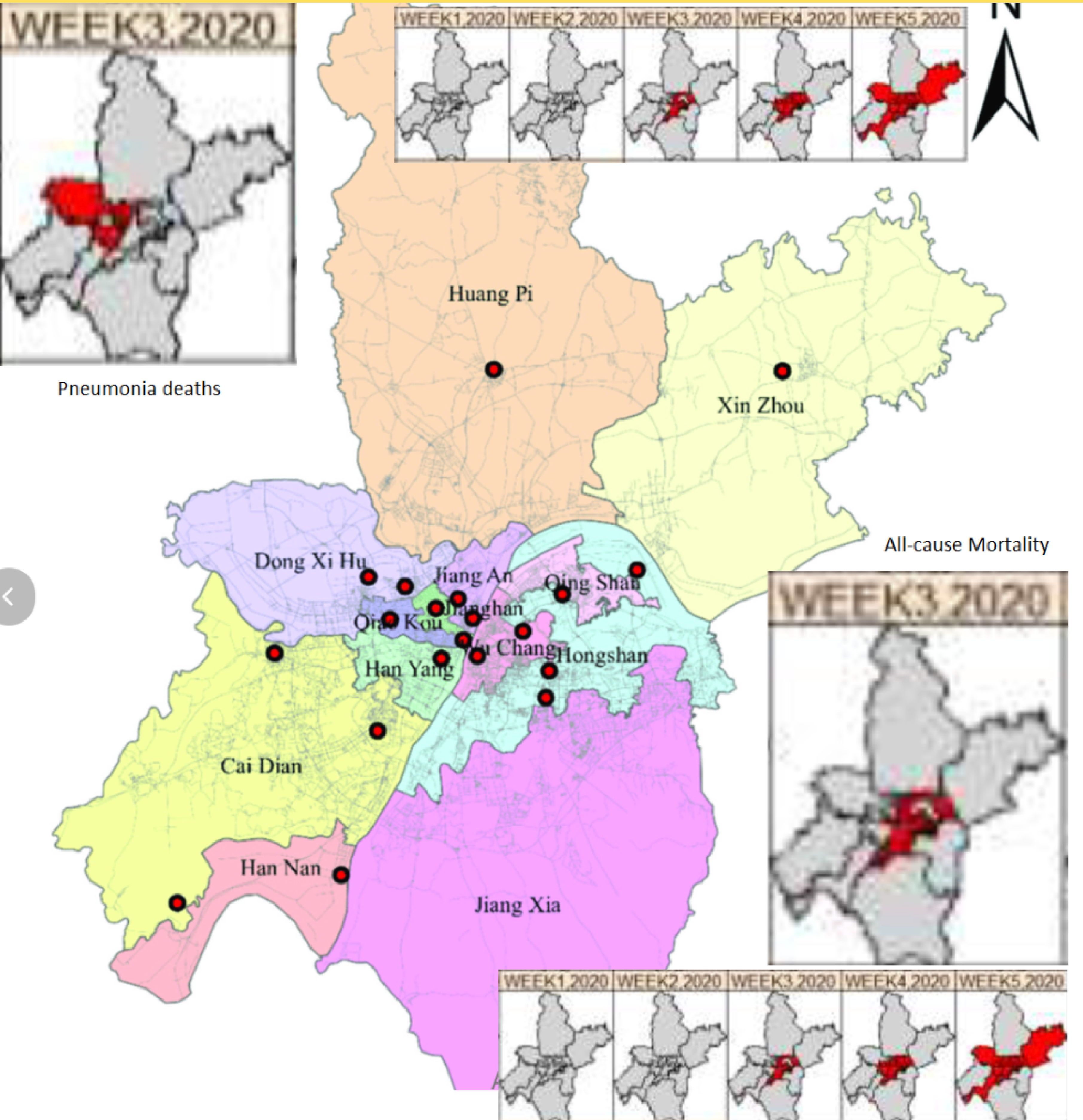
Unbiased Cases not Centered on HSM



In fact, when looking only at early Weibo reports, the epicenter is actually near the WIV. We think this is a coincidence as we don't really expect lab leak cases to center around a lab, but rather a location frequented by a lab worker. However, it demonstrates the risk of retrospective pattern matching.

https://www.mdpi.com/2220-9964/9/6/402/htm

Unbiased Cases not Centered on HSM



Deaths data (which lag behind cases 2-3 weeks) don’t show any bias towards the market district (Jianghan). All cause mortality is actually more dominant across the river, where WIV is located.

Source: Fig. 20 and 21 in WHO-convened global study of origins of SARS-CoV-2

Unbiased Cases not Centered on HSM

The district of the Huanan market actually showed lower seropositivity rates in April 2020, relative to neighboring districts.

Wuhan went into lockdown on 23rd January 2020, thus seropositivity is a good indication of early cases.

When looking at unbiased data - seropositivity, social networks, mortality - the bias to the market disappears.

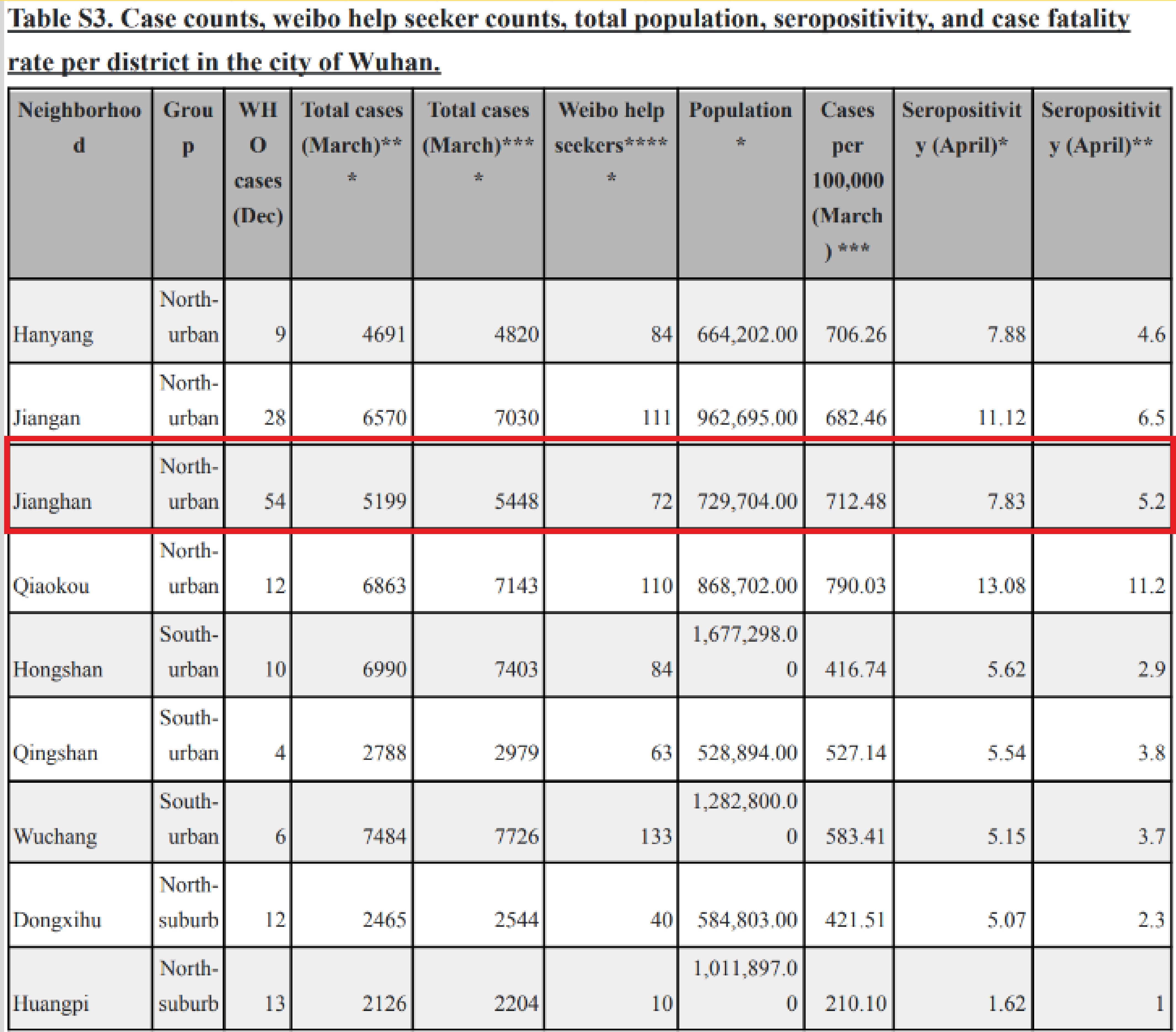
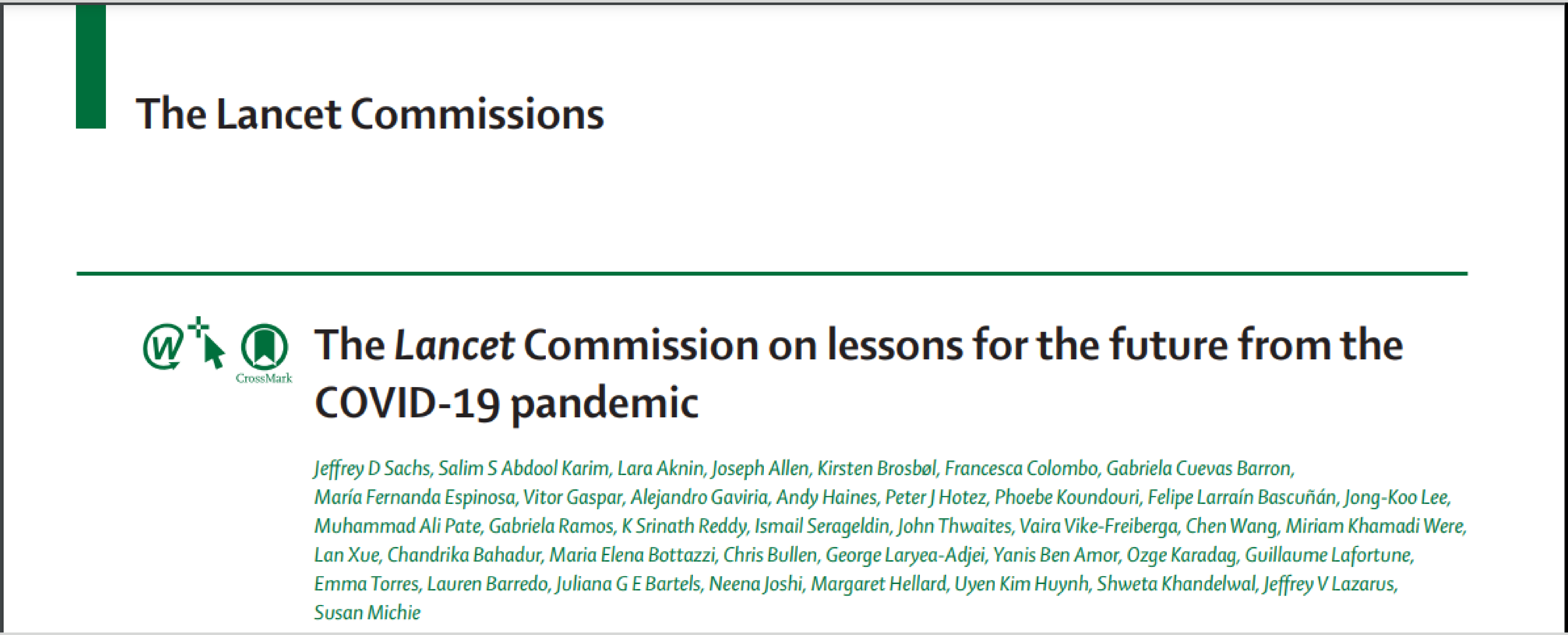


Table S3. Case counts, weibo help seeker counts, total population, seropositivity, and case fatality rate per district in the city of Wuhan.

Neighborhood	Group	WHO cases (Dec)	Total cases (March)***	Total cases (March)****	Weibo help seekers*****	Population*	Cases per 100,000 (March) ***	Seropositivity (April)*	Seropositivity (April)**
Hanyang	North-urban	9	4691	4820	84	664,202.00	706.26	7.88	4.6
Jiangan	North-urban	28	6570	7030	111	962,695.00	682.46	11.12	6.5
Jianghan	North-urban	54	5199	5448	72	729,704.00	712.48	7.83	5.2
Qiaokou	North-urban	12	6863	7143	110	868,702.00	790.03	13.08	11.2
Hongshan	South-urban	10	6990	7403	84	1,677,298.00	416.74	5.62	2.9
Qingshan	South-urban	4	2788	2979	63	528,894.00	527.14	5.54	3.8
Wuchang	South-urban	6	7484	7726	133	1,282,800.00	583.41	5.15	3.7
Dongxihu	North-suburb	12	2465	2544	40	584,803.00	421.51	5.07	2.3
Huangpi	North-suburb	13	2126	2204	10	1,011,897.00	210.10	1.62	1

No Positive Animals



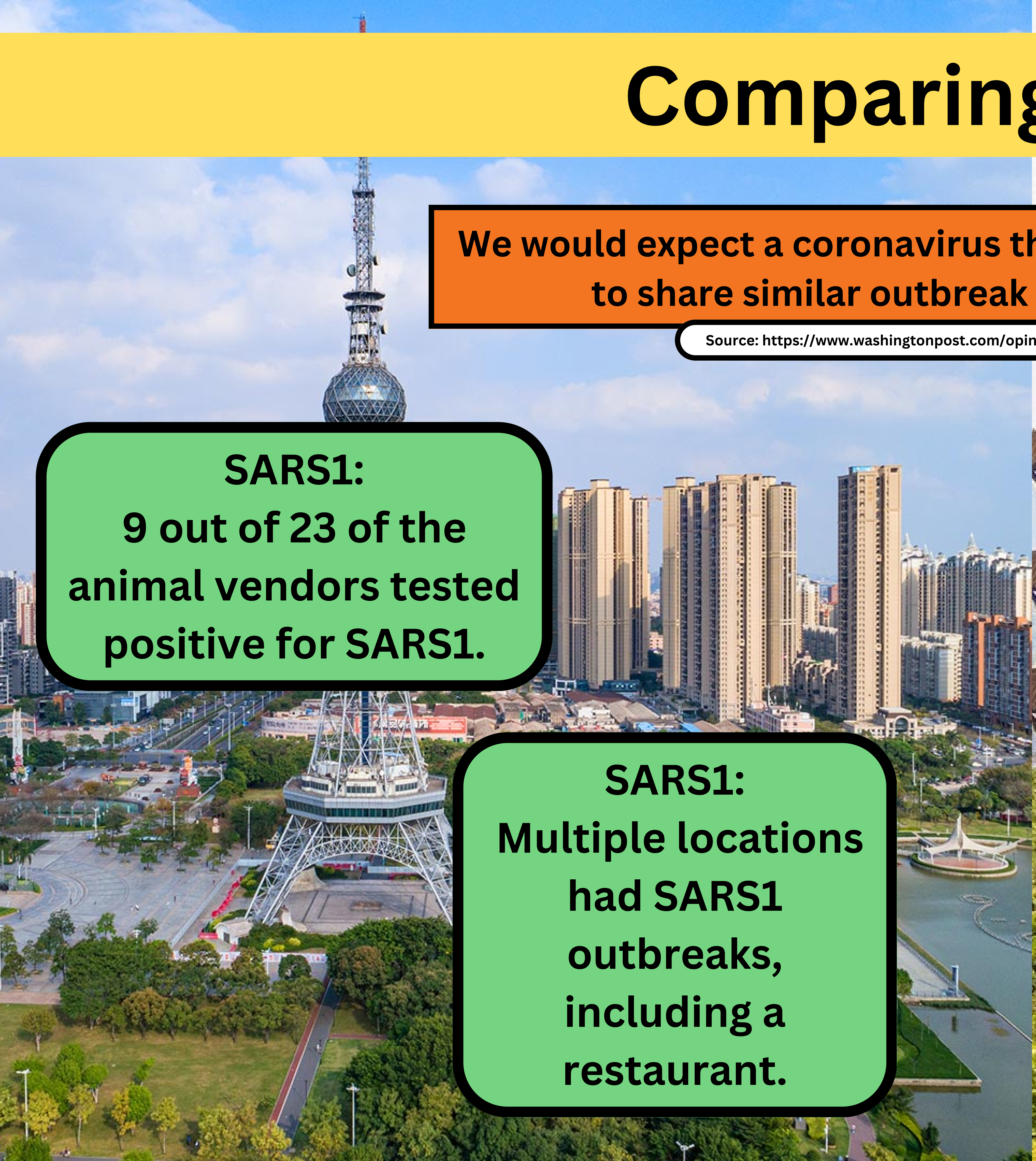
The Lancet Commissions

The *Lancet* Commission on lessons for the future from the COVID-19 pandemic

Jeffrey D Sachs, Salim S Abdool Karim, Lara Aknin, Joseph Allen, Kirsten Brosbøl, Francesca Colombo, Gabriela Cuevas Barron, María Fernanda Espinosa, Vitor Gaspar, Alejandro Gaviria, Andy Haines, Peter J Hotez, Phoebe Koundouri, Felipe Larraín Bascuñán, Jong-Koo Lee, Muhammad Ali Pate, Gabriela Ramos, K Srinath Reddy, Ismail Serageldin, John Thwaites, Vaira Vike-Freiberga, Chen Wang, Miriam Khamadi Were, Lan Xue, Chandrika Bahadur, Maria Elena Bottazzi, Chris Bullen, George Laryea-Adjei, Yanis Ben Amor, Ozge Karadag, Guillaume Lafortune, Emma Torres, Lauren Barredo, Juliana G E Bartels, Neena Joshi, Margaret Hellard, Uyen Kim Huynh, Shweta Khandelwal, Jeffrey V Lazarus, Susan Michie

"Despite the testing of more than 80000 samples from a range of wild and farm animal species in China collected between 2015 and March, 2020, no cases of SARS-CoV-2 infection have been identified".

Comparing to SARS1



We would expect a coronavirus that also originated from a market to share similar outbreak characteristics to SARS1.

Source: https://www.washingtonpost.com/opinions/2023/03/02/china-covid-origins-answer/

SARS1:
9 out of 23 of the animal vendors tested positive for SARS1.

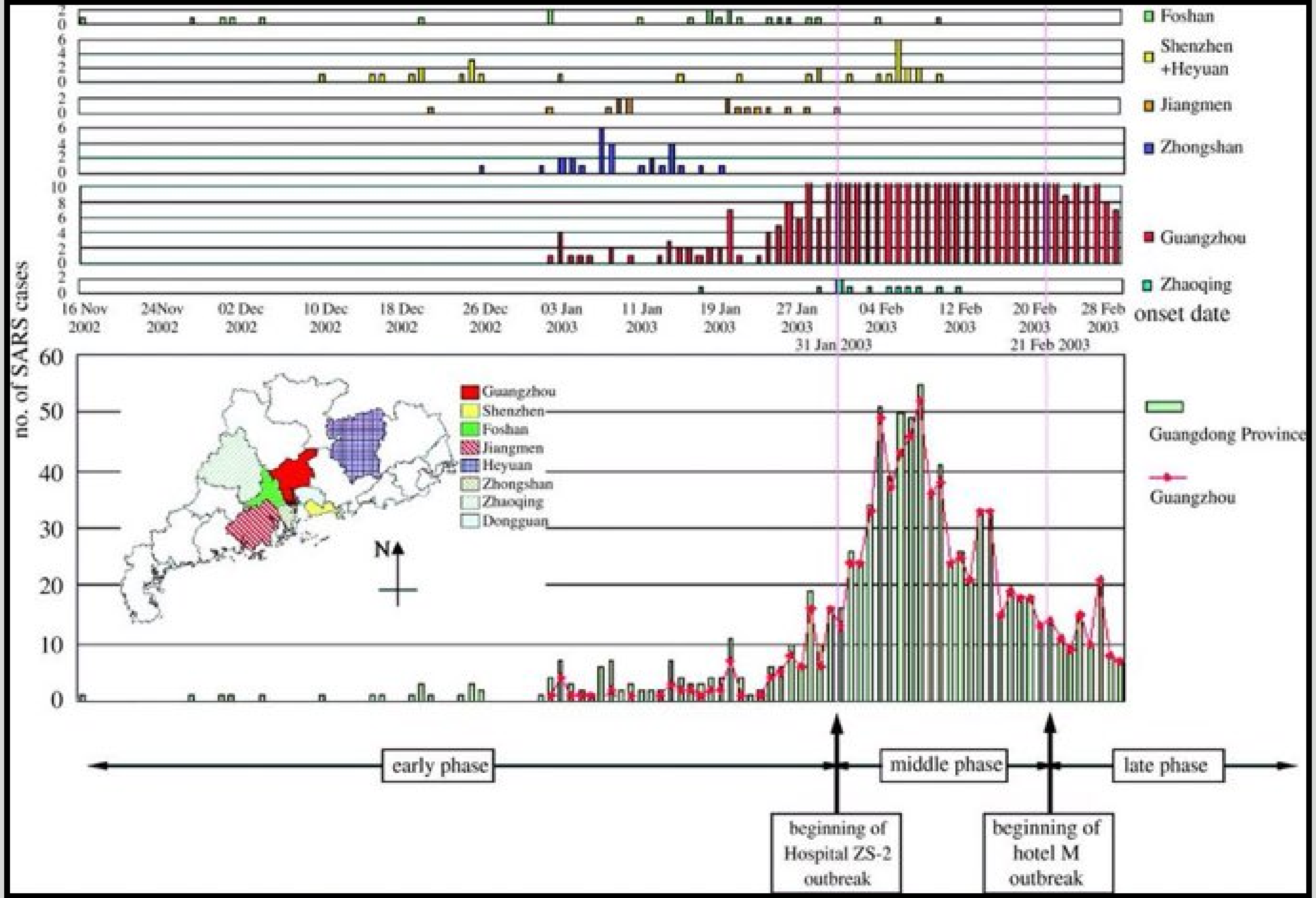
SARS2:
None of the animal vendors tested positive for SARS2.

SARS1:
Multiple locations had SARS1 outbreaks, including a restaurant.

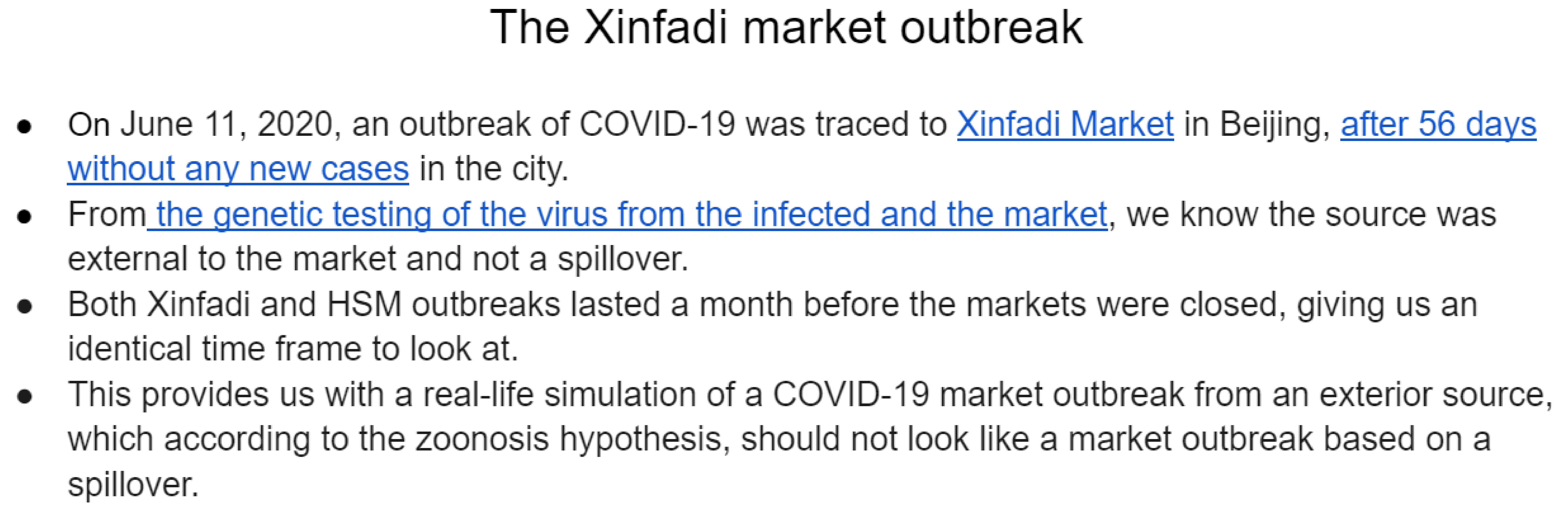
SARS2:
All other outbreaks were connected to the original outbreak in Wuhan.

Comparing to SARS1

SARS Infections Over Time



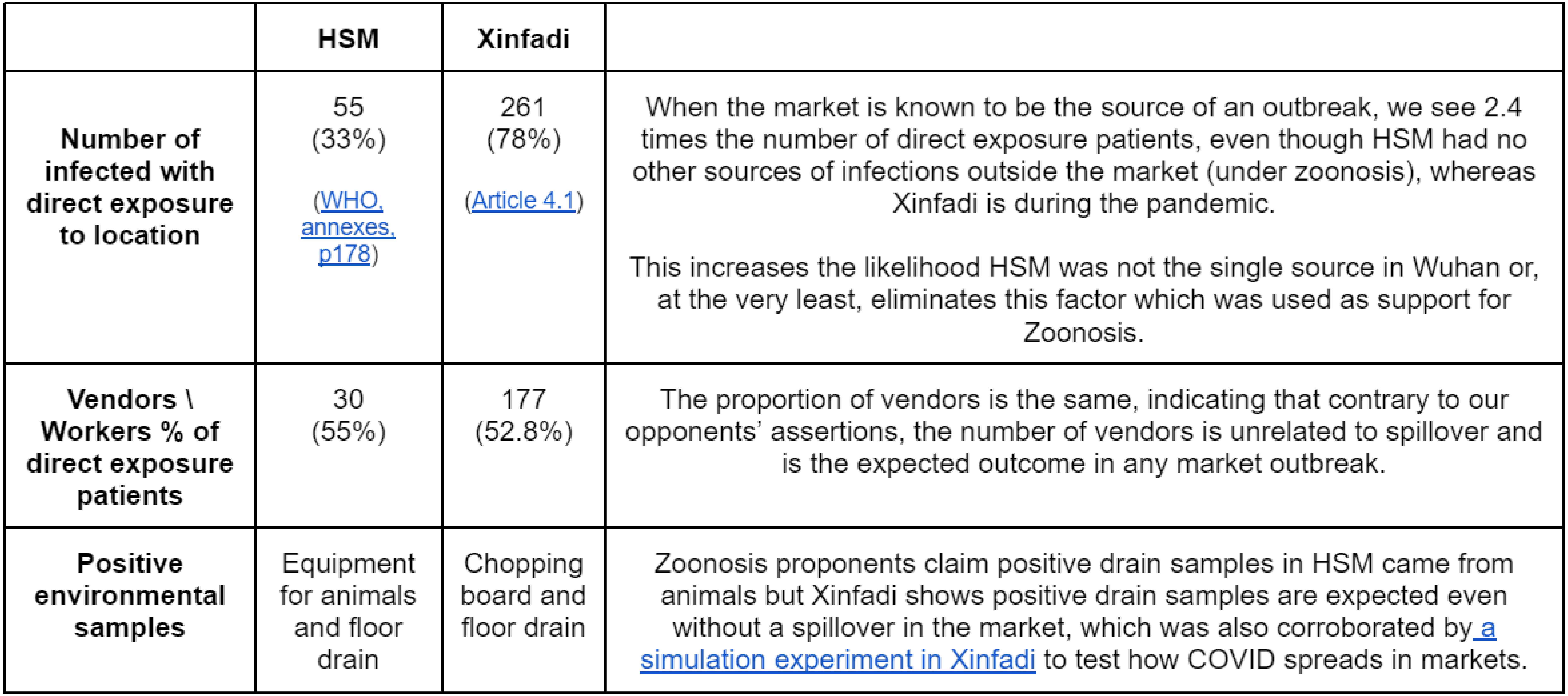
Comparing to Xinfadi



The Xinfadi market outbreak

- On June 11, 2020, an outbreak of COVID-19 was traced to Xinfadi Market in Beijing, after 56 days without any new cases in the city.
- From the genetic testing of the virus from the infected and the market, we know the source was external to the market and not a spillover.
- Both Xinfadi and HSM outbreaks lasted a month before the markets were closed, giving us an identical time frame to look at.
- This provides us with a real-life simulation of a COVID-19 market outbreak from an exterior source, which according to the zoonosis hypothesis, should not look like a market outbreak based on a spillover.

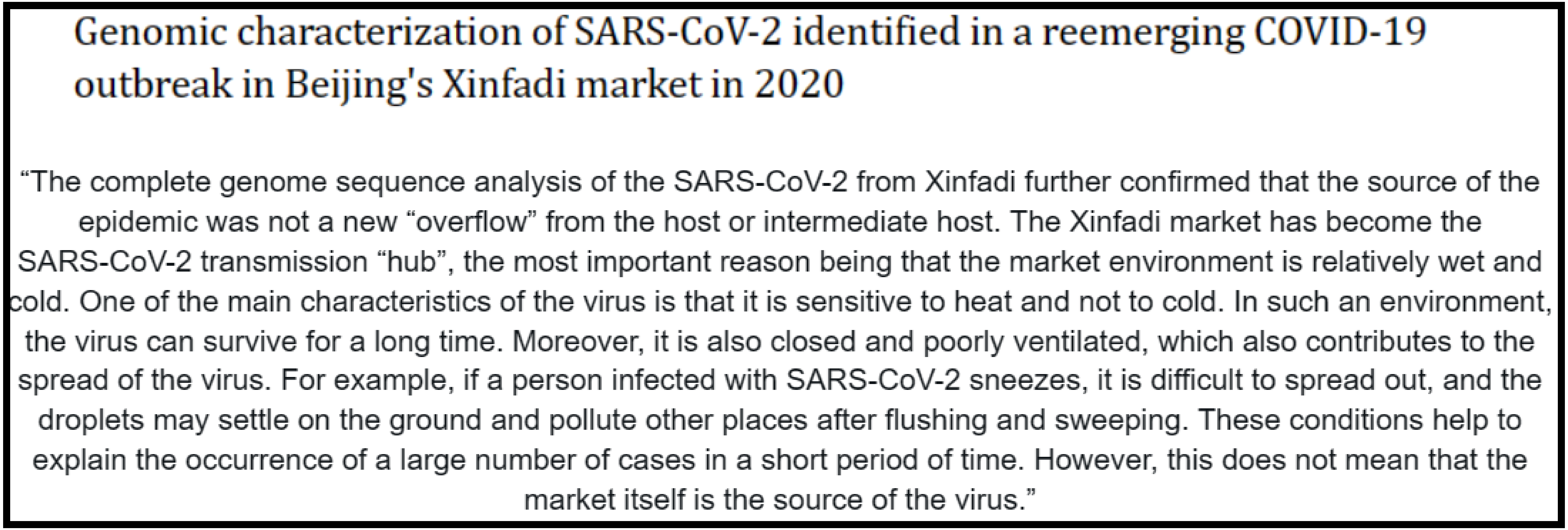
Comparing to Xinfadi



	HSM	Xinfadi	
Number of infected with direct exposure to location	55 (33%) (WHO, annexes, p178)	261 (78%) (Article 4.1)	When the market is known to be the source of an outbreak, we see 2.4 times the number of direct exposure patients, even though HSM had no other sources of infections outside the market (under zoonosis), whereas Xinfadi is during the pandemic. This increases the likelihood HSM was not the single source in Wuhan or, at the very least, eliminates this factor which was used as support for Zoonosis.
Vendors \ Workers % of direct exposure patients	30 (55%)	177 (52.8%)	The proportion of vendors is the same, indicating that contrary to our opponents' assertions, the number of vendors is unrelated to spillover and is the expected outcome in any market outbreak.
Positive environmental samples	Equipment for animals and floor drain	Chopping board and floor drain	Zoonosis proponents claim positive drain samples in HSM came from animals but Xinfadi shows positive drain samples are expected even without a spillover in the market, which was also corroborated by a simulation experiment in Xinfadi to test how COVID spreads in markets.

Comparing to Xinfadi

Papers describing how Xinfadi became such a large outbreak point to the same conditions that existed in HSM and most markets

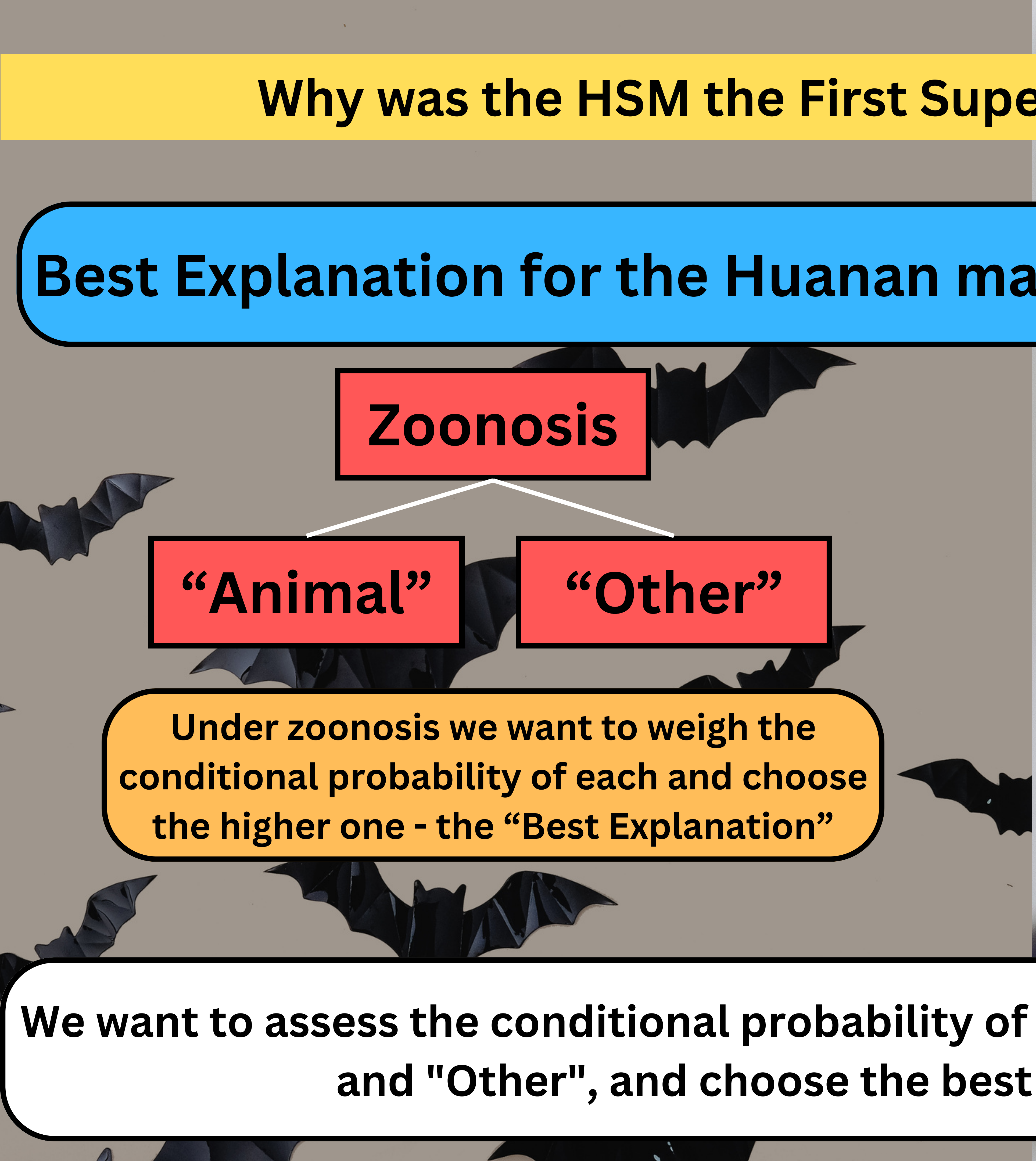


Genomic characterization of SARS-CoV-2 identified in a reemerging COVID-19 outbreak in Beijing's Xinfadi market in 2020

"The complete genome sequence analysis of the SARS-CoV-2 from Xinfadi further confirmed that the source of the epidemic was not a new "overflow" from the host or intermediate host. The Xinfadi market has become the SARS-CoV-2 transmission "hub", the most important reason being that the market environment is relatively wet and cold. One of the main characteristics of the virus is that it is sensitive to heat and not to cold. In such an environment, the virus can survive for a long time. Moreover, it is also closed and poorly ventilated, which also contributes to the spread of the virus. For example, if a person infected with SARS-CoV-2 sneezes, it is difficult to spread out, and the droplets may settle on the ground and pollute other places after flushing and sweeping. These conditions help to explain the occurrence of a large number of cases in a short period of time. However, this does not mean that the market itself is the source of the virus."

Why was the HSM the First Superspreader Event to be Noticed?

Best Explanation for the Huanan market being the first location noticed

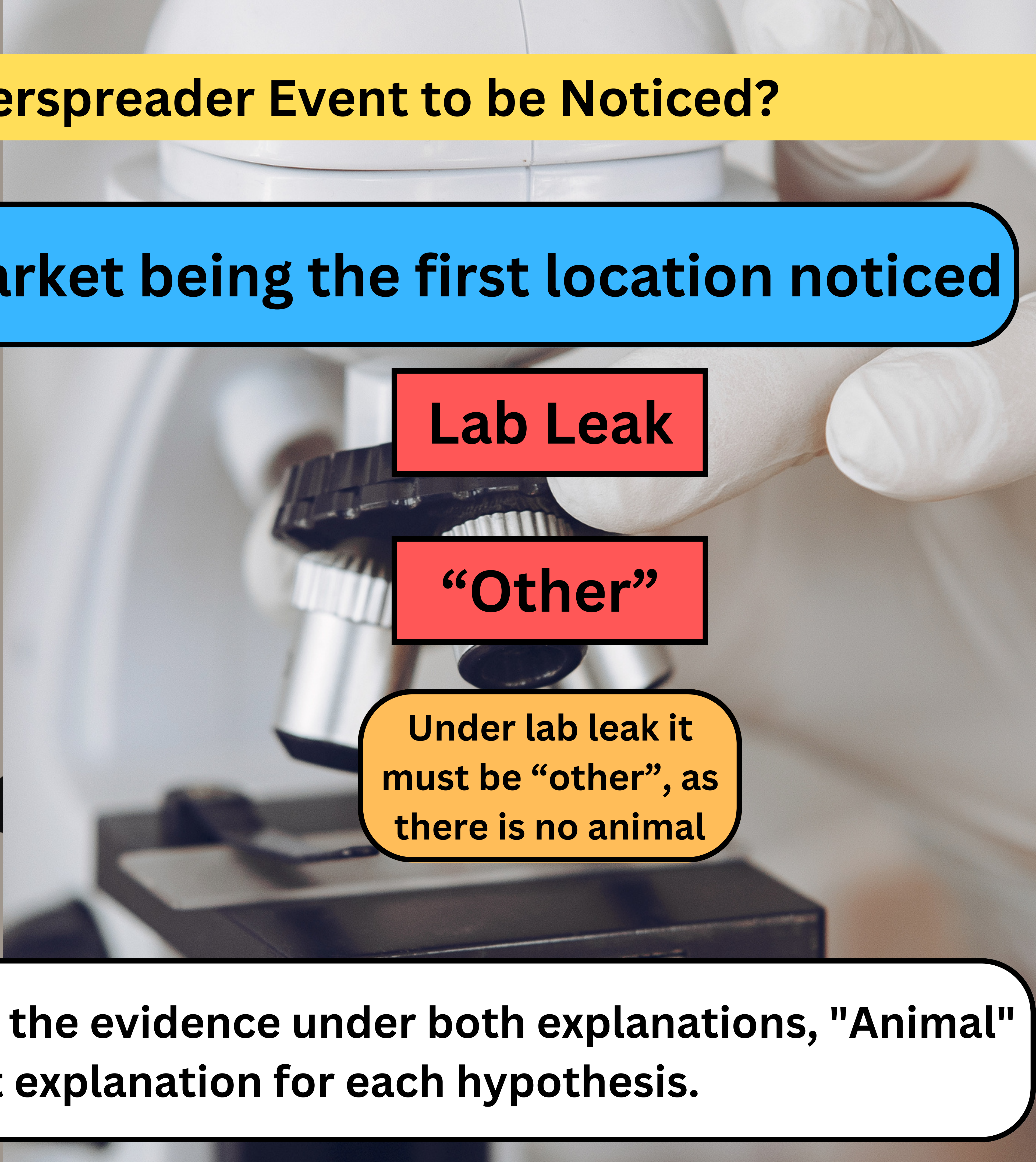


Zoonosis

“Animal”

“Other”

Under zoonosis we want to weigh the conditional probability of each and choose the higher one - the “Best Explanation”

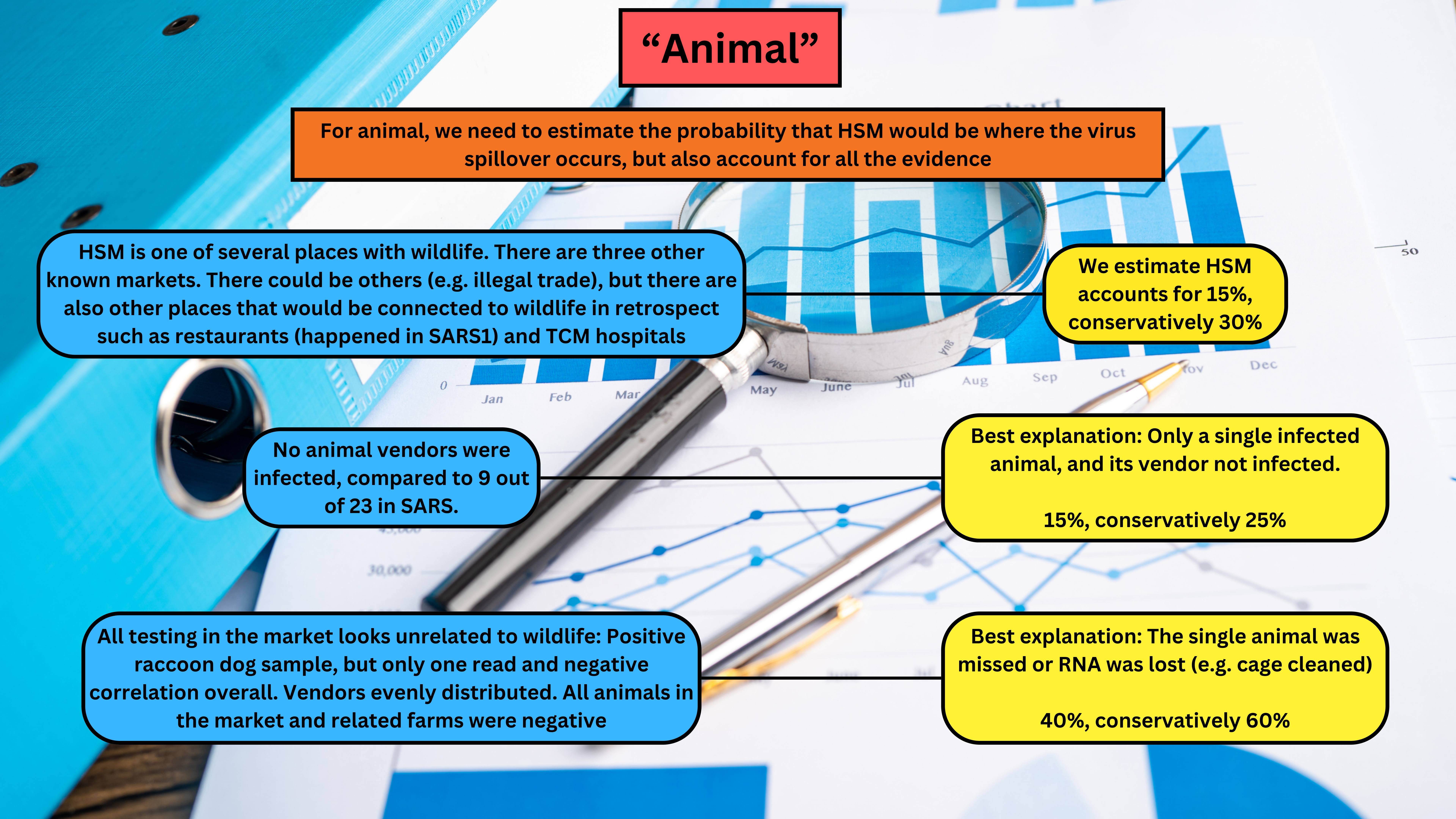


Lab Leak

“Other”

Under lab leak it must be “other”, as there is no animal

We want to assess the conditional probability of the evidence under both explanations, "Animal" and "Other", and choose the best explanation for each hypothesis.



“Animal”

For animal, we need to estimate the probability that HSM would be where the virus spillover occurs, but also account for all the evidence

HSM is one of several places with wildlife. There are three other known markets. There could be others (e.g. illegal trade), but there are also other places that would be connected to wildlife in retrospect such as restaurants (happened in SARS1) and TCM hospitals

We estimate HSM accounts for 15%, conservatively 30%

No animal vendors were infected, compared to 9 out of 23 in SARS.

Best explanation: Only a single infected animal, and its vendor not infected.

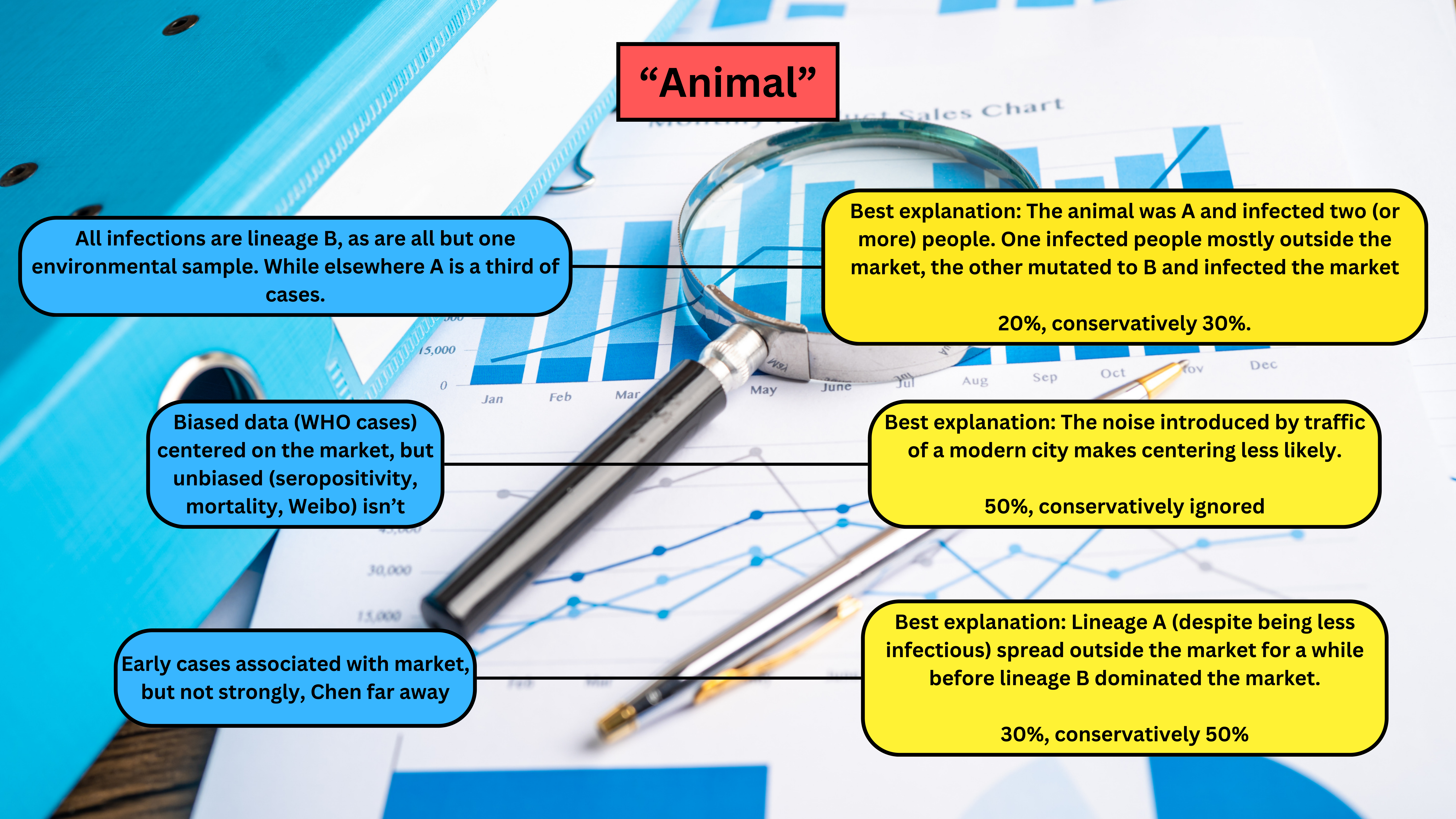
15%, conservatively 25%

All testing in the market looks unrelated to wildlife: Positive raccoon dog sample, but only one read and negative correlation overall. Vendors evenly distributed. All animals in the market and related farms were negative

Best explanation: The single animal was missed or RNA was lost (e.g. cage cleaned)

40%, conservatively 60%

“Animal”



All infections are lineage B, as are all but one environmental sample. While elsewhere A is a third of cases.

Best explanation: The animal was A and infected two (or more) people. One infected people mostly outside the market, the other mutated to B and infected the market

20%, conservatively 30%.

Biased data (WHO cases) centered on the market, but unbiased (seropositivity, mortality, Weibo) isn’t

Best explanation: The noise introduced by traffic of a modern city makes centering less likely.

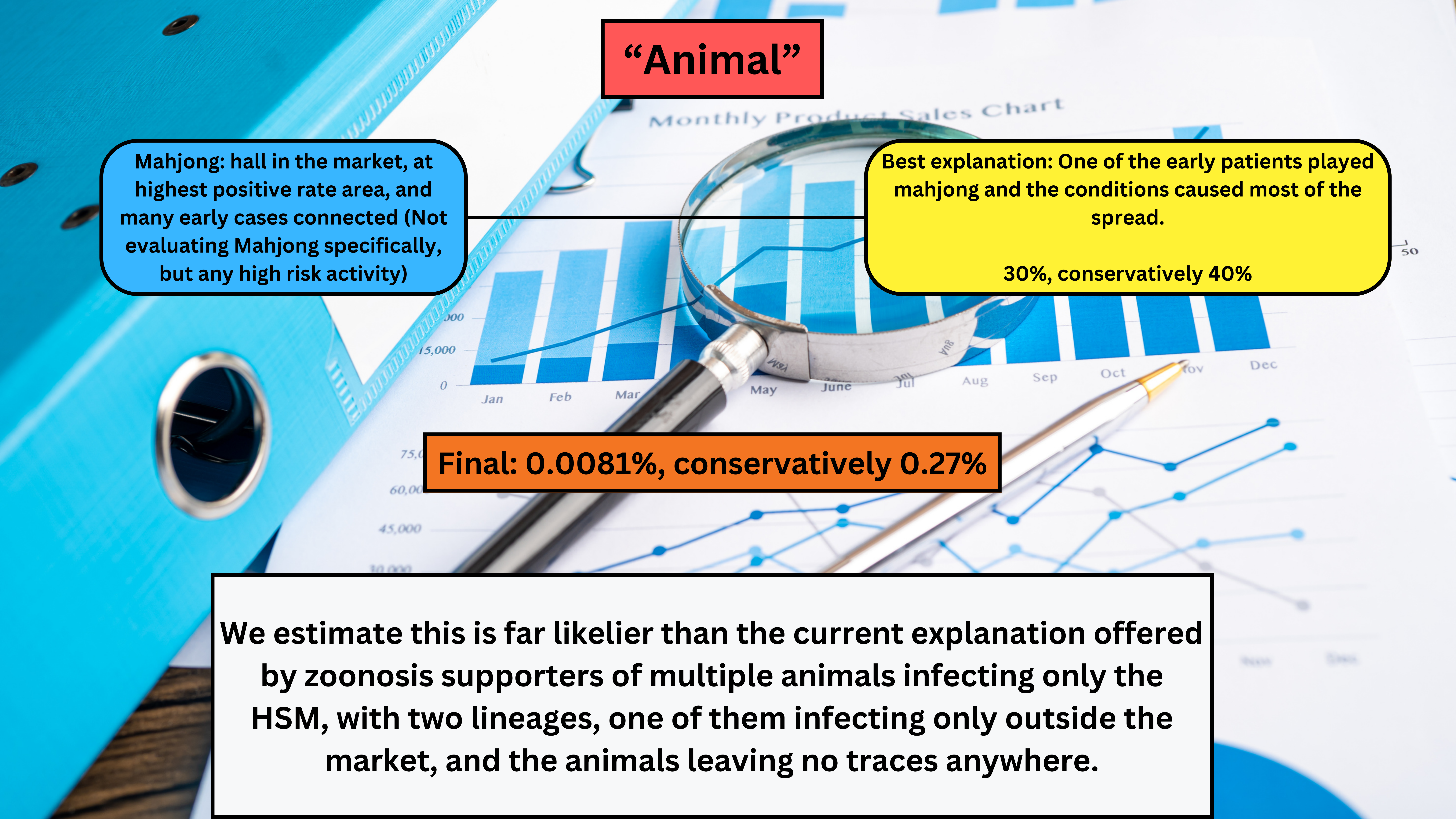
50%, conservatively ignored

Early cases associated with market, but not strongly, Chen far away

Best explanation: Lineage A (despite being less infectious) spread outside the market for a while before lineage B dominated the market.

30%, conservatively 50%

"Animal"



Mahjong: hall in the market, at highest positive rate area, and many early cases connected (Not evaluating Mahjong specifically, but any high risk activity)

Best explanation: One of the early patients played mahjong and the conditions caused most of the spread.

30%, conservatively 40%

Final: 0.0081%, conservatively 0.27%

We estimate this is far likelier than the current explanation offered by zoonosis supporters of multiple animals infecting only the HSM, with two lineages, one of them infecting only outside the market, and the animals leaving no traces anywhere.

“Other”

For other, we need to estimate the probability of the coincidence of HSM being the first place noticed, which is not strong as claimed, because:

How likely is the infected lab worker (or their close contact) to visit HSM? HSM has more traffic than claimed by check-ins: 10000/d

0.1% of population (assuming people visit one place a day where they’re likely to infect others), conservatively 0.05%

Location that can become a superspreader location. Ideally has:

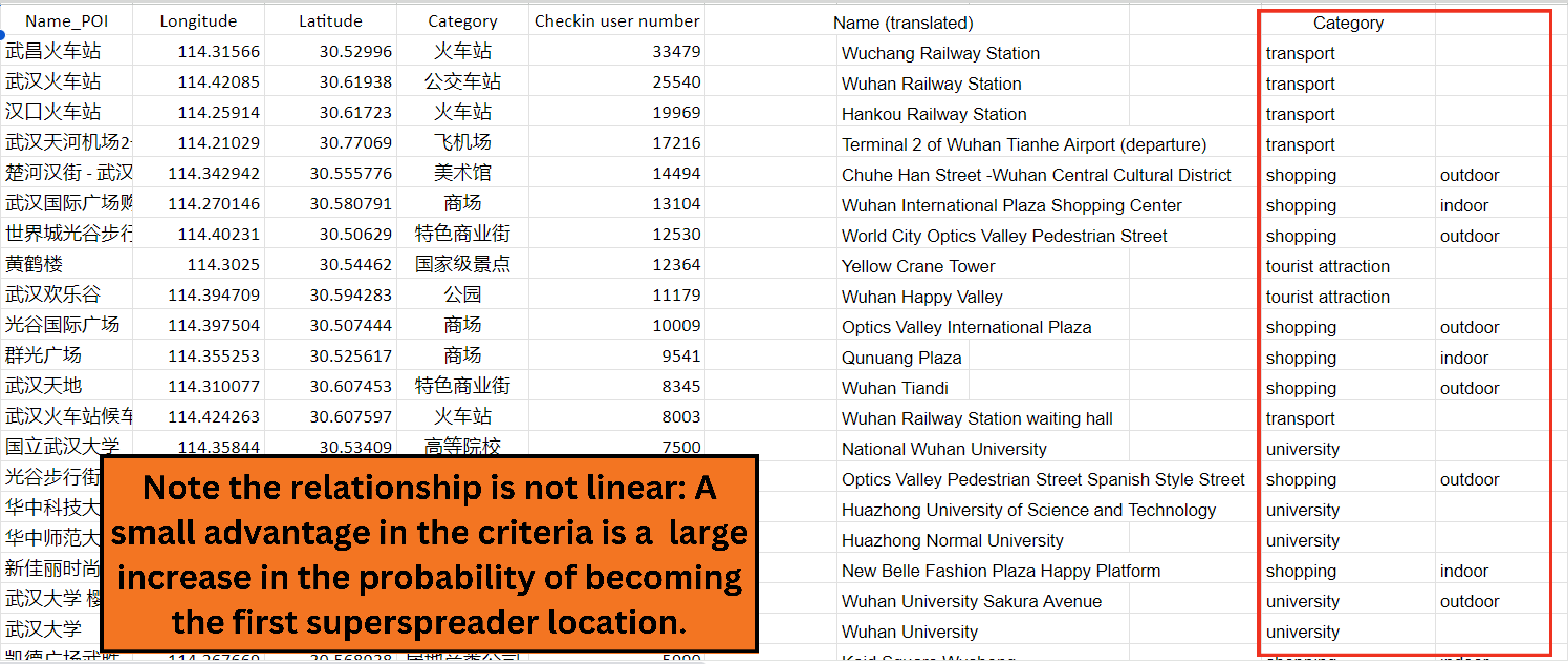
1. High traffic - to bring the virus in when it is still rare (already accounted for above)
2. Permanent residents - to amplify the virus locally. Without this (e.g. a train station) the location just serves to amplify the virus all over the city
3. Enclosed, poor ventilation.

Few places have all three.

- Of the top 20 Weibo check-in locations (where HSM is 1,676th), 6 are shopping areas, mostly outdoor, 5 are universities, 5 are transportation hubs, and 1 is a commercial building. None of these are as susceptible as HSM. The indoor malls are close, but are likely far better ventilated, and involve less close interaction among the permanent residents.
- Interestingly, the next superspreader event after lockdowns was also a market (Xinfadi wholesale agricultural market), demonstrating it is a likely location regardless of wildlife.

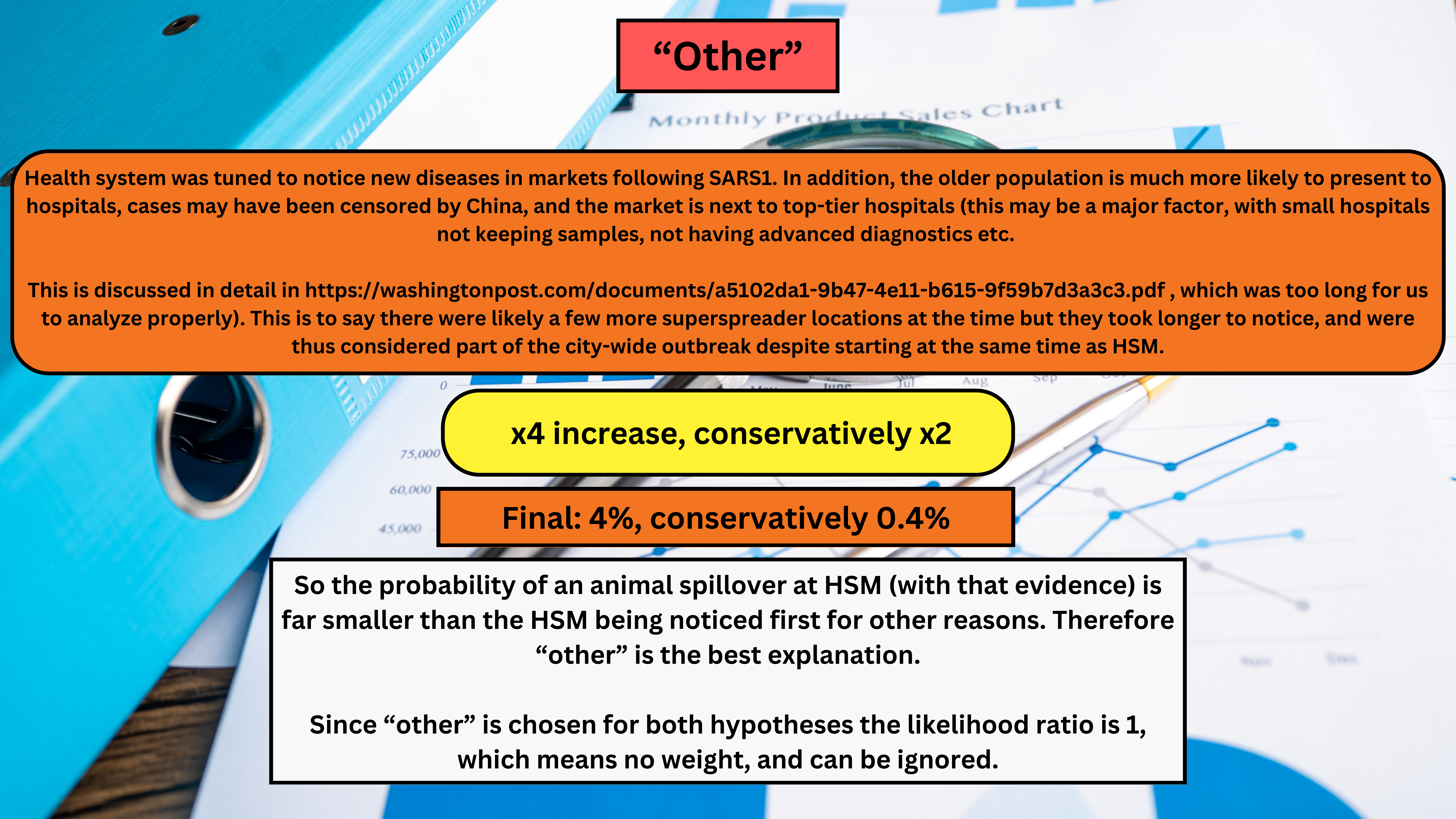
x10 increase, conservatively x4

Check-ins Analysis: The market has high superspreader location potential



Name_POI	Longitude	Latitude	Category	Checkin user number	Name (translated)	Category	
武昌火车站	114.31566	30.52996	火车站	33479	Wuchang Railway Station	transport	
武汉火车站	114.42085	30.61938	公交车站	25540	Wuhan Railway Station	transport	
汉口火车站	114.25914	30.61723	火车站	19969	Hankou Railway Station	transport	
武汉天河机场2	114.21029	30.77069	飞机场	17216	Terminal 2 of Wuhan Tianhe Airport (departure)	transport	
楚河汉街 - 武汉	114.342942	30.555776	美术馆	14494	Chuhe Han Street -Wuhan Central Cultural District	shopping	outdoor
武汉国际广场	114.270146	30.580791	商场	13104	Wuhan International Plaza Shopping Center	shopping	indoor
世界城光谷步	114.40231	30.50629	特色商业街	12530	World City Optics Valley Pedestrian Street	shopping	outdoor
黄鹤楼	114.3025	30.54462	国家级景点	12364	Yellow Crane Tower	tourist attraction	
武汉欢乐谷	114.394709	30.594283	公园	11179	Wuhan Happy Valley	tourist attraction	
光谷国际广场	114.397504	30.507444	商场	10009	Optics Valley International Plaza	shopping	outdoor
群光广场	114.355253	30.525617	商场	9541	Qunuang Plaza	shopping	indoor
武汉天地	114.310077	30.607453	特色商业街	8345	Wuhan Tiandi	shopping	outdoor
武汉火车站候	114.424263	30.607597	火车站	8003	Wuhan Railway Station waiting hall	transport	
国立武汉大学	114.35844	30.53409	高等院校	7500	National Wuhan University	university	
光谷步行街					Optics Valley Pedestrian Street Spanish Style Street	shopping	outdoor
华中科技大					Huazhong University of Science and Technology	university	
华中师范大					Huazhong Normal University	university	
新佳丽时尚					New Belle Fashion Plaza Happy Platform	shopping	indoor
武汉大学					Wuhan University Sakura Avenue	university	outdoor
武汉大学					Wuhan University	university	

Note the relationship is not linear: A small advantage in the criteria is a large increase in the probability of becoming the first superspreader location.



“Other”

Health system was tuned to notice new diseases in markets following SARS1. In addition, the older population is much more likely to present to hospitals, cases may have been censored by China, and the market is next to top-tier hospitals (this may be a major factor, with small hospitals not keeping samples, not having advanced diagnostics etc.

This is discussed in detail in https://washingtonpost.com/documents/a5102da1-9b47-4e11-b615-9f59b7d3a3c3.pdf , which was too long for us to analyze properly). This is to say there were likely a few more superspreader locations at the time but they took longer to notice, and were thus considered part of the city-wide outbreak despite starting at the same time as HSM.

x4 increase, conservatively x2

Final: 4%, conservatively 0.4%

So the probability of an animal spillover at HSM (with that evidence) is far smaller than the HSM being noticed first for other reasons. Therefore “other” is the best explanation.

Since “other” is chosen for both hypotheses the likelihood ratio is 1, which means no weight, and can be ignored.

The Mahjong Halls Hypothesis

While all the evidence points against the market being the epicenter, it is true that it was the earliest superspreader event to be noticed. The HSM Mahjong hall explains this while matching the evidence far better than the wildlife hypothesis.

- Mahjong rooms are perfect:
  - Crowded
  - Unventilated
  - Older population
  - Repeat visitors
    - Allow for an exponential growth within that population, even when the overall infection rate is low.

- The disease initially spread through Mahjong rooms in Wuhan.
- The room in the HSM was especially susceptible due to its high density location near a major train station.
- From there it spread to the vendors and the entire HSM, due to similar reasons.
- The HSM was then noticed early due to bias from SARS1, and proximity to top tier hospitals.

Mahjong Hall Early Cases Evidence

"I heard that four people were playing at one table, and all four got sick" source

"had heard about [..] some mah-jongg infections" source

" most of the 27 infected people first reported by the government[56] had a common hobby - they like to play maahjong." source

"a friend of mine is in the hospital with it. [..] He thinks he might have got it while playing mahjong, reckons the air in the room was stuffy, a lot of people in there." source

"heard on the morning of December 31 that three store owners who often played mahjong at stalls near 10th Street were hospitalized two days ago.He sent WeChat greetings to one of the bosses, who replied "infected with the virus"." source

"The owner of the shop was a man in his 40s and 50s who usually likes to stay up late and play mahjong. Recently, he "didn't care" after catching a cold. He didn't go to the doctor at first. After a few days, he found that his condition was getting worse before going to the hospital. He was eventually diagnosed with pneumonia." source

"Our boss was sick on December 19 (2019), sick before playing mahjong with a player who sells frozen chicken and frozen duck, who was also admitted to hospital for pneumonia." source

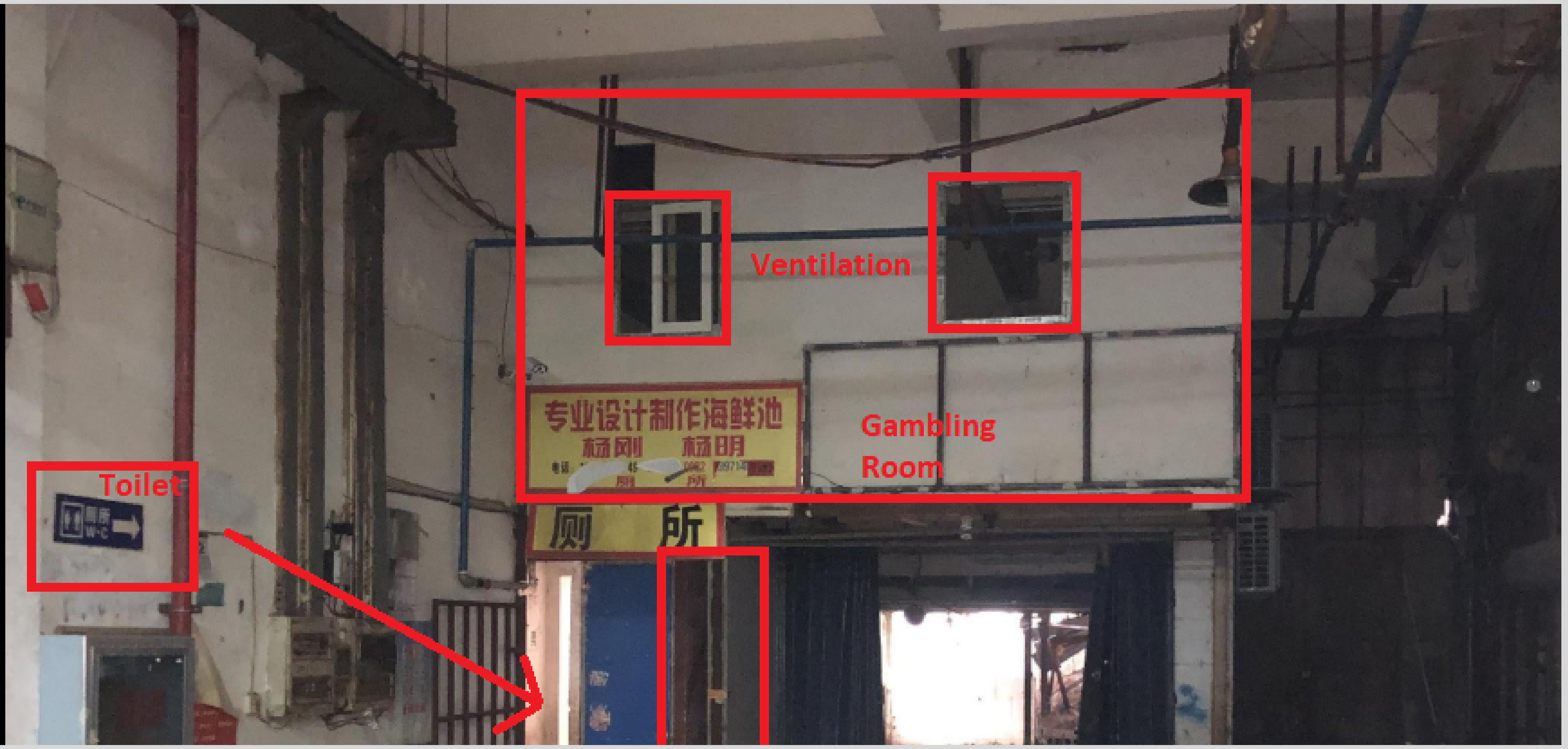
"At the end of December, we had already judged that this infectious virus was related to the South China Seafood Market because most of their patients knew each other. [..] They are either a family or people who play mahjong together." source

Testimonies from 8 people, collected by Chinese & Western media, include people working in HSM, a Wuhan journalist and the head of the respiratory department at Jinyintan hospital. Together, they say more than 35 early HSM cases were among Mahjong players.

The Mahjong Halls Hypothesis

Location

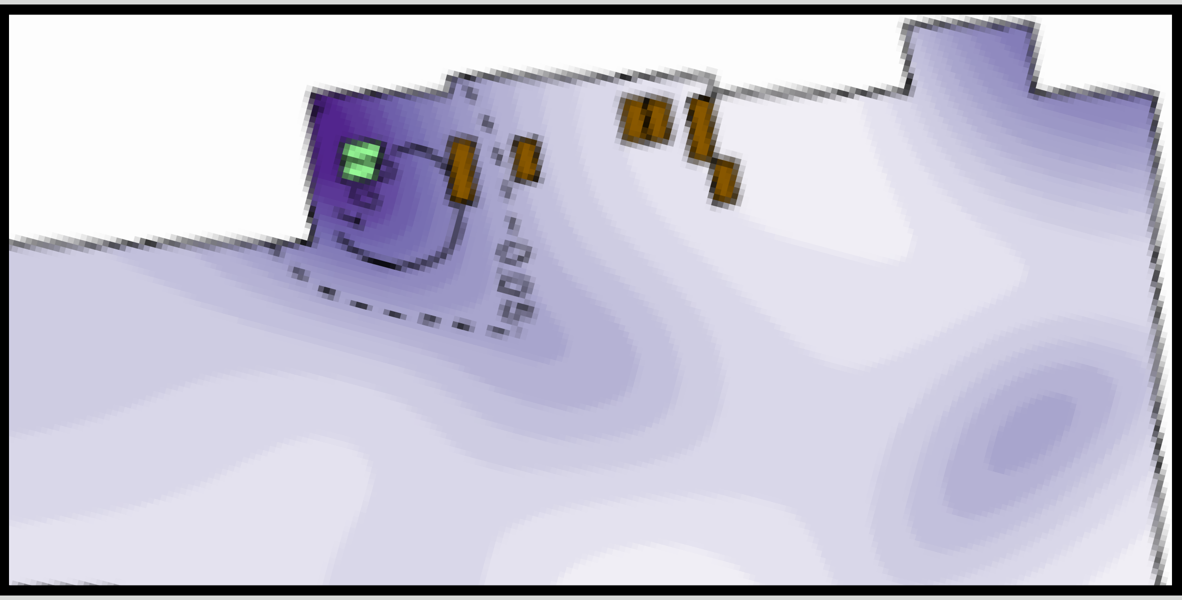
The Majhong Hall was located in a small corner of the market, in a closed space - next to the public bathrooms of the Huanan Market



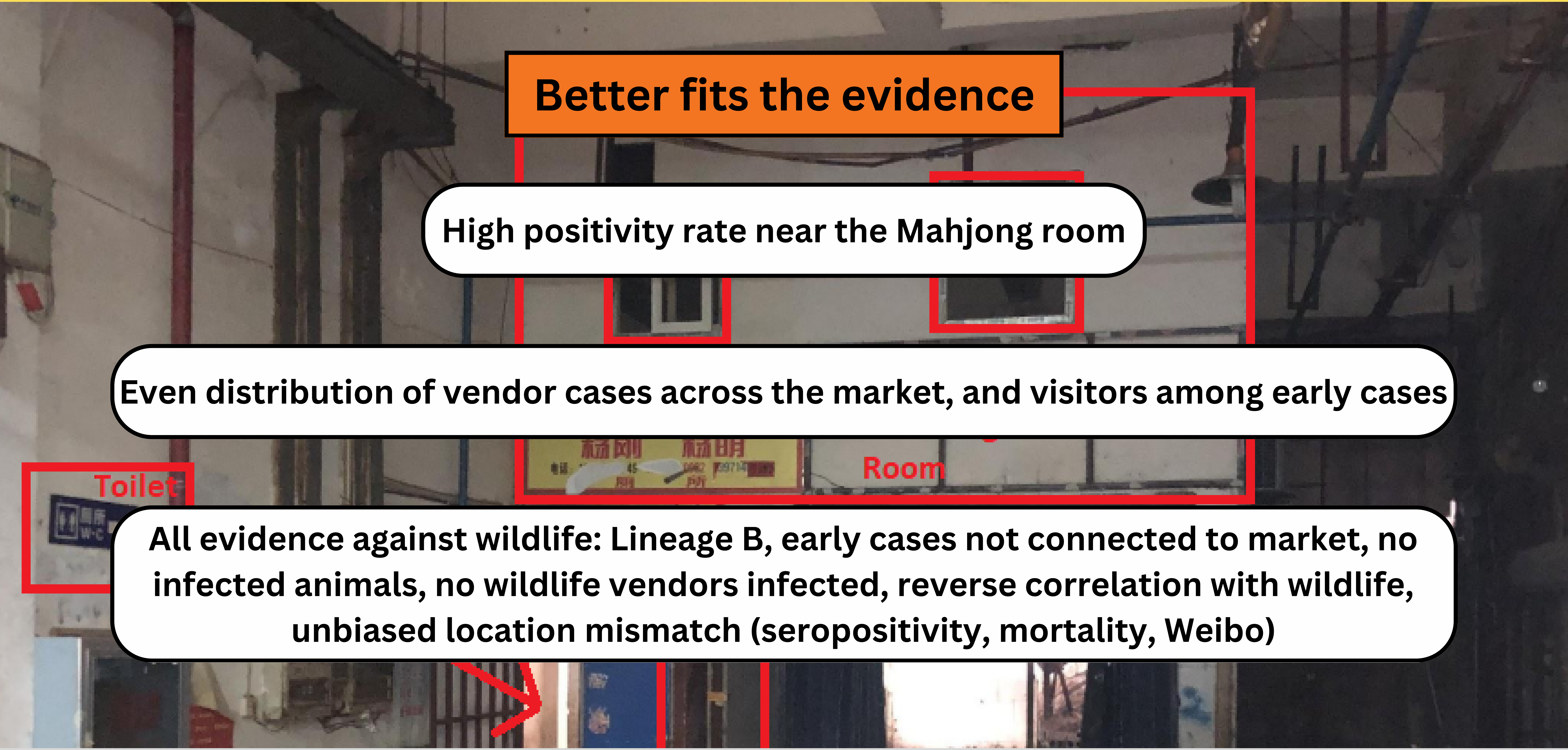
Huanan Market Study Results

Environmental samples exhibit a strong bias toward a specific corner of the market, coinciding with the location of the Mahjong Hall.

Official data records only 2 Mahjong players, but witness accounts suggest around 35.



The Mahjong Halls Hypothesis



Better fits the evidence

High positivity rate near the Mahjong room

Even distribution of vendor cases across the market, and visitors among early cases

All evidence against wildlife: Lineage B, early cases not connected to market, no infected animals, no wildlife vendors infected, reverse correlation with wildlife, unbiased location mismatch (seropositivity, mortality, Weibo)

If the Market is the Epicenter

Another potential for market as source: CDC Move

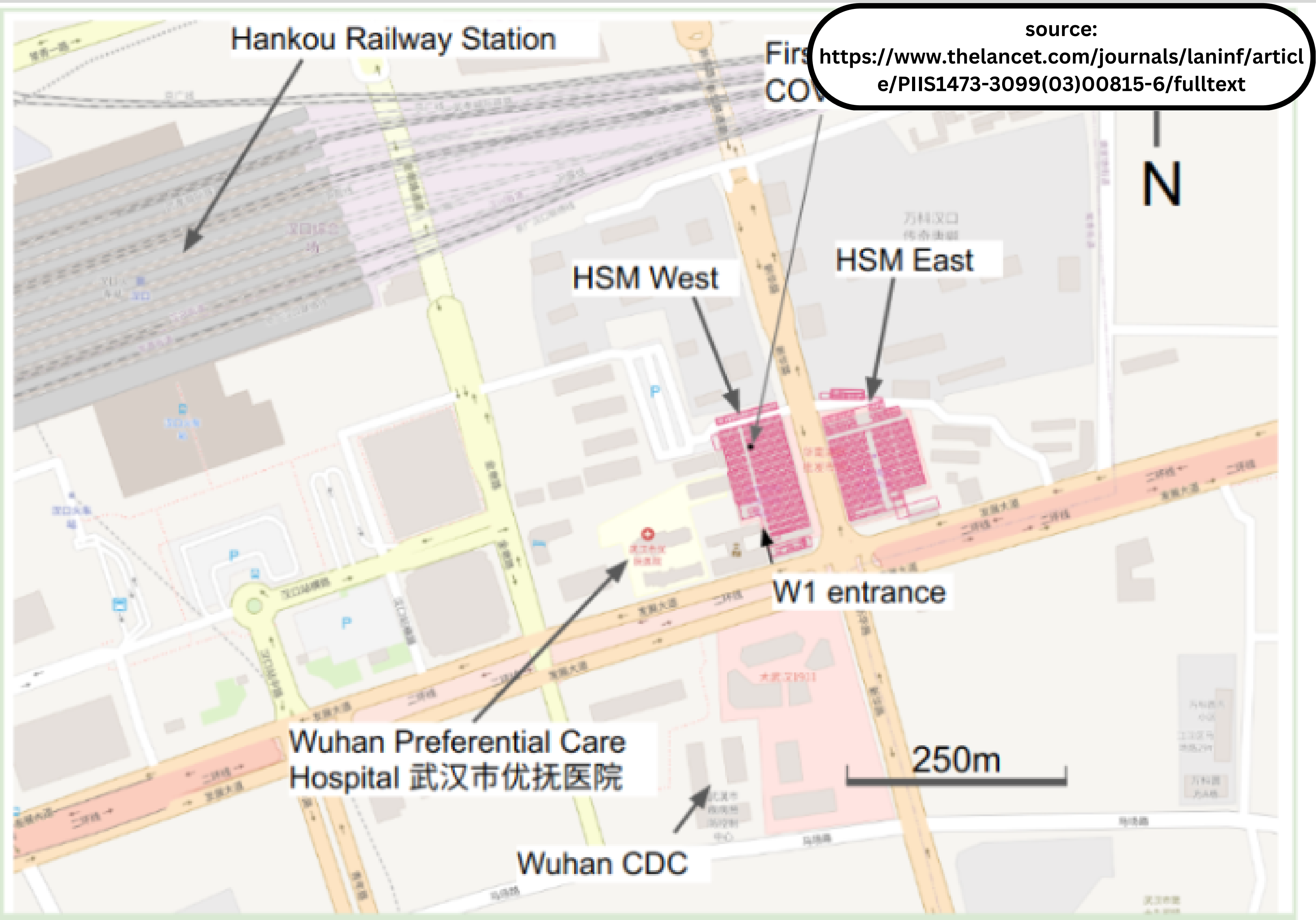
The CDC moved its laboratories on the 2nd of December 2019 to a location close to the market, leading to a higher probability of a breach of containment occurring during the move and thus strengthening the lab-leak hypothesis.

CDC move could be relevant if they interacted with the WIV, for example by:

- **exchange of equipment**
- **meetings between personnel**

“The Wuhan CDC laboratory moved on 2nd December 2019 to a new location near the Huanan market. **Such moves can be disruptive for the operations of any laboratory.”**

source: https://www.who.int/publications/i/item/who-convened-global-study-of-origins-of-sars-cov-2-china-part page 119



source: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(03)00815-6/fulltext

Fig. 1. Map of Huanan Seafood Market location in Wuhan, location of the Hankou railway station, Wuhan Preferential Care Hospital and Southwestern entrance ‘W1’.

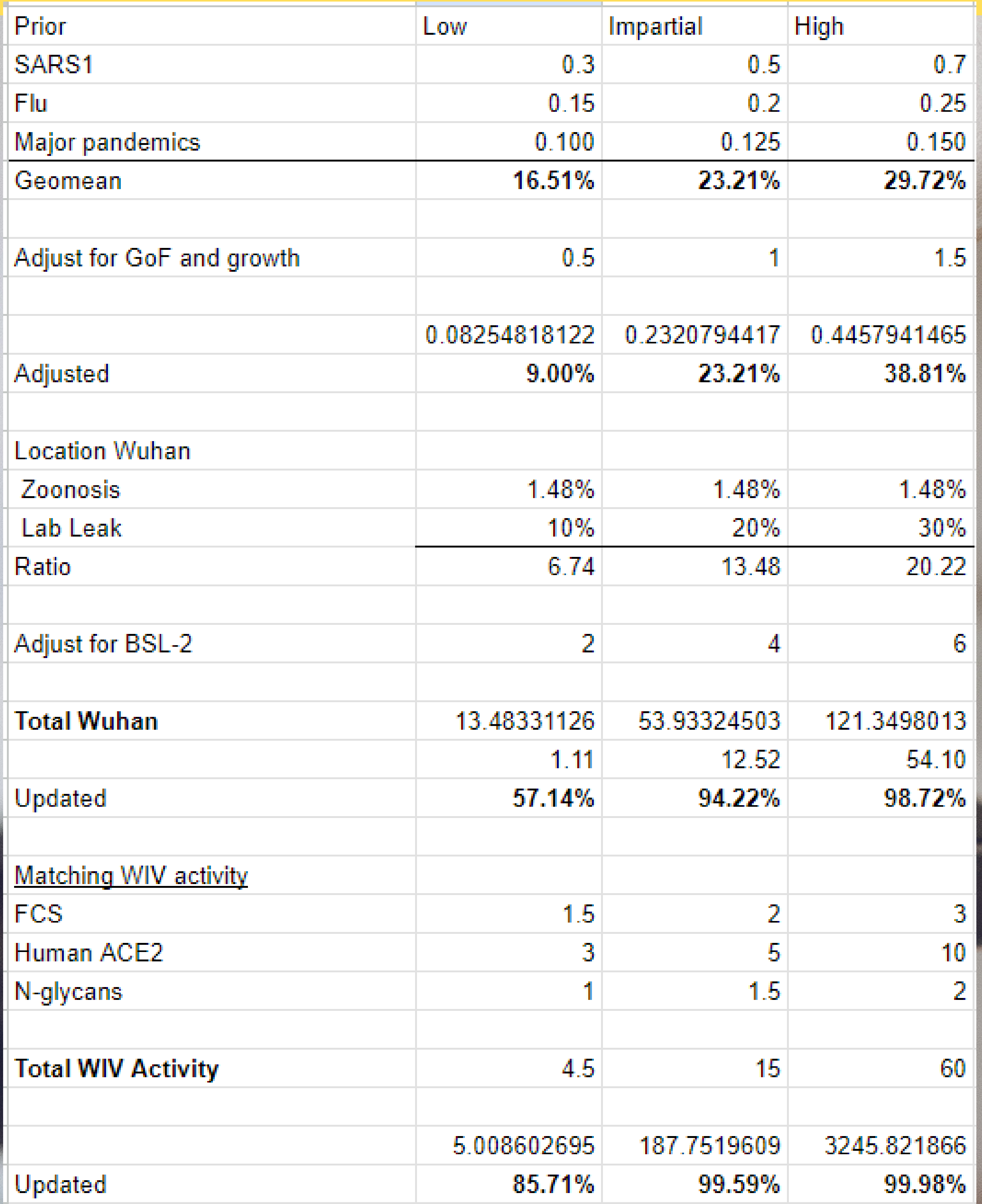
In 2003, during the SARS outbreak a 27-year old doctoral student was infected from SARS while working on the virus. An investigation showed that because the Department of Pathology BSL-2 laboratories were being renovated, mixed BSL-2/BSL-3 activities were in progress in the BSL-3 facility - jeopardising good safety practices. The move between laboratories leaves considerable room for mistakes to occur and procedures to go astray as the 2003 incident showcases.

Expectations vs reality

If the Huanan seafood market were the epicenter of the pandemic and the virus arrived to humans via zoonosis, we would expect most data showing Covid traveling from an intermediate animal in HSM outwards to the rest of the market and then into Wuhan, yet this is what we find:

Expected (under zoonosis)	Found
Earliest patients would be HSM-related and Wuhan “catching up” with some delay	Wuhan & HSM cases “increased simultaneously” (WHO)
Infected animals in the market	None
Infected vendors selling possible intermediate species	None
First cases from market would be people spending the longest time there, especially next to the infected animals (e.g., vendors)	First 2 HSM-related cases are visitors
First cases would have a shared location inside HSM or repeat locations individually	“it was found that none of the 5 [earliest] cases had similar exposure history [Inside HSM]”[WHO]
Amongst infected vendors, infection rate would be highest among (alive or frozen) animal vendors	Highest infection rate was among the vegetable vendors
Market infections would be from the strain closest to nature	Lineage B dominates, while the earlier lineage A is found elsewhere in the city

Summary



Prior	Low	Impartial	High
SARS1	0.3	0.5	0.7
Flu	0.15	0.2	0.25
Major pandemics	0.100	0.125	0.150
Geomean	**16.51%**	**23.21%**	**29.72%**
Adjust for GoF and growth	0.5	1	1.5
	0.08254818122	0.2320794417	0.4457941465
Adjusted	**9.00%**	**23.21%**	**38.81%**
Location Wuhan			
Zoonosis	1.48%	1.48%	1.48%
Lab Leak	10%	20%	30%
Ratio	6.74	13.48	20.22
Adjust for BSL-2	2	4	6
Total Wuhan	13.48331126	53.93324503	121.3498013
	1.11	12.52	54.10
Updated	**57.14%**	**94.22%**	**98.72%**
Matching WIV activity			
FCS	1.5	2	3
Human ACE2	3	5	10
N-glycans	1	1.5	2
Total WIV Activity	4.5	15	60
	5.008602695	187.7519609	3245.821866
Updated	**85.71%**	**99.59%**	**99.98%**

Weighted: 95%