A Mojiang Mine Origin of SARS-CoV-2?

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Introduction:

Of the SARS-CoV-2 novel variants of concern (such as *Alpha*, *Beta*, *Epsilon*, *lota*, *Gamma*, and *Omicron*), most arose within single individuals who were immuno-compromised. In these patients virus evolution accelerated significantly. Here, we describe how SARS-CoV-2 itself might have emerged via the same single-patient pathway. Such an explanation–in the context of a disease outbreak at the Mojiang copper mine in Yunnan, China, in 2012–can uniquely account for all of the particularities of SARS-CoV-2, including its 2019 emergence in Wuhan.

(1) SARS-COV-2's closest ancestral coronaviruses



are found in and near to the Mojiang mine:

SARS-CoV-2 most likely spilled out from *Rhinolophid* bats, its reservoir hosts, near to the border where Northern Laos meets Southern Yunnan. This small region is over 1,000 miles from Wuhan but it is where all the wild bat coronaviruses most similar to SARS-CoV-2 have been found (Hassanin and Rambaud, 2023).

In 2013, one of the very closest of these bat viruses, RaTG13, was collected from the disused Mojiang copper mine in Southern Yunnan. It was collected because, shortly before, this mine had been the site of a lethal respiratory disease outbreak (Xu, 2013; Ge *et al.*, 2016).

Significant for this origin explanation, these highly similar bat viruses have Spike proteins that naturally bind with exceptionally high affinity to the human ACE2 receptor (Temmam *et al.*, 2022; Ou *et al.*, 2023). Hence, though they are ordinarily enteric pathogens of bats, they can infect human lung cells very efficiently (Temmam *et al.*, 2022; Ou *et al.*, 2023; Fujita *et al.*, 2024).

(2) The Mojiang mine outbreak:

On April 2nd, 2012, four miners began clearing bat guano from the entrance to the Mojiang mine; the mine, they recalled, was heavily populated by *Rhinolophid* bats (Xu, 2013). After 14 days work these miners became too sick to continue. Two younger miners replaced them. They too became ill. All six developed coughs, breathing difficulties, and fevers (the latter indicating infection and not toxicity). Between April 26 and May 2nd, all six were admitted to the 1st Affiliated Hospital in Kunming, Yunnan. Ultimately, only three survived.

(3) The six miners probably contracted a <u>novel</u> bat-origin coronavirus

The admission, illness, and treatment, of the miners by their supervising doctor, Li Xu, are known from his Master's thesis (Xu, 2013). Their symptoms included: dry cough, high fevers, limb soreness, ground glass opacities, interstitial bilateral pneumonia and Acute Respiratory Distress Syndrome (ARDS). These symptoms closely resemble patients with severe COVID-19 (Rahalkar and Bahulikar, 2021). Of the miners, from initial exposure to final discharge (or death), patient 3 (144 days, died) and patient 4 (161 days, discharged) experienced especially long-term infections.

(5) How did SARS-CoV-2 reach Wuhan?

In Kunming, doctors took throat swabs, a thymus, a lung fluid sample, and multiple blood samples from the sick miners (Xu, 2013). Except for 13 serum samples sent to the Shi lab at the WIV and a throat swab sent to the Army CDC in Chengdu, the destinations of these samples are unknown. However, transport of these clinical samples to the WIV can explain how SARS-CoV-2 reached Wuhan from Yunnan, since the Shi lab, as coronavirus specialists, was specifically called on to investigate the miner's illnesses and the mine outbreak (Zhou *et al.*, 2020).

As also indicated by their immune biomarkers and their co-infections, all six miners suffered from immune suppression. Moreover, their treatment regimes included high dose steroids, whose side effects are immune suppression.

The coronavirus laboratory of Zheng Li Shi at the Wuhan Institute of Virology (WIV) was called in to supply a molecular diagnosis. According to the Master's thesis clinical samples were sent there and a coronavirus was detected. The Shi lab has denied detecting any coronavirus (Zhou *et al.*, 2020, addendum). However, this diagnosis was confirmed both by another thesis and again in 2020 by George Gao, head of China's CDC. The final diagnosis of Li Xu was that the outbreak was caused by a *novel* coronavirus.

(6) Research at the WIV:

We thus hypothesise that the WIV obtained SARS-CoV-2 in clinical samples sent from Kunming. Compatible with this, the unpublished research direction of the Shi lab after mid-2012 is consistent with them believing that the mine outbreak resulted from a novel coronavirus (Wang, 2014; Zeng, 2017).

(7) How might a lab-related spillover in Wuhan have happened?

The obvious first step for researchers who suspect clinical samples contain a novel coronavirus is to isolate and culture the virus. Culturing a virus is imperative for validating an isolate, for conserving it, and for amplifying it for subsequent experimentation and testing. Virus culture incurs a high probability of laboratory acquired infections, particularly with respiratory viruses. This is because the goal is to achieve high titres of the infectious agent. Such laboratory infections occurred multiple times with SARS-CoV-2 itself during the pandemic (Young, 2023). Moreover, it is known that, prior to the pandemic, WIV researchers used low biosafety (BSL-2-level) laboratories to culture recombinant coronaviruses (Wang, 2014; Zeng, 2014).

Once infected with SARS-CoV-2, a lab worker may or may not have had symptoms. In either case, transmission of the virus to colleagues, family, or friends, knowingly or unknowingly, can be readily envisaged.

(4) How SARS-CoV-2 could have evolved in a miner:

Long-term infections and their associated immuno-suppression are now known as preconditions favouring rapid evolution and adaptation of SARS-CoV-2 (e.g. Choi et al., 2020; Kemp et al., 2021). Thus it is now presumed that Alpha, Beta, Gamma, Epsilon, Omicron, JN.1, and other SARS-CoV-2 variants each arose during long-term infections of a single immuno-suppressed patient (Harari et al., 2022; Planas et al., 2024). Exactly why immuno-compromised individuals generate radically novel and highly adapted genotypes of SARS-CoV-2 is not fully known, but presumably a major contributing factor is that in patients who fail to clear their infections, genetic bottlenecks resulting from interpersonal transmission are absent. This allows retention of adaptive mutations and the consequent expanded viral diversity accelerates normal viral evolutionary processes. We propose that SARS-CoV-2 evolved in the miners in an equivalent evolutionary process. First, the miners' work exposed their lungs to one (or more) SARS-CoV-2-like bat viruses with high affinity for hACE2. This initially enteric bat virus evolved inside them to become the human-adapted and lung-adapted SARS-CoV-2 in what was a near-ideal selective environment. Given the extended duration of their illnesses we also propose that SARS-CoV-2 most likely evolved in either of patients 3 or 4 (Xu, 2013). This origin explanation, a direct bat-to-human jump coupled to an evolutionary hothouse situation can account for numerous otherwise puzzling biological features of SARS-CoV-2, including 1) the non-discovery of an intermediate host and the lack of intermediate viruses; 2) why SARS-CoV-2 was so well adapted, both to humans and the respiratory system from the outset of the pandemic; 3) why SARS-CoV-2 initially favoured the lower respiratory tract (i.e. the alveoli of the lungs), before switching gradually to the upper respiratory tract (Hui et al., 2022); 4) and why SARS-CoV-2 has mutations (Spike T372A and H519N) that signal an evolutionary adaptation away from a formerly enteric life-history.

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