

Zoonosis at the Huanan Seafood Market: A Critique

Daoyu Zhang¹, Gilles Demaneuf², Adrian Jones³, Steven E. Massey⁴, Steven Quay⁵, Yuri Deigin⁶, Louis R. Nemzer⁷

¹ Independent Genetics Researcher, Sydney, Australia

² Engineer and Data Scientist, New Zealand; ORCID 0000-0001-7277-9533

³ Independent Bioinformatics Researcher, Melbourne, Australia; ORCID 0000-0001-7355-0052

⁴ Biology Dept, University of Puerto Rico-Rio Piedras, San Juan, Puerto Rico, USA

⁵ Atossa Therapeutics, Inc., Seattle, WA USA; ORCID 0000-0002-0363-7651

⁶ Youthereum Genetics Inc., Toronto, Ontario, Canada; ORCID 0000-0002-3397-5811

⁷ Department of Chemistry and Physics, Halmos College of Arts and Sciences, Nova Southeastern University; ORCID 0000-0001-8861-0898

Abstract

Since the Huanan Seafood Market (HSM) in Wuhan, China was first suggested as the source of the COVID-19 pandemic in late January 2020, debate has continued over the evidence supporting this claim. Here, we assess the evidence provided in support of zoonotic spillover at the HSM as the origin of human infection by SARS-CoV-2. We find that the datasets and analyses put forward in support of zoonosis are biased, and lack sufficient verifiable data to support this hypothesis. The earliest COVID-19 case at the HSM was not at or near a wildlife stall, rather the distribution of cases at the HSM is consistent with a Poisson point process model, i.e. randomly distributed, and the distribution of wildlife stalls and COVID-19 cases are consistent with independent Poisson point processes. No statistical correlation is found between cases and wildlife stall locations. The random distribution of cases and several isolated clusters is consistent with human-to-human transmission in shared areas such as eating areas, toilets, and social gathering areas. Sampling bias is evident in specimen collection at the market, with over-sampling evident in the SW corner of the market relative to the rest of the market. Notwithstanding this bias, environmental positive PCR samples are more consistent with contamination by infected COVID-19 cases and aerosol spread from the HSM toilets, rather than from wildlife stalls. Although proposed as the intermediate spillover host, raccoon dogs were unlikely to be linked with the outbreak, as they were sold in Wuhan in small numbers relative to other parts of China, and there is no epidemiological evidence indicating any infection of a raccoon dog, or any other wild or domestic animal, before or during the early pandemic, at any market elsewhere in Wuhan, or even in the rest of China. These considerations indicate that HSM was instead likely a super-spreader location, with only tenuous evidence to support a zoonotic spillover there. Consequently, we conclude there is insufficient evidence to indicate the HSM was the location of the first human infections by SARS-CoV-2.

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Introduction

On January 22, 2020, the Chinese Center for Disease Control and Prevention stated that the source of SARS-CoV-2, the virus responsible for COVID-19, was wild animals illegally traded at the HSM [1]. Subsequently, on January 23, Zhou et al. (2020) also claimed the HSM as the source of the outbreak. However, no evidence was presented initially to support these claims, and questions quickly arose as to the strength of the argument in favor of animal-to-human zoonotic transmission at the HSM (Cohen 2020a). Later, Gao Fu, the director of the Chinese CDC, ruled out the HSM as the origin of the pandemic on May 26, 2020 [2]. Since then, a recent detailed study of environmental samples concluded that “*the market might have acted as an amplifier due to the high number of visitors every day, causing many initially identified infection clusters in the early stage of the outbreak*” (Gao et al., 2022). This scenario is very similar to the Beijing's Xinfadi Market outbreak in June 2020, which occurred after 56 days without a new case Beijing, but lead to a super-spreader cluster of 368 PCR-confirmed cases before it was brought under control (Tan et al., 2020; Luo et al., 2022). Additionally, this was also the opinion of Pekar et al. in early 2021, who concluded that the “*market cluster is unlikely to have denoted the beginning of the pandemic*” (Pekar et al., 2021).

Recently, in a preprint by some of the same authors, Worobey et al. reversed course and claimed to have ‘dispositive’ evidence for the emergence of SARS-CoV-2 from the live wildlife trade, and that the initial spillover to humans occurred wild animals at the HSM (Worobey et al., 2022a). After peer review, the final paper softened the conclusion, and removed the definitive language (Pekar et al., 2022). The authors currently claim that the HSM was the epicenter, not necessarily the source, of the COVID-19 pandemic (Worobey et al., 2022b). In addition, Pekar et al. posited that SARS-CoV-2 likely resulted from multiple zoonotic spillover events at the HSM in late November 2019 (Pekar et al., 2022). However, other research throws into question the animal spillover hypothesis, with several COVID-19 cases at the HSM likely occurring through human-to-human transmission (Courtier-Orgogozo and de Ribera 2022). Furthermore, Stoyan and Chiu (2022) show that the assumptions, methods and tests used by Worobey et al. (2022b) to conclude that the HSM was the epicenter of the COVID-19 outbreak in Wuhan are statistically invalid, and cannot be used to prove the hypothesis that HSM as the epicenter of the of the pandemic.

Ascertainment bias is evident in the early diagnosis of cases in Wuhan. The Wuhan Municipal Health Commission (WMHC) reporting standard for “Entering and Discharging Viral Pneumonia of Unknown Causes”, introduced on 03 January 2020, was retrospective [3, 3a]. Any case suspected of being “Viral Pneumonia of Unknown Cause”, retrospectively backdated to December 1, 2019, had to meet stringent criterion in order for the case to meet reporting standards and be officially diagnosed. The key criterion was recent contact with the HSM. This fact alone likely introduced a strong bias into the dataset, especially because many cases of COVID-19 are mild or confused with other respiratory diseases. Thus, the data used for all future analyses was almost certainly missing many cases, particularly those without a known connection to the HSM.

The Pneumonia of Unknown Etiology (PUE) Surveillance System was established in China in 2004 (Xiang et al., 2019) as part of a National Notifiable Disease Reporting System (also known as the CISDCP) (Jia and Yang 2020) [6, 6a]. However, in a 2016 study of China's PUE surveillance system, it appears to have been little known or understood by clinicians (Xiang et al., 2019). Of the 335 cases analyzed at two hospitals in Anhui province that met the criterion for reporting PUE, none were actually entered into the system (Xiang et al., 2019). We further note that the PUE reporting standard requires meeting a series of checks that can only be commenced by clinicians at a county-level hospital [4, 4a]. Clinics and secondary hospitals were likely the dominant first point of contact for pneumonia of unknown origin cases in the early phase of the epidemic [5, 5a]. As such, many early cases may not have had CT examinations, been severe enough or wanted to transfer to Wuhan's municipal level hospitals where PUE case investigation could be commenced.

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 Jiangnan 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.

Here, we focus on analysis of data within the HSM itself and examine the arguments adduced in support of the zoonotic origin at the HSM. We conclude that there is insufficient evidence to support this hypothesis, and conclude that the HSM was likely a super-spreader location for SARS-CoV-2, which had been brought to the market by a person infected elsewhere.

Spatiotemporal distribution of COVID-19 cases

The HSM is split into two sections, “West” and “East”, divided by a main road (Fig. 1). The Western section of the HSM is located approximately 750 m from the Hankou railway station, one of the three main railway stations in Wuhan.

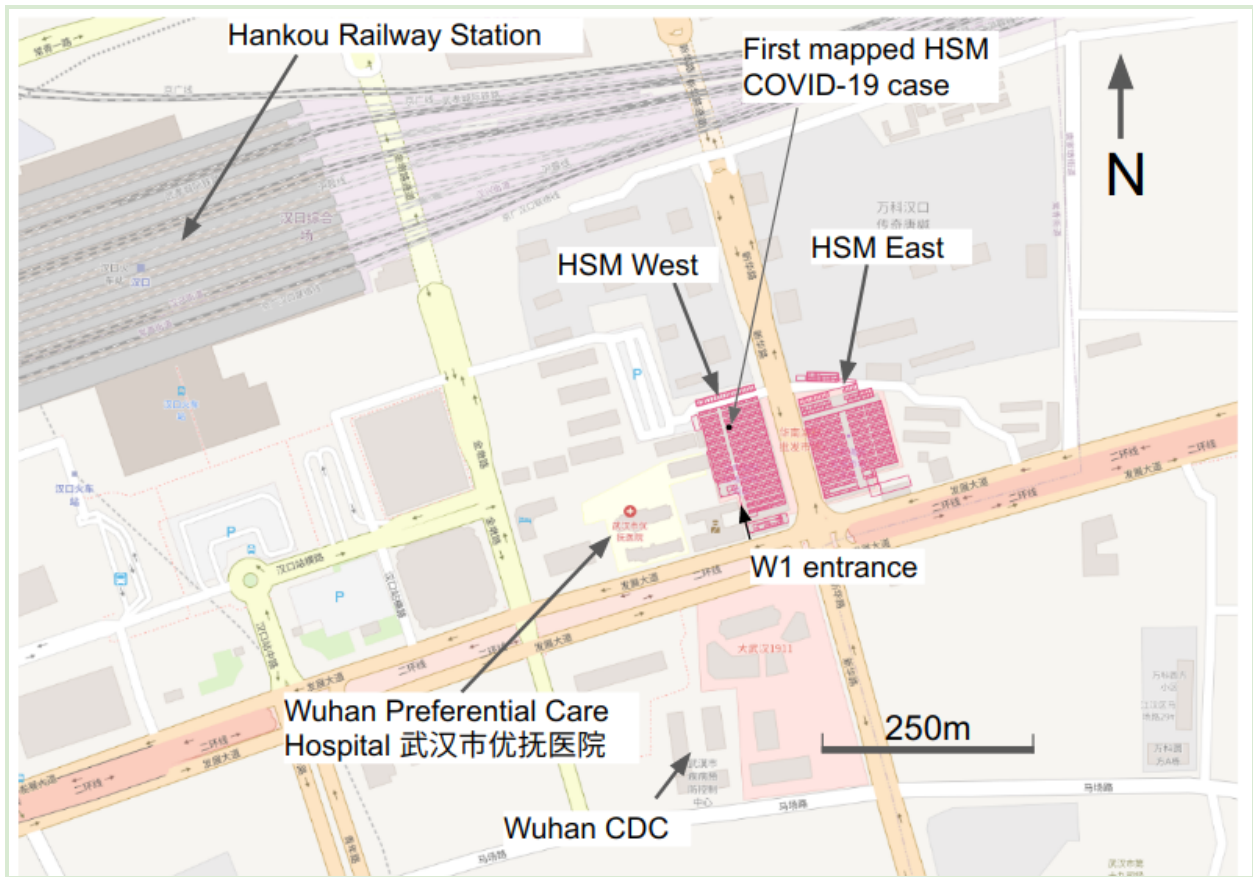


Fig. 1. Map of Huanan Seafood Market location in Wuhan, location of the Hankou railway station, Wuhan Preferential Care Hospital and Southwestern entrance 'W1'.

COVID-19 has a demonstrated high transmission risk for train passengers, with distance from an infected patient being a key factor (Hu et al., 2021), and enclosed spaces facilitating transmission (Qiu et al., 2020). COVID-19 transmission has also been demonstrated in similar enclosed spaces on buses (Luo et al., 2020; Shen et al., 2020). As such, the Hankou railway station, located 750 m from the HSM, is a potential high-risk area for SARS-CoV-2 transmission. The HSM is also located approximately 150 m from the Wuhan Preferential Care Hospital (Youfu Hospital), a 400-bed general hospital with psychiatric specialty [7, 8, 9]. It is worth noting that hospitals were documented COVID-19 transmission locations early in the COVID-19 pandemic (Wang et al., 2020; Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention 2020). However, no environmental test results for SARS-CoV-2 in early January 2020 at the Hankou railway station have been published. Nor have environmental SARS-CoV-2 sampling test maps been provided for the nearby Wuhan Preferential Care Hospital, or for Glasses City upstairs at the HSM. All of these locations were potential entry points for SARS-CoV-2 to the HSM. Indeed, no environmental sampling maps or studies of any detail have been published for anywhere in Wuhan in early January 2020 other than for the HSM. Gao et al. (2022) briefly mention "One sample was collected from other market in Wuhan and 3 collected from sewerage wells in surrounding areas" and the Joint WHO-China report (2021a) in Table 1 p.g. 95 mention 30 samples taken from Dongxihu

Market and Huanggang Center Market and 14 samples from “Warehouses related to the Huanan market”. However, these descriptions and tables provide little further detail, and do not constitute effective negative controls that can be used to detect confounding variables (Lipsitch et al., 2010).

The Western section of the HSM has four entrances, with entrance ‘W1’ located adjacent to the Glasses City entrance (upstairs at the HSM), and at the Southwestern end of a line of restaurants at the front of the HSM complex (Fig. 2). Due to the proximity of these restaurants to the Huanan market, it is likely that at least some infected vendors and shoppers would have (potentially frequently) entered and exited the market through entrance ‘W1’ in order to eat at the restaurants, leading to greater levels of environmental contamination en route to the restaurants, and facilitating transmission at the restaurants themselves.

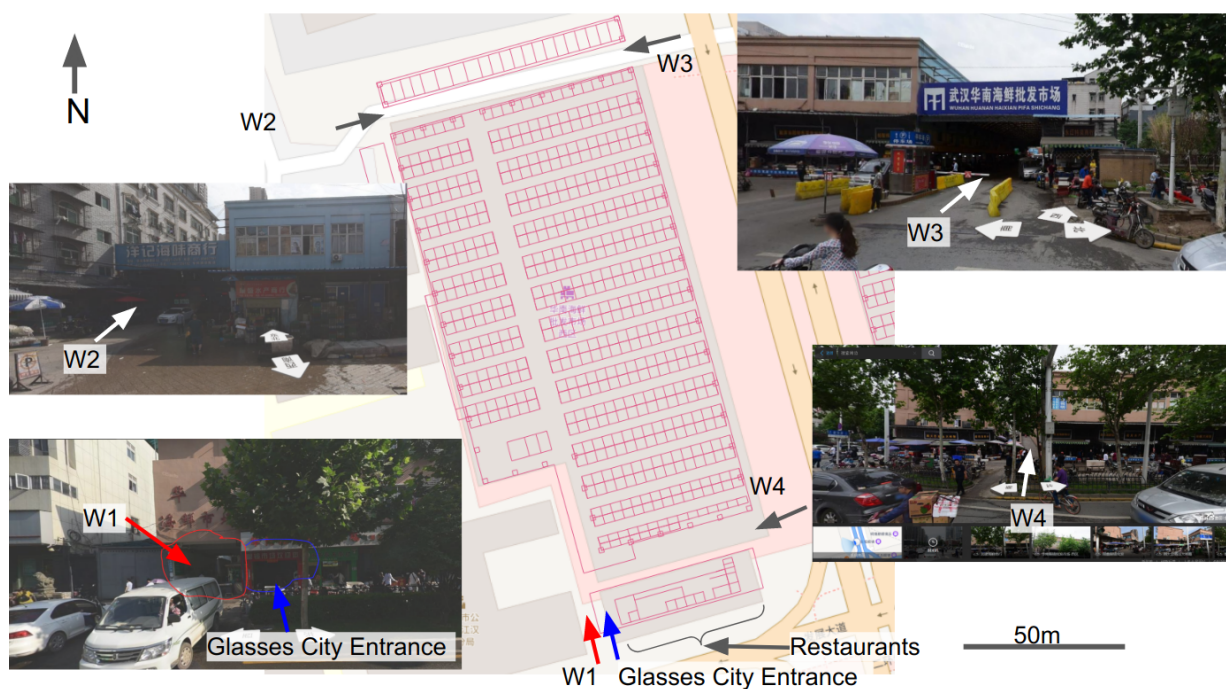


Fig. 2. Location of entrances to the Western section of the Huanan Seafood Market.

Wildlife was sold in two locations in the market, the Southwest corner of the West section and the Northwest corner of the East section (Fig. 3). The toilets for the Western section of the market are located in the Southwestern corner (Supp. Fig. 1), while restaurants were located immediately South of market stalls on the West side of the HSM (Figs. 2 and 3). Although Gao et al. (2022) discuss sampling of “public toilets, public activity rooms and other places where people gathered in the market”, and while sewer samples were also discussed, no environmental sample locations were published from the HSM toilets or restaurants. Indeed, neither the location of the HSM (Western) toilets or location of restaurants were discussed in Joint WHO-China Study (2021a), Gao et al. (2022) or Worobey et al. (2022b).



Fig. 3. Plan view of the Huanan Seafood Market, after Joint WHO-China Study (2021b). Street numbers shown for Western section.

As can be seen in the spatial map of cases over time for the period of 13 December 2019 to 31 December 2019, there is no clear relationship between the location of either of the two wildlife sections (West and East parts of the market) and case locations (Fig. 4). In particular, the earliest COVID-19 case maps showing cases on 13 December 2019 and 20 December 2019 were located in the Northern and Eastern parts of the West section of the market. They were not located in the Southwestern corner, and not near the Northwestern part of the Eastern section of the market where wildlife stalls were located (Fig. 4).

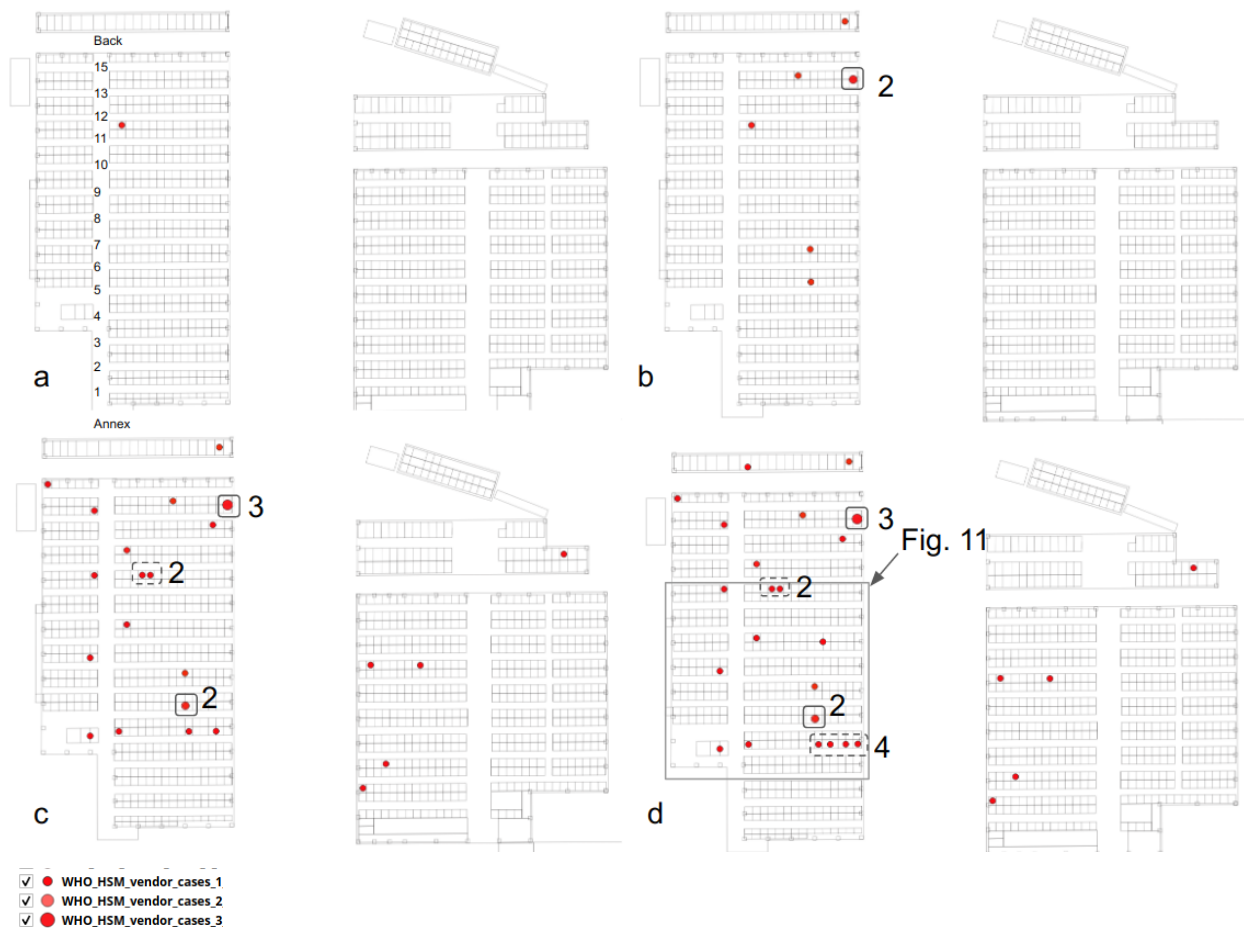


Fig. 4. Partial distribution of cases on a) 13 December 2019 (1 case), b) 20 December 2019 (7 cases), c) 27 December 2019 (26 cases) and d) 31 December 2019 (30 cases). After Joint WHO-China Study (2021b). Multiple cases at the same stall indicated by solid boxes, multiple cases in close proximity across stalls indicated by dashed line boxes.

COVID-19 case distribution

To statistically analyze the pattern of COVID-19 case distribution (Joint WHO-China Study 2021b), we undertook a nearest-neighbor distance analysis of COVID-19 case locations at the HSM as at 31 December 2019 using spatstat (Baddeley and Turner 2005). Stationary processes were assumed. Ripley's G (distribution of distances from an arbitrary event to its nearest neighbors), K ($1/\lambda$ times the expected number of other points of the process within a distance r of a typical point of the process, with the expectation of a homogeneous Poisson process is $K(r) = \pi r^2$ and λ is the density of COVID-19 cases) and L (transform of K to straight line) functions (Ripley 1977) were simulated (Fig. 5). The observed case distribution falls within a randomly simulated envelope of nearest-neighbor distances, except for distances 0-1 m, for which significant clustering of cases occurs. Overall, the case distribution is consistent with some clustering of cases at less than 5 m from each other, where the observed Ripley's G and L functions sit above the expected mean

distribution, but with the bulk of cases following a homogeneous Poisson-process distribution (i.e randomly distributed) thought the HSM.

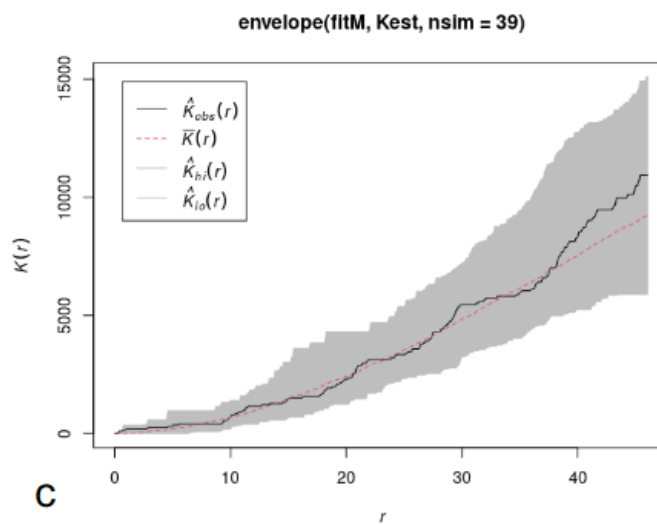
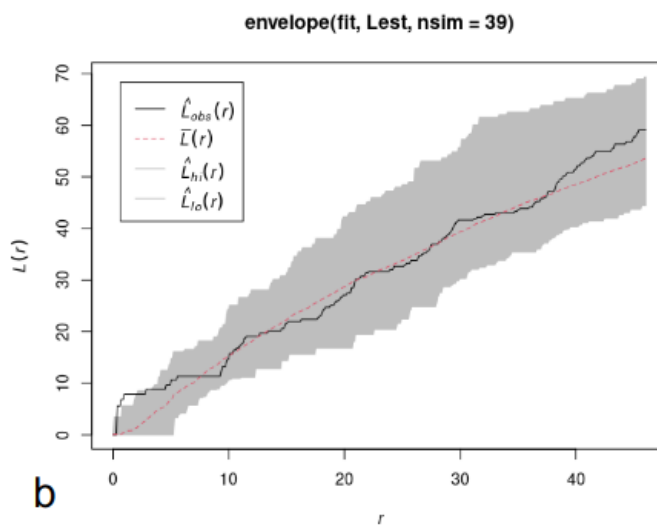
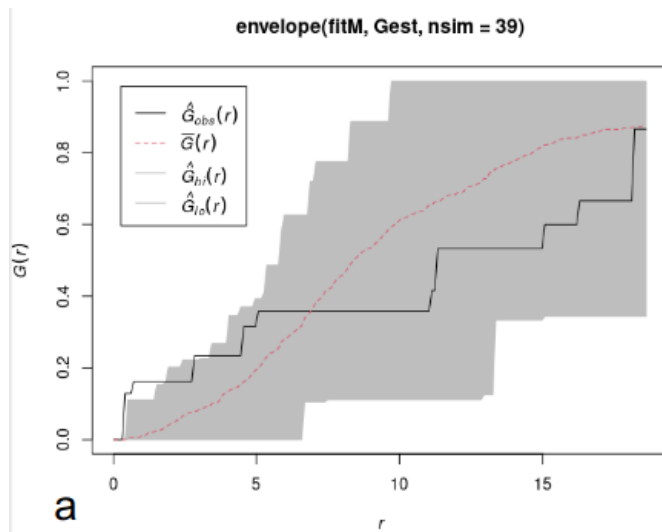


Fig. 5. Ripley's G, L, and K function plots with simulated poisson models using Matérn cluster process (a-c) showing the distribution of distances for all identified COVID-19 cases as at 31 December 2019 at the HSM.

COVID-19 transmission occurs primarily via the airborne route in indoor settings (Prather et al., 2020; Greenhalgh et al., 2021; Jimenez et al., 2022), with super-spreader events responsible for a significant proportion of infections (Lewis 2021). Crowded indoor spaces with poor ventilation are particularly high risk areas (Lewis 2021) with an association between poor ventilation and increased transmission risk (Greenhalgh et al., 2022; Peng et al., 2022). While there is some indication of transmission over distances shorter than 3 m at the HSM, with multiple cases occurring at the same stall and several stalls in close proximity, overall the distribution at the market as of 31 December is consistent with that expected from a spatial Poisson point process model. That is, it can be considered essentially random (Figs. 4 and 5). Indeed, Courtier-Orgogozo and de Ribera (2022) find that the 20-40 m distance between the week 2 and the week 1 COVID-19 cases and the distance between week 2 cases (Figs. 4a and b) is not consistent with direct infection from a unique source, and suggest that HSM cases may have infected each other in common areas at the HSM, such as shared eating/gambling areas and toilets (Courtier-Orgogozo and de Ribera 2022). Plots with a 3-m radius around each case for the four time periods provided in the Joint WHO-China Study (2021b) and kernel density estimation (KDE) plots further show some possible local transmission on the order of 3 m or less between cases, but otherwise no clear point source for cases exists (Supp. Figs. 2-6). We note that both restaurants (at the Southern end of the Western section of the HSM) (Fig. 2) and toilets (Fig. 3), both with relatively small enclosed spaces and likely high people density, are located within easy access for workers and shoppers at the Western section of the HSM. Given the mostly random pattern of cases at the market, it is plausible that some transmission may have occurred in either or both of these areas.

Cases and Wildlife stalls

To analyze a potential spatial relationship between COVID-19 case locations and wildlife stall locations, we statistically tested the relationships of case locations as of 31 December 2019 with wildlife stall positions again using spatstat (Baddeley and Turner 2005). Distances from each COVID-19 case to each wildlife stall was computed using Ripley's K and L cross functions (Baddeley and Turner 2005) (Fig. 6). $K_{B,A}(r)$ is $1/\lambda_A$ times the expected number of COVID-19 cases (A) within a distance r of a wildlife stall (B) and where λ_A is the density (intensity) of COVID-19 cases. The distances fall within a simulated expectation of independent Poisson point processes with a noticeable deviation (repulsion) from expected values for distances less than 10 m. This is expected as no COVID-19 cases occurred within 10 m of a wildlife stall. The modeling results also exhibit indications of possible clustering at >50 m which may be influenced by the separation of the West and East sections of the market.

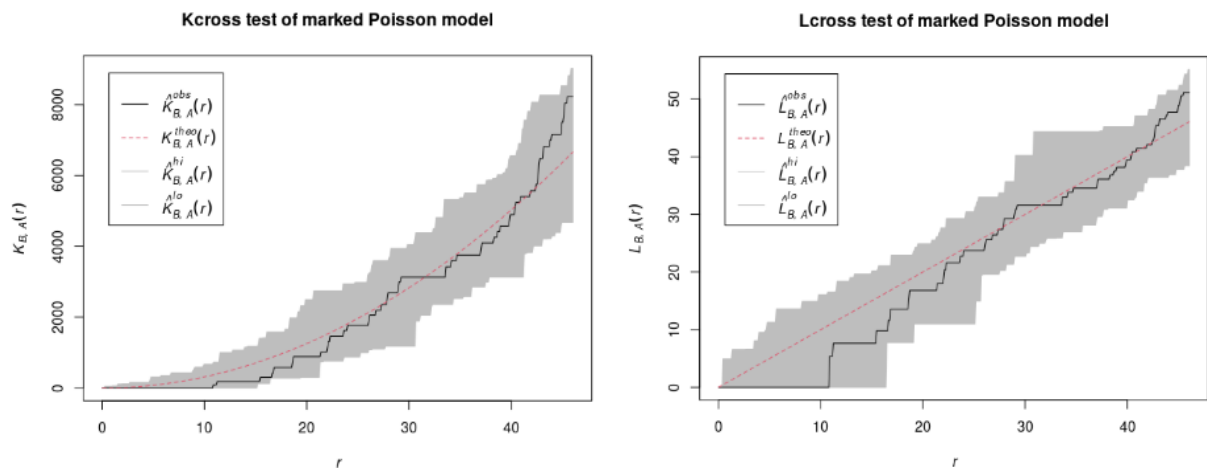


Fig. 6. Ripley's K and L cross-distance function plots with simulated Poisson point process distances for all COVID-19 cases (as at 31 December at the HSM) relative to the position of wildlife stalls. $K_{B,A}(r)$ is $1/\lambda_A$ times the expected number of points of type A (case) within a distance r of a typical point of type B (Wildlife stall). $L_{B,A}(r)$ is a variation on the K function and defined by $\text{Sqrt}(K_{B,A}(r)/\pi)$. $K_{B,A}^{\text{theo}}(r)$ the theoretical value of $K_{B,A}(r)$ for a marked Poisson process (i.e. πr^2).

Ripley's multitype K function ($K_{B,A}(r)$) was then applied to the West section of the market only (Supp. Fig. 7). The observed distribution generally follows simulated independent Poisson point processes at $r > 10$ m for the entire HSM analysis, but with a greater 'repulsion' from that observed for an entire market simulation. This indicates that there is no causal correlation between COVID-19 case locations and wildlife stalls in the Western section of the HSM.

We then analyzed the distances from each COVID-19 case as at 20 December 2019 to wildlife stalls on the West side of the market (Supp. Fig. 8). Cases to wildlife stall locations were more separated than would be expected from independent Poisson point processes (null hypothesis). Again, this does not support a zoonosis hypothesis for which some clustering of cases near wildlife stalls would have been expected.

Additional cases

On Jun 14, 2021, two and a half months after the publication of the Joint WHO-China Study (2021a) a separate set of HSM case maps was provided by M. Koopmans [10]. Sixty-one cases were shown (compared with 30 official cases in the Joint WHO-China Study (2021b)) with significant differences both in the number of clustered cases and case distribution on the West side of the market (Supp. Fig. 9). On the West side of the market, cases in the Joint WHO-China Study (2021b) represent a subset of Koopmans cases [10], while on the East side the two sets are equivalent but with 2 cases with shifted locations (Supp. Fig. 10). Notably, 20% of cases in the Joint WHO-China Study (2021b) in the Western section of the market were clustered at the same stall, whereas 50% of cases in Koopmans [10] were located at the same stall.

Koopmans			Joint WHO-China Study		
N	West count	East count	N	West count	East count
1	28	5	1	20	5
2	7		2	1	
3	2		3	1	
4	2				
Total	56	5		25	5

Table 1. HSM COVID-19 case number shown by Koopmans [10] is more than double declared in Joint WHO-China Study (2021b). N represents the number of cases at the same location.

We analyzed the spatial distribution of COVID-19 cases as per Koopmans [10] against the distribution of wildlife stalls in the Western section of the HSM assuming independent Poisson point processes (Supp. Fig. 11). The results using Ripley’s G and K functions generally lie within a simulated independent Poisson point process model, with an indication of a ‘repulsion’ from a mean of simulated cases. Similar to Joint WHO-China Study (2021b) case location simulations, the analysis does not support a causal link between COVID-19 cases and wildlife stall locations.

A lack of statistical support for a correlation of COVID-19 case locations and wildlife stalls within the HSM is also consistent with the empirical observation that no cases of COVID-19 were recorded in the westernmost block of the market where wildlife stalls were located until the week from 21 December to 27 December 2019. This was more than one to two weeks after the first case, and in the week when cases became widely spread across the market (Figs. 3 and 4) (Joint WHO-China Study 2021b). We note however, the differences between Koopmans [10] and the Joint-WHO China report (2021) should be clarified as the case at West 7/26-28 in Joint WHO-China Study (2021b) appears in 21 December to 27 December 2019 map, but is one of two cases on the 15 December 2019 map of Koopmans [10]. Additionally, a case in the Westernmost block of the HSM at West 8/26-28 appears in Koopmans [10] on 15 December 2019, but this case is not reported in the Joint WHO-China Study (2021a).

Notably, no wildlife vendor with an identified COVID-19 case was found at the HSM. This contrasts markedly with the SARS outbreak in Guangdong in November 2002, in which 9 of 23 early cases were food animal handlers (Xu et al., 2004).

First market case

The first HSM-linked case that can be identified in Joint WHO-China Study (2021a) is seafood vendor 57F (stall West 2/14, 44m from nearest wildlife stall), who experienced symptom onset on 11 December. She first visited Zhongshan clinic near the HSM and then

the Eleventh Hospital but was not given an official diagnosis; however, the case was widely reported in the media [11,12,13]. She believes that she may have contracted COVID-19 in the HSM public toilets. The first HSM case that can be identified in Joint WHO-China Study (2021b) market maps was 65M of 武汉市江汉区昌盛海鲜食品批发部 Wuhan Jiangnan District Changsheng Seafood Wholesale Department (Figs. 4a, Supp. Fig. 12)[14]. This stall, positioned at West 12/21, was located 25 m from the closest wildlife vendor at West 10/29 (Figs. 3 and 11). An earlier case, 48F, had no documented link with the HSM, and presented on December 10 with an elevated temperature (38 °C), soreness and fatigue [15,15a](Li et al., 2020). She was a patient at Tongji Hospital on December 27, but the admission date and detailed clinical history are unknown. 62M is another non HSM market linked case from which the first lineage A genome was sequenced (IME-WH01), and experienced onset on December 12 (Zhou et al., 2020) (December 1 in Huang et al. (2020)). 62F, the wife of 62M experienced COVID-19 onset 3 days later on December 15. The infection date of their son is unknown, and his case was only identified after a CT scan at Xinhua hospital [5,5a]. Three other HSM linked cases had onset on 12 December: 44M2 a HSM transportation worker (Qian et al., 2020); 49M of cluster 3 in Li et al. (2020) (48F2, wife of 49M experienced onset on December 15); and 69M1 (seafood buyer for Jingzhou hotel [16,16a]). 41M1 was an accountant living in Jiangxia district on the East side of the Yangtze river (Worobey et al., 2021; Babarlephant et al., 2022). An intriguing possible COVID-19 case '69M0', was a HSM merchant who visited Youfu outpatient clinic on 12 December with a dry cough and reported 7-8 merchants at a nearby stall at the HSM who had fever and a dry cough for several days [5,5a].

10	11	12	13	14	15	16
48F	57F lin.B	49M	65M1 lin.B		48F2	
		62M lin.A			62F lin.A*	41M1 lin.B
		44M2			son?	
		69M1				

Table 2. Early December timeline of first official case and documented possible earlier December cases at and outside the HSM. Dates of onset of HSM cases that can be identified in Joint WHO-China Study (2021a,b) in blue; HSM linked case onsets in orange, non HSM linked case onsets in gray. References: 48F [15,15a](Li et al., 2020); 57F [11,12,13]; 49M (Li et al., 2020); 62M (Zhou et al., 2020); 44M2 (Qian et al., 2020); 69M1 [16,16a]; 65M1 (Babarlephant et al., 2022); 48F2 (Li et al., 2020); 62F (Joint WHO-China Study 2021a); 41M1 (Worobey et al., 2021; Babarlephant et al., 2022). Where known, lineage (lin.) is indicated. * lineage inferred.

That four of ten of the earliest identifiable cases were not linked to the HSM, including 48F with onset on December 10 prior to the first identifiable HSM market case 57F (Joint WHO-China Study 2021a) [11,12,13], indicates human-to-human transmission was occurring outside the HSM in early December, prior to the outbreak on December 12

identified here, and prior to the large outbreak at the HSM between December 20 and December 27 (Joint WHO-China Study 2021a).

Environmental Sampling

While the COVID-19 case maps at four dates in December clearly document the spatiotemporal spread of COVID-19 at the HSM (Fig. 4), environmental sampling after the market was closed gives an indication as to where, out of the sampled locations, SARS-CoV-2 particles were present in sufficient quantity to be detected.

The main environmental sampling process at the HSM was conducted on January 1, 2020 after the HSM had been closed, and approximately three weeks after the first identified COVID-19 case at the market (Gao et al., 2022) [17, 17a]. A second sampling process was conducted on 12 January, with multiple additional restricted sampling events continuing through to 02 March 2020 (Gao et al., 2022).

When the total number of environmental samples, both positive and negative, are plotted, it is evident that the process was heavily skewed towards oversampling the SW corner of the market (Fig. 7, Supp. Figs. 13-17).

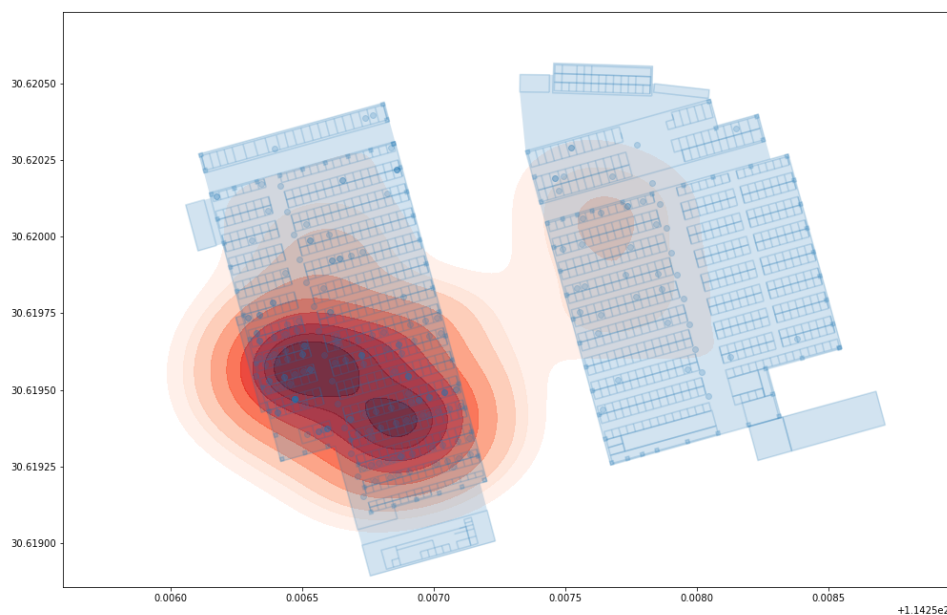


Fig. 7. Kernel density estimation (KDE) of total environmental samples taken at the Huanan Seafood Market. Data sourced from Worobey et al. (2022b).

Given this sampling bias, to assess the statistical significance of environmental positive locations, Worobey et al. (2022b) used a kernel density based relative risk function estimator. The ratio of 2D-kernel density estimates for environmental positive sample locations to a control consisting of all environmental samples (both positive and negative) was implemented using a fixed kernel bandwidth in sparr (Davies et al., 2018). Using the

same dataset and methodology, we overlaid the position of wildlife stalls and the HSM toilets on a spatial relative risk analysis map of environmental positive samples relative to a null model of all sampled stalls (Fig. 8a). The highest statistically significant elevation in density of positive environmental samples relative to sampled stall distribution is centered on the HSM toilets. We note 26 stalls plus 4 sewer locations that tested positive by PCR or Next Generation Sequencing (NGS) are located within a 45m radius of the HSM toilets.

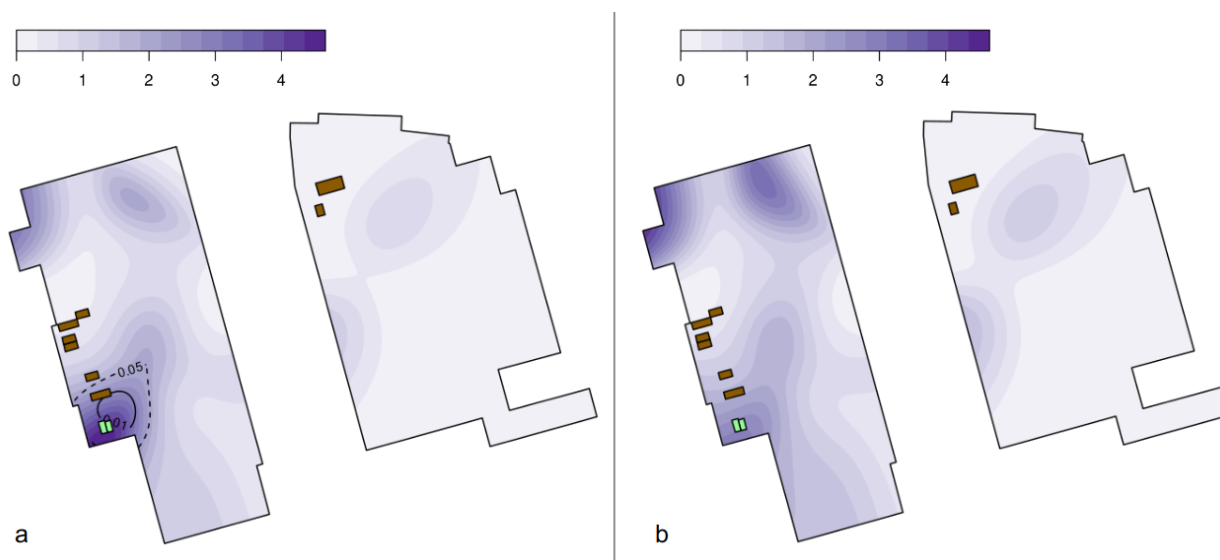


Fig. 8. Relative risk analysis of environmental positive samples using sparr (Davies et al., 2018). a) Ratio of the environmental positive density to control density (environmental positive and negative) using the same dataset and methodology as Worobey et al. (2022b). Statistically significant elevated risk regions indicated by dashed and solid contours; b) Ratio of the environmental positive density to control density (environmental positive and negative), where, in stalls with multiple positive environmental samples, only a single positive is used, and environmental negative data has been de-duplicated. Brown polygons: wildlife stall locations; green polygons: toilets for Western section.

We repeated this process, however for stalls with multiple environmental positive samples, only a single environmental positive sample was used. This addresses one potential source of bias in the datasets, whereby the number of environmental negative samples in stalls with positive samples was not reported at all. However, a potential inherent bias still remains in that even for stalls with one positive sample, the number of negative samples taken at the same stall are unknown. The greatest increase in density of positive environmental samples relative to sampled stall distribution is located at two locations in the northern section of Western part of the HSM, while a third high-risk positive region over a null model is centered on the HSM western section toilets (Fig. 8b).

We then repeated the analysis again using a single sample location for stalls with multiple environmental positive samples, but with a control consisting of (de-duplicated) environmental negative samples (Supp. Fig. 18a). To mitigate potential asymptotic bias, a single kernel bandwidth was used for both high and low point density smoothing with a spatially adaptive kernel bandwidth estimator (Davies et al., 2018) (Supp. Fig. 18b). For

both scenarios, elevated spatial risk over a null model is found for two regions in the Northern end of the Western side of the market, and over the HSM toilets.

It is now known that SARS-CoV-2 viral shedding in stools is common in COVID-19 patients (van Doorn et al., 2020) and toilet flushing has been demonstrated to generate large numbers of droplets in the size range 0.3 - 3 μm (Schreck et al., 2021). Indoors, sub 20 μm particle motion is more strongly controlled by air flow than gravity (Nazaroff 2022). Fecal aerosol transmission of SARS-CoV-2 generated through toilet flushing was a likely cause of a community outbreak in Guangdong apartments (Kang et al., 2020). We note public toilets commonly do not have a lid that can help suppress the generation of aerosolized droplets (Cai et al., 2022). While aerosolized SARS-CoV-2 particles linked to aerosol generation from the HSM toilets may be associated with a number of environment PCR-positive sample locations surrounding the toilets, there does not appear to be a strong spatial link between case locations and the PCR-positive sample locations in the Southwestern corner. As such, it is not clear that the PCR-positive stalls in the Southwestern corner were linked with transmission.

The spread of SARS-CoV-2 virus particles from the HSM toilets is also consistent with the poor ventilation documented in the Southwestern corner of the market [18, 18a]. Interestingly, a Caixin article discussing cases at the HSM mentions *“the patients were mainly distributed in the stalls in the west district, but the east area was also affected. In contrast, the sanitary environment in the west district is even worse, and the pedestrian area in front of the stalls is full of sewage and poor ventilation.”* [17, 17a].

Gao et al. (2022) found that *“All the four sewerage wells in the market tested positive”* and suggested that *“either contaminated sewage may have played a role in the cluster of cases in the market or that the infected people in the market contaminated the sewage”*.

When the HSM map is divided into a grid, and the percentage of environmental samples showing positive PCR tests is calculated per cell, the Western side of the market shows more cells with a higher percentage positive, regardless of grid size (Supp. Figs. 19-21). However, both the Northern part of the Western section and the Southwestern parts of the Western section mostly show higher percentage positives than other parts of the market. Indeed, the distribution reflects a relative risk based analysis approach (Fig. 8, Supp. Fig. 18). While the distribution of PCR positive stalls in the Southwest corner of the market may be related to aerosol spread from the HSM toilets -given the highest estimated relative risk probability at or around the toilets- the increased relative risk relative to a null model in the Northern section of the Western part of the HSM approximately correspond to grid cells with higher than average percent positive sample results. We infer this is likely a result of SARS-CoV-2 shedding by infected human cases.

Worobey et al. (2022b) completely ignored the location of the HSM toilets, which may have erroneously led to implicating a link to several wildlife stalls as the source SARS-CoV-2 at the HSM. We observe that environmental-positive stalls in the Western section of the market (Gao et al., 2022), rather than any association with animals at wildlife stalls, are

more consistent with a combination of: 1) contamination by COVID-19 infected vendors traveling to and from the Western section toilets and HSM restaurants, 2) aerosol spread from the HSM toilets, 3) viral shedding by infected vendors and shoppers as they moved through streets and visited stalls, and 4) positive stall locations coinciding with confirmed COVID-19 cases.

Market cleanup

A timeline of HSM environmental sampling and closure is shown in Fig. 9. The initial sampling occurred on 30 December, with all environmental samples testing negative. Over 500 environmental samples were collected on 01 January 2020, and a second round of environmental sampling was conducted on 12 January (Gao et al., 2022)

Dec 30	<ul style="list-style-type: none"> • "Emergency Notice on Doing a Good Job in the Treatment of Pneumonia of Unknown Cause" internally issued by the Wuhan Municipal Health Commission [28, 28a] • 7 suspected SARS cases at Wuhan Central Hospital reported by Li Wenliang [28, 28a, 29] • City-wide screening targeting cases with "exposure history with Huanan market" (Joint WHO-China Study. 2021b) • Wuhan CDC and Jiangnan CDC visit Huanan market for environment sample collection, all negative
31	<ul style="list-style-type: none"> • Epidemic prevention personnel appeared in the Huanan Seafood Market to disinfect [28, 28a] • First floor of Infectious Diseases Department of Union Hospital converted to 24 bed respiratory infectious disease isolation ward [28, 28a] • Affected by the "pneumonia incident of unknown cause", a significant drop in traffic to HSM was noted by HSM vendors "in recent days" [18, 18a] • Pneumonia epidemic reported by Wuhan Municipal Health Commission, 27 cases identified, 7 in serious condition [30, 30a] • Continued epidemiology surveillance focussed solely at several hospitals close to HSM, HSM and HSM neighborhood (Joint WHO-China Study. 2021b)
Jan 01	<ul style="list-style-type: none"> • 8am Huanan Seafood Market closed [17, 17a, 28, 28a] • Staff wearing white anti-chemical suits appeared and prepared for further disinfection [28,28a] • Environmental sampling, 27 samples found PCR +ve (Gao et al. 2022)
02	<ul style="list-style-type: none"> • Large number of sanitation workers carried out cleaning operations at the Huanan Seafood Market "sampling all over the market"[28,28a]
03	<ul style="list-style-type: none"> • Wuhan Municipal Health Commission "completed the environmental sanitation disposal of Huanan Seafood City, further hygiene investigations underway" [31,31a] • Urgent Notice on Doing a Good Job in the Treatment of Pneumonia of Unknown Cause officially published by Wuhan Municipal Health Commission [32, 32a]
12	<ul style="list-style-type: none"> • Second major environmental sampling event at HSM, c. 70 samples, 3 PCR +ve (Gao et al. 2022)

Fig. 9. Timeline of the events happening at and near the Huanan Seafood Market between 30 December 2019 and 12 January 2020.

Six SARS-CoV-2 positive environmental samples were sampled on 12 January, in the second major sampling event (Gao et al., 2022). Unlike other samples, these six samples lacked a PCR Ct (PCR cycle threshold crossover) value, and instead were identified as "PCR+" or "PCR\)", and were only confirmed through NGS. We note that three of these samples: Q37, Q64, and Q70, which include the iron container or "cage" in the inner room, as well as the "inner surface of freezer" in stall 08-25, were the only samples where RT-PCR testing was negative amongst all the samples that were confirmed through NGS (Gao et al., 2022), indicating low nucleic acid content for these samples. We further note that NGS using the Illumina MiSeq is index-hopping prone, and has a higher base call error rate (median 0.473% with standard deviation 0.938%) compared with other Illumina platforms (Stoler and Nekrutenko 2021). This raises the possibility that these three PCR-negative samples

may not have been positive at the time of sampling. However, neither the NGS coverage nor the genomes from the samples were available, so the exact nature of these samples and their coverage are impossible to ascertain.

Stall type risk

A lack of a clustering of environmental PCR-positive stalls distributed around wildlife stalls is inconsistent with the widespread infection of animals. Only a single wildlife stall, West 6/29-33, tested PCR-positive in the entire HSM (Joint WHO-China Study 2021b; Gao et al., 2022) (Figs. 3 and 11). Curiously, although Gao et al. (2022) detected SARS-CoV-2 in sewers or sewerage wells outside this stall, no other stalls in the entire 6th street showed positive environmental samples. Any animal transmission at this stall would need to have been localized, without further spread to nearby wildlife stalls. Indeed, we find the distribution of PCR positive stalls at the market more consistent with human environmental contamination following human-to-human transmission, as the distribution of PCR positive across the categories of products sold was rather homogeneous, with a slight increase over average for vegetables and poultry (Fig. 10a).

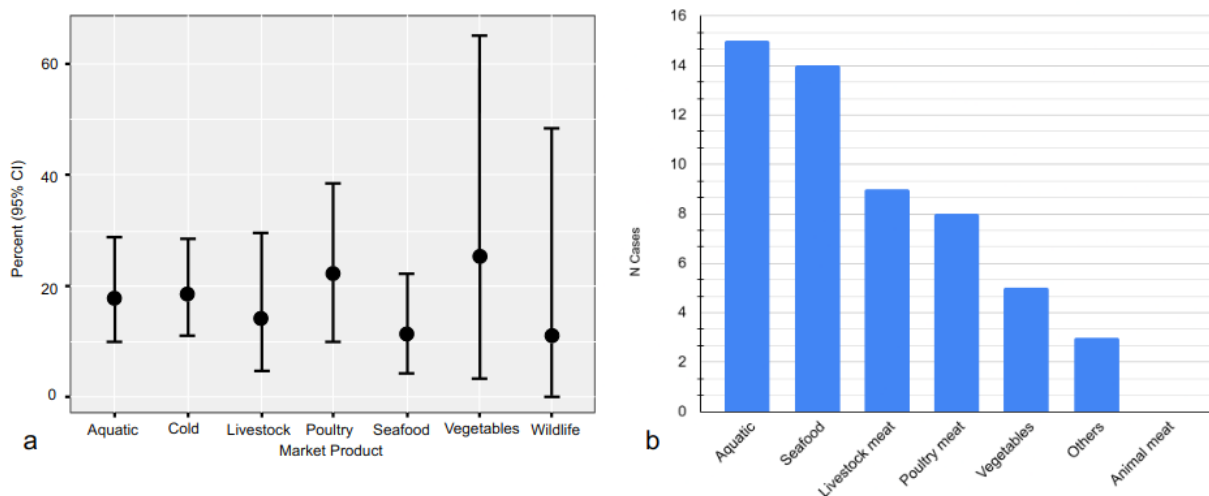


Fig. 10. a) Percentage positive environmental samples associated with different products in the HSM. Data from Joint WHO-China Study (2021a). Nine of the ten stalls selling farmed wildlife products were sampled. **b)** Case numbers by vendor produce type. Note, there were 30 cases in total, with several vendors selling more than one produce type and counted more than once. Data from Joint WHO-China Study (2021b).

Case numbers by type of goods sold show the highest case numbers for aquatic products vendors, which is consistent with a significant percentage of stall owners involved in freshwater aquatic products (48%) and seafood (42%) businesses. Livestock meat sellers did not show any higher prevalence of infection. In fact, the highest infection rates were for vegetable sellers (Fig. 10b, Table 3).

Group	N Cases	Total	Morbidity (%)
Vegetables	5	108	4.6
Poultry meat	8	230	3.5
Seafood	14	484	2.9
Livestock meat	9	318	2.8
Freshwater aquatic products	15	559	2.7
Others	3	266	1.1
Domesticated animal meat	0	15	0

Table 3. Total cases by vendor sale category. Data from Joint WHO-China Study (2021b).

We further note that the only three environmental samples from which Gao et al. (2022) were able to isolate SARS-CoV-2 viruses were all located in the Eastern block of the Western section of the market, not in the Southwestern section where wildlife stalls were located (Supp. Fig. 22).

Wildlife stalls

We reviewed photographic and video evidence where available, for wildlife selling and ‘unknown meat’ stalls in the Southwestern section section of the market (Fig. 11) (Worobey et al., 2022b)[19]. Stall West 8/25 was categorized as ‘Domesticated wildlife’ by Worobey et al. (2022b). The Joint WHO-China Study (2021b) (Appendix F, Table 3) documents this stall as only licensed to sell snakes. The stall business name was 武汉市江汉区鄂东红星野味经销部 (Edong Red Star Game Distribution Department). Worobey et al. (2022b) note that the name of the company contains the word ‘game’ and that the stall owner was fined for selling hedgehogs that lacked a valid certificate of origin in May 2019 [20,20a]. However we note that hedgehogs are an implausible intermediate host for SARS-CoV-2. Hedgehog ACE2 has been found to have low affinity with the receptor binding domain (RBD) of SARS-CoV-2, and no record of infection of hedgehogs with SARS-CoV-2 have been reported to date (Andy 2021; Niu et al., 2022)[21]. In addition, hedgehog ACE2 has been found to be unable to support SARS-CoV-2 pseudotyped virus entry (Xiong et al., 2022).

Furthermore, given the fine, it is plausible to assume the owner may not have wanted to risk a more serious penalty by continuing to trade illegal wildlife. On review of videos of this stall in the 2017-2019 period, we found no evidence for sales of any animals other than snakes, indicating hedgehog sales in this period may have been limited (Supp. Figs. 23-26).

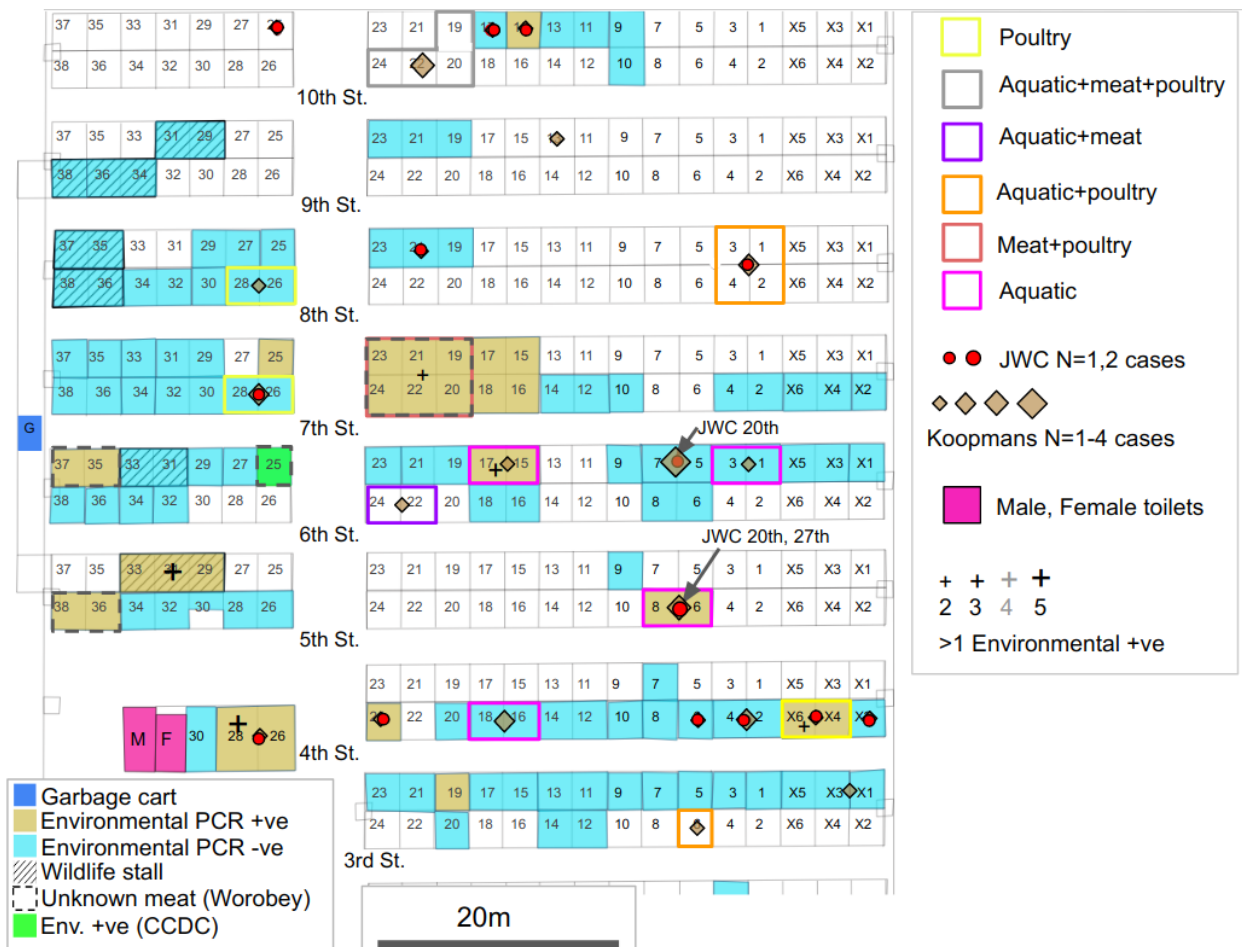


Fig. 11. Southern and Central portions of the Western section of the HSM showing wildlife stalls, environmental PCR tested stalls and COVID-19 cases. A stall fined for illegally trading hedgehogs is located at West 6/29-33. Stall West 7/25 (green) was noted in a CCDC report as environmental positive (Guizhen 2020), but was shown to be environmental PCR negative in both Joint WHO-China Study (2021a) and Gao et al. (2022). Joint WHO-China Study (2021a) (JWC) COVID-19 cases shown as red dots, all cases are in week 3: 20-27 December except two cases in the week of 13-20 December 2019 as indicated. Koopmans [10] cases shown as diamonds.

Stall West 8/19-23 and West 7/20-24 “腊味香食品有限公司” (company name in 2016 registered as “武汉市江汉区平平腊味香商行” is a large corner stall (Fig. 11). The stall sold frozen, packaged, and cured livestock meat (Supp. Figs. 27-29) [19]. The stall was categorized by Worobey et al. (2022b) as ‘Unknown meat’, yet we can find no indication that any meat other than livestock meat was sold at this stall.

Stall West 7/25 “荣昌冻品” was also classified by Worobey et al. (2022b) as ‘Unknown meat’, inferred from photographic evidence. However on review, we find that it was a frozen food cart, with no evidence for meat sales [19] (Supp. Figs. 30 and 31).

Stall West 7/31-33, is categorized as a wildlife stall in both Joint WHO-China Study (2021b) and Gao et al. (2022), and was sampled as environmental negative for SARS-CoV-2. The stall is poorly captured in available video footage, but no cages can be seen outside the stall in December 2019 [19](Supp. Figs. 31 and 32).

Stall West 6/29-33 was photographed selling caged raccoon dogs in 2014 by Prof. Eddie Holmes, and was suggested by Holmes on August 2, 2022 to be the specific stall from which SARS-CoV-2 spilled over from animals “*We can’t prove it is this exact stall but the data is very suggestive*” [22]. This statement raises the specter of not one but two logical fallacies. The first being a *conjunction* fallacy, in which a strict subset is illogically considered to be more probable than a larger set that contains it. It is already a vastly implausible claim that, out of all the hundreds of thousands of caged wild animals in China, zoonotic spillover coincidentally happened to occur in a city with extremely low wild animal consumption compared with cities and villages in Southern China, no known bat sales at markets, no SARS-CoV-2 related viruses in the surrounding province, and such a low risk of spillover that the city was used as negative control for SARS seropositivity (Wang et al., 2018). It then becomes even *more* constrained and improbable - not less, as the authors apparently hope - to additionally claim that one of them (might have) photographed that exact stall years previously. The second problem is what can be considered a *hidden variable fallacy*. The reason Prof. Holmes photographed those particular cages, as opposed to any others in the country, was that he was visiting the Wuhan CDC, which at the time was located near the Jianbei Branch of the Xinhua Hospital, 3.8km SE of the HSM.

In a prior commentary showing the same caged raccoon dog photos, Holmes notes the role of the HSM in the emergence of SARS-CoV-2 is uncertain (Zhang and Holmes 2020). We were only able to find video footage of this stall on 31 December 2019 with a closed roller-door (Supp. Fig. 33). The business owner was fined for illegally selling hedgehogs on May 7, 2019, along with two other stall owners [20,20a]. We note that these stall owners were not fined for illegally selling any other types of wild animals.

We also note that stalls West 6/29-33 and West 8/25 appear to have been closed on 31 December 2019, before the initial sampling on 01 January 2020. As such, the stalls may have been unsampled on 01 January, and potentially not decontaminated the following day on 02 January.

Environmental samples at stalls West 5/36 and West 5/38 were found to be positive for SARS-CoV-2 (Joint WHO-China Study 2021b). Worobey et al. (2022b) classified this stall as ‘Unknown meat’ inferred from photographic evidence. We note that on 13 February 2020, the stall had no sign and as such it is not clear if the stall was occupied in December 2019 (Supp. Fig. 34).

Seafood stall West 7/15-17 had three environmental positive samples one of which, sample A20, was found to be lineage A and, as we discuss below, has several anomalies. The stall was shown by Koopmans [10] to have a COVID-19 case as at 15 December 2019, but the case was not reported in the Joint WHO-China Study (2021a). Video footage showing fish in plastic containers was found for this stall (Supp. Fig. 35).

Lineage A sample A20 inconsistencies

SARS-CoV-2 lineage A and lineage B strains were both circulating in Wuhan by the end of December 2019. Two of six COVID-19 cases in a family which visited Wuhan in the period 29 December 2019 - 4 January 2020 had samples fully sequenced and were found to be lineage A (HKU-SZ-002a (MN938384) and HKU-SZ-005b (MN975262)). The family had no contact with the HSM, and initial infection was likely through a Wuhan hospital visit on December 29 (Chan et al., 2020). Additionally, case 62M with onset either on December 1 (Huang et al., 2020) or December 12 (Zhou et al., 2020), was also infected by the lineage A strain.

A lineage A genome was recovered from environmental sampling on 01 January at the HSM at stall West 7/15-17 (sample A20). We note sample A20 is a statistical outlier relative to other samples sequenced by NGS with anomalous Ct to read depth ratio (Supp. Info.). It is important to note also that this solitary lineage A genome recovered contains two additional mutations C6145T and G26262T, both rare and appear only in later SARS-CoV-2 genomes (Supp. Info.). We further note a highly variable read depth around position 28144 and cannot rule out amplicon or cross-sample contamination without access to raw data (Supp. Info.). Worobey et al. (2022b) used this as their sole piece of physical evidence linking lineage A to the market, but these issues have placed its reliability into doubt.

We further note that the description of the collection of samples A20 and A18 from “gloves” and “Shoe covers and soles” is ambiguous and it is unclear if environmental sampling personnel PPE or vendor footwear and gloves left at stalls were sampled (Supp. Info.).

Xinfadi COVID-19 outbreak

It is instructive to compare the December 2019 COVID-19 outbreak at the HSM with a similar occurrence at the Xinfadi wholesale market in Beijing in June 2020. After the outbreak at the Xinfadi market, 5,342 environmental samples were collected from the surfaces of vending booths and food packages (Pang et al., 2020). Of these, 368 SARS-CoV-2 qRT-PCR positive environmental samples were found (Pang et al., 2020). Normile (2020) and Yang et al. (2021) noted that the combination of poor hygienic conditions, and cool humid air may have provided an ideal amplification environment for SARS-CoV-2 at the Xinfadi market, and Normile (2020) concluded that “*the virus was spread by people working and visiting in the markets.*” The expected conditions at the HSM, with a cool December temperature (3-11°C), and likely significant humidity given the seafood nature of the HSM (with abundant seafood on ice and live fish in water in plastic containers) and documented poor ventilation [17,17a] may have also been favorable for SARS-CoV-2 spread. Environmental PCR-positive sample distribution at the Xinfadi market appears moderately correlated with locations of employee COVID-19 cases. Although a direct comparison with the HSM is difficult, as no density of environmental sampling maps are provided for the Xinfadi market sampling, and a strong location-dependent sampling bias is evident at the

HSM, the overall case and PCR positive environmental sample distribution is not markedly dissimilar to the HSM.

Additional Sampling and Testing

On 10 February 2020, Wu et al. (2021) collected 80 environmental samples in and around wildlife stalls in the Western section of the HSM. These 80 samples plus an additional 22 environmental samples from animal stall utensils, products and surface swabs at the HSM that had been in cold storage, were analyzed for coronaviruses (CoVs). Four CoV strains were identified in samples, two from blocks and knives in cold storage: Rabbit CoV HKU14 (JN874561.1); Erinaceus hedgehog CoV HKU31 (MK907287.1) and surprisingly, even after 40 days of market closure, two CoVs were identified from the ground of wildlife selling stalls: Canine coronavirus strain 1-71 (JQ404409.1); and rat CoV Longquan- 370 (KF294371.1). Four pools for a total of 37 samples from chopping blocks and knives from animal selling stalls were analyzed. Chopping blocks and knives are likely to have been exposed to tissue and blood from numerous animals at stalls. However, no SARS-CoV-2 related viruses were found on these items, or indeed, any environmental samples at stalls analyzed by Wu et al. (2021). These positive results for multiple animal hosted coronaviruses, but negative results for SARS-CoV-2 related viruses, led Wu et al. (2021) to conclude that spillover from animals to humans may not have occurred at the HSM.

A team from the Wuhan Institute of Virology (WIV) together with researchers from the Huazhong Agricultural University (HZAU) tested both environmental samples and frozen animal samples from the HSM on 12 January 2020 (Cohen 2020b) [23,23a]. SARS-CoV-2 RNA was detected in environmental samples, but not in any animal samples. This led Shi Zhengli from the WIV to conclude, like Gao Fu [2], and Gao et al. (2022) that the HSM was likely a super-spreader location, and not the source of human SARS-CoV-2 infection (Cohen 2020b).

Summary

- No live animal samples or animal samples from cold storage were found to be positive for SARS2r-CoVs (Wu et al., 2021; Cohen 2020b; Joint WHO-China Study, 2021a; Gao et al. 2022) and no samples from knives or chopping blocks at wildlife stalls were found to be positive for SARS-CoV-2 (Wu et al., 2021).
- The locations of COVID-19 infections at the market were each more than 10 m from the closest wildlife stall (Fig. 3). With the earliest cases (up to December 20) located more than 20 m from nearest wildlife stall (Joint WHO-China Study 2021b) and greater than 10 m away in Koopmans maps [10].
- The COVID-19 case distribution at the HSM is effectively random, and consistent with human-to-human transmission in shared communal areas, with no evidence of spread from a local point source.

- There is no statistical correlation between the location of cases and wildlife stalls at the HSM. No evidence was found supporting the hypothesis of sustained transmission from wild animals to humans.
- The highest relative risk for environmental positive samples relative to a null hypothesis is centered on the HSM toilets, with areas in the northern section of the Western part of the HSM also higher relative risk.
- Only a single wildlife stall out of six in the Western section was found to be PCR-positive, which is consistent with the base rate of environmental positivity for stalls in the Western section of the HSM.
- The distribution of environmental PCR-positive stalls is consistent with contamination by COVID-19 cases and with aerosol spread from the HSM toilets, with no clear evidence to support the idea that environmental positive samples were related with animals at wildlife stalls.
- Four of the 10 earliest cases were unrelated to the market, which shows that human to human transmission was occurring in Wuhan outside the HSM at the same time as the first known cases at the HSM.
- Lineage A sample A20 is anomalous both because the relationship of Ct values to read depth make it an outlier, and because it contains SNVs not seen in Wuhan until much later in 2020. This sample also exhibits highly variable read depth within 60 nt of position 28144. Thus, we cannot rule out potential contamination of this sample.
- There is significant evidence for human-to-human transmission, with multiple cases occurring at the same stall evident in Joint WHO-China Study (2021b) maps. This is even more apparent in the map of cases by Koopmans [10], with 50% of cases (with clusters of up to 4) located at the same stalls.

Market Animals are an unlikely introduction source

Only a few potentially susceptible live animals were sold at the HSM in November and December 2019. We consider the following wild animals as candidate intermediate hosts: Siberian Weasel, Mink, Raccoon dog, Red fox, and the following species of unknown potential as intermediate hosts: Pallas squirrel, Marmot, Coypu, Chinese bamboo rat, Red squirrel and Complex-toothed flying squirrel (Supp. Table 2, Supp. Data). For these animals, for the four Wuhan markets with animal trade, a total monthly mean of 190 sales was estimated by Xiao et al (2022). We expect the winter months to have significantly less sales, and estimate the number to be approximately 50 per month sold at the HSM in November and December. While rabbits have been shown to be susceptible to SARS-CoV-2, peak virus titres post infection were found to be lower than the minimal dose required for infection and we infer that sustained transmission between animals is unlikely (Mykytyn et al., 2021). We estimate approximately 60 Chinese hares were sold per month in November and December at the HSM. Even combining all potential host animals and animals of unknown

SARS-CoV-2 susceptibility sold at the HSM, the total caged animal population was small. This fact is difficult to reconcile with an animal introduction to humans, leading to human adaptation at the animal-human interface in the market. The reservoir of animals was simply too limited, and given their low numbers, the number of humans in contact with them was also very few. This is a very different situation from a wildlife farm, where the animal reservoir is large and the human employees in contact with them are far more numerous.

CNN footage (Stout 2020) showed a market in Qingyuan, a city of 4 million people in Southern China several hundred kilometers South of Wuhan, that had far more intense live mammal and wild animal trade. Indeed, it can be considered tens to hundreds of times larger than the wild animal trade in Wuhan. This indicates that the wildlife trade in Southern China dwarfs in magnitude the numbers at the HSM in Wuhan. This is important for location exclusivity, as it is significantly more likely that any spillover would happen in large wildlife markets prevalent in Southern China, where both the number of mammal sales was far greater, and the geographical proximity to bat reservoirs much closer, compared with Wuhan where very little such trade exists.

An alternative explanation could then be that the viral adaptation to humans happened on a farm, and not at the HSM. However, given that so few animals were sold in Wuhan, such a farm would have to sell to many other markets. But then the probability of this farm triggering an infection in Wuhan, of all the places it would have to sell to, becomes small. So, while a random infection in China via such a farm remains a possibility, it only represents a small zoonosis risk factor to have been observed in Wuhan of all places, while research-related risk factors are predominant in Wuhan and not similarly applicable in other areas.

One may try to argue that such a farm could actually be based in Hubei and have near exclusive connection to Wuhan (or maybe a few more cities in Hubei). Still, given the small number of animals sold in Wuhan, even if that farm was selling the same number of animals in about ten other places in Hubei, it still would be hardly viable as a commercial venture, as we estimate no more than 150 (250 including rabbits) potentially SARS2r-CoV susceptible animals were sold in Wuhan markets in November. In addition, no evidence of SARS-CoV-2 infection in any of the farms that supplied animals to the HSM was found (Wang et al., 2022; He et al., 2022).

No evidence of coronaviruses with a RBD or RNA-dependent RNA polymerase (RdRp) closely related to those found in SARS-CoV-2 has been detected in bats in Hubei, despite years of intensive sampling done by the WIV (Hou et al., 2010; Fan et al., 2019; Latinne et al., 2020). It has been noted that SARS-CoV-2-like BatCoVs are mostly located in the river valley ecological corridors from Yunnan, China to Laos and Vietnam. So, not only would a Hubei spillover argument suppose BatCoV undersampling in Hubei (Yu et al., 2019; Latinne et al., 2020; Wu et al., 2021), but it would go against our understanding of the distribution of these SARS-CoV-2-like bat Covs across very specific Southern ecological corridors.

We note that such a problem did not exist with the identification of the source of SARS, for which links were easily made between these ecological corridors and patterns of trade. This extended up to the point at which SARS emerged at the Eastern end of that network, with multiple cases in animal handlers, restaurants and animal stocks detected in Guangdong province (Fig. 13).

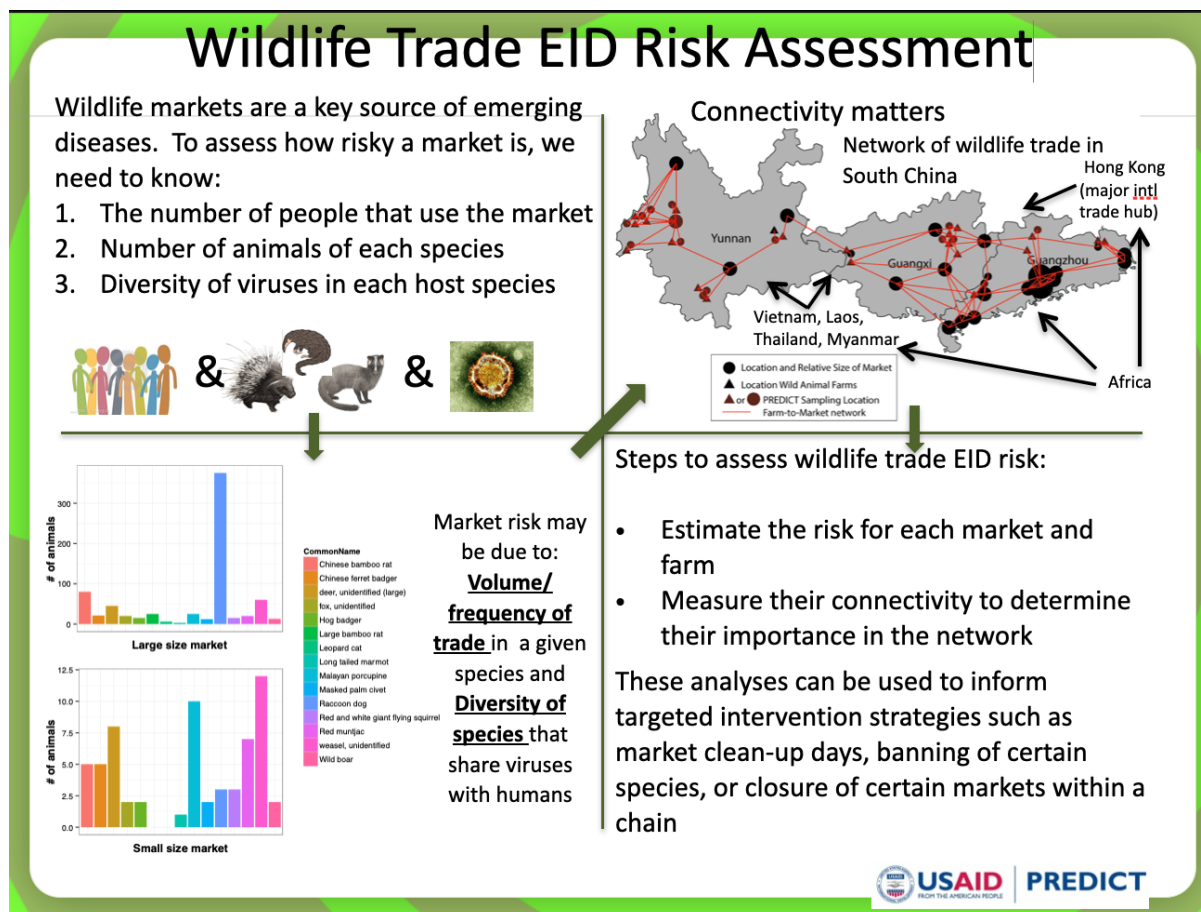


Fig. 13. Wildlife trade risk assessment by United States Agency for International Development (USAID). An early wildlife trade network analysis connecting Yunnan to Guangzhou, which was used to deduce the route of which (in 1990-2002) SARS-CoV was brought from Yunnan to Guangzhou.

Raccoon dogs are an unlikely cause of the outbreak in Wuhan

The most favored intermediate animals for a hypothesized spillover at the HSM are raccoon dogs (Maxmen 2022). Despite their name, raccoon dogs (*Nyctereutes procyonoides*) are neither raccoon nor dog, and come with a history of being suspected as virus carriers. Several were infected with SARS during the outbreak in 2002 (Guan et al., 2003). That prompted some scientists to wonder if they were the intermediate hosts of the virus and had spread it to humans. But the evidence and suspicions fell more heavily on the masked palm civet, and never left. The consensus remains that the original culprit was the

masked palm civet, with raccoon dogs being innocent bystanders, caged in the wrong place at the wrong time in Guangdong wet markets, in proximity to SARS-infected civets.

However, this consensus is not unanimous. Dr. Zhengli Shi of the WIV speculated that the wrong suspect had been identified. Shi and Hu wrote: *"It remains unclear whether the raccoon dogs were infected by the virus from the masked palm civets or the other way around. It is also possible that both animals were infected by the virus from a hitherto unidentified host."* (Shi and Hu 2008). Shi and Hu also noted that *"very limited research has been conducted to survey wild or farmed raccoon dogs."*

It wasn't until May 2003, seven months after the outbreak, that SARS was identified in animals (six masked palm civets and one raccoon dog). But it was a second outbreak, in December 2003, that more decisively identified civets as the animal host of the virus. So, it is natural for some scientists to consider raccoon dogs to be a potential intermediate host of SARS-CoV-2, having obtained the virus from horseshoe bats, its presumptive natural reservoir, and relaying it to humans in Wuhan.

The animals were sold live in small numbers at Wuhan's wet markets (Xiao et al., 2021). A monthly mean of 38 raccoon dogs and 11 palm civets sold in all Wuhan markets (2 vendors at Baishazhou market; 7 vendors at the HSM; 4 vendors at Dijiao market and 4 vendors at Qiyimen market) between May 2017 and November 2019 (Xiao et al., 2021). However, we notice a very high standard deviation in monthly numbers (mean 38.33 ± 17.24), and also note the absence of detailed monthly data. A report by the Joint WHO-China Study (2021a) documents that no raccoon dogs (or minks or foxes) were sold in December 2019 at the HSM, and that no substantial changes in type of animals sold at the 10 wildlife stalls at the HSM in 2019. We also notice that enforcement against selling legitimate likely privately bred hedgehogs (Joint WHO-China Study 2021b, Annex F Table 3) without showing a valid certificate of origin was policed at the HSM [20,20a]. However no evidence of the illicit trade of live wild animals, many of which are on the nationally endangered and on the protected species list in China as indicated by Xiao et al. (2021), was found in the enforcement records of the Wuhan Park and Forestry Bureau in 2019 [20,20a]. Although we assume yearly stationarity and estimate of approximately 50 potentially susceptible animals per month at the HSM in late 2019 (110 including Chinese hares), it is also possible that the wild-caught illegal wildlife trade at the HSM had been mostly curtailed by 2019. If the Joint WHO-China Study (2021a) Table 4 (Supp. Table 3) is used as a proxy for live animals on sale at the HSM in November/December, this indicates little wild game was on sale at the HSM at the end of 2019. Additionally, minimal wildlife trade at the HSM in 2019 would allow Xiao et al. (2021), the Joint WHO-China Study (2021a) and the enforcement records of the Wuhan Park and Forestry Bureau in 2019 [20,20a] to be consistent with each other. If so, this may have potentially been due to a ban that was put in place in 2018 that targeted the consumption of *"wild animals that lacked a valid certificate of origin, or an animal that is on the list of nationally endangered and protected species in China"* [24,24a].

A monthly mean of 38 raccoon dogs sold in Wuhan is an exceedingly small number relative to the 12 million raccoon dog pelts that were produced in China in 2018, according to the China Leather Industry Association, the entity entrusted by the China Ministry of Forestry to compile data on the domestic fur industry [25]. The vast majority of raccoon dog farms are in China's Northeast provinces. In 2017, only 3.55% of raccoon dog pelts were produced outside the Northeast.

Whether the raccoon dogs sold in Wuhan's wet markets were wild-caught locally, farm-raised locally, or imported from afar, is an important question to resolve. The answer would help guide how the search for SARS-CoV-2 in raccoon dogs is conducted. In a February 27 2022 article in Nature (Maxmen 2022), Maxmen wrote that Andersen, an immunologist at the Scripps Research Institute, suggested that raccoon dogs may have been infected on a farm then sold in Wuhan, where they spread the virus to people handling them, or to buyers. The comment was suggested to Maxmen by Andersen for the article. However, that contradicts Andersen's co-authored paper (Worobey et al., 2022b), which notes that the raccoon dogs photographed in the HSM in December 2019, just as the outbreak was beginning, *"appear to be local, wild-caught common raccoon dogs rather than farmed raccoon dogs and that their plush coats are consistent with those observed in the winter"*.

The distinction between locally wild-caught and farmed raccoon dogs is important for two reasons. First, local raccoon dogs are probably less likely to have been infected by SARS-CoV-2 than their cousins in Southwest China, whose habitats are in closer proximity to the Yunnan and Laotian caves that are home to the horseshoe bats, the natural reservoirs of the viruses closest genetically to SARS-CoV-2. It is possible there are bats in close proximity to Wuhan that harbor a SARS-CoV-2-like virus, and that could then go on to infect a local raccoon dog. However, no such bat has yet been found, nor has any raccoon dog in Hubei province been found to harbor a SARS-CoV-2-like virus.

In fact, Dr. Zhengli Shi of the WIV stated in July 2021, *"We have done bat virus surveillance in Hubei Province for many years, but have not found that bats in Wuhan or even the wider Hubei Province carry any coronaviruses that are closely related to SARS-CoV-2. I don't think the spillover from bats to humans occurred in Wuhan or in Hubei Province"* (Cohen 2020b).

Although small sample sizes, fifteen raccoon dogs, seven Siberian weasels, three hog badgers, and three Reeves's muntjacs were collected in rural Wuhan early in the pandemic in January 2020 and tested for SARS-CoVs, with none found (Wang et al., 2022). A larger, China-wide study sampled 1,941 game animals and tested for viruses including 423 Civets, and 95 raccoon dogs (He et al., 2022). All samples except for 11 pangolin and 7 Malayan porcupine samples were taken between February 2020 and 2021. No SARS-CoVs were identified. Additionally, 18 species were sampled from refrigerated and frozen samples from the HSM and warehouses supplying the HSM between January 1st and March 2nd. This included 7 wild animal species, and none were SARS-CoV-2 positive by nucleic acid test (Joint WHO-China Study 2021a)(Supp. Table 3). These results are consistent with

extensive sampling between May and September 2020, during which 27,000 wild animals across China were sampled for SARS-CoVs with all results negative (Joint WHO-China Study 2021a).

Raccoon Dog SARS-CoV-2 susceptibility

We note that the sole published infection experiment of raccoon dogs was performed using the G614 Muc-IMB-1 strain of SARS-CoV-2 (Freuling et al., 2020). The experimental R_0 value was 1. The D614G mutation has been experimentally found to improve infectivity for the *Canis lupus* ACE2 receptor by 2.8X-3.4X (Zhang et al., 2021; Yurkovetskiy et al., 2020). With carnivore (ferret) ACE2, a SARS-CoV-2 D614G variant was found to successfully transmit, but not with ancestral D614 (Xiao et al., 2021; Yurkovetskiy et al., 2020; Zhou et al., 2021). Raccoon dog ACE2 has a 99.24% amino acid identity to *Canis lupus* ACE2, with 100% identity for 18 residues at the dog ACE2/RBD interface. Consequently, we infer that a progenitor D614 strain would have a reduced transmissibility if infection of raccoon dogs by this strain were possible. As such, we infer that intra-raccoon dog transmission would likely be limited, and unlikely to sustain a reservoir of the ancestral D614 strain. The increase of infectivity of the G614 SARS-CoV-2 spike protein was found to be generalizable on all cell lines and ACE2 molecules tested (Zhou et al., 2021), suggesting that this result is robust to a large variety of species and tissues.

In a study of molecular affinity for SARS-CoV-2 binding to ACE2 from a range of potential hosts, raccoon dog ACE2 binding affinity to SARS-CoV-2 is lower than for cow and rabbit ACE2, species that are known to have either very poor susceptibility to (cow) or poor capability for transmission (rabbit) of SARS-CoV-2 Wuhan-Hu-1. Raccoon dog ACE2 has a similar binding affinity to SARS-CoV-2 as for dog ACE2 (Wu et al., 2020).

Using ACE2 receptors from a variety of species, Zhao et al. (2020) undertook receptor binding to SARS-CoV-2 lentiviral vectors using HEK293T cells. Immunoprecipitation (IP) assays show only human, monkey and feline ACE2 as susceptible (in that order). Rabbit ACE2 binding affinity is borderline, while raccoon dog ACE2 does not show any infectivity using an IP assay. While lentiviral infection of HEK293T cells shows borderline raccoon dog ACE2 susceptibility with a furin cleavage site (FCS), without a FCS, susceptibility using this system increased for raccoon dogs to be on the same level as feline ACE2. However, we infer that IP represents the real infectivity as spinoculation (centrifugal inoculation) with lentivirus has a tendency to over-represent the real infectivity with the lenti-293T system. As such, lentiviral infection of HEK293T cells may over-represent true infectivity.

More recently, a Danish study sampled and tested 12 raccoon dogs alongside 144 other carnivores near a mink farm that had been infected by SARS-CoV-2. None of these samples were found to be positive for SARS-CoV-2 by qRT-PCR (Boklund et al., 2021).

Summary

Market animals at the HSM are an unlikely introduction source for humans given that:

- The evidence of human cases in the market did not begin in the stalls with animals or even near those stalls.
- The early January statistically significant elevation in density of positive environmental samples is located over market toilets, a known source of prior coronavirus transmission, or at two locations at the North end of the Western section of the HSM, and associated with human cases.
- Potential intermediate hosts were sold in very small numbers in Wuhan (although records are likely incomplete), with the probability of spillover far more likely in other parts of China where wildlife trade, farming and consumption is significantly greater.
- The introduction of SARS-CoV-2 at a farm in Hubei is extremely unlikely, given the absence of detection of SARS-CoV-2 related coronaviruses within the local bat reservoir.

Raccoon dogs specifically are an unlikely cause of the outbreak for the following reasons:

- Experimental infection of raccoon dogs used a more infectious D614G strain than ancestral D614, as such the viability of raccoon dogs as a viable host reservoir to a SARS-CoV-2 progenitor virus should be considered to be unproven.
- There have been no natural infections of a raccoon dog documented by any strain of SARS-CoV-2 anywhere in the world (World Organisation for Animal Health 2022; Boklund et al., 2021).
- Raccoon dogs sold in Wuhan likely originated from Hubei Province, where SARS-CoV-2-related coronaviruses have not been detected.
- Raccoon dogs were sold in Wuhan in very small numbers relative to their overall trade in China (likely less than 10 per month at the HSM in late 2019) making the likelihood that a raccoon dog would be the culprit in Wuhan, of all places, and *only* Wuhan, exceedingly small.

Biases and confounding factors

Ascertainment bias: Sampling methodology

Ascertainment bias, in which certain types of data are more likely to be observed than others due to factors such as ease of collection or even the expectations of the

experimenters, can significantly impact the validity of the final conclusions. In this instance, bias in the sampling process is evident in the distribution of specimens taken at the HSM, as well as in the sampling methodology - particularly the number of samples taken per stall (Joint WHO-China Study 2021b). Neither the methodology of sampling, nor the density of samples per stall as described in the WHO-China joint report specified that a uniform sampling pattern was used (Joint WHO-China Study 2021b). On the contrary, rather than a uniform sampling distribution based on a per-stall or per-unit area of the market basis, environmental sampling was focused on animal stalls and stalls with human cases.

This accords with specimen collectors exhibiting an *a priori* expectation that animals were involved. The initial focus on sampling of the HSM appears to have been partially based on an assumption that wildlife sales within the market may have been the origin of the virus, as indicated by large sampling bias in the southwestern corner (Gao et al., 2022). This preconception of animal involvement is even more evident in the second main sampling effort on 12/01/2020, during which 70 samples were taken by the WIV solely focussed on wildlife stalls (Gao et al., 2022)[23,23a]. These 70 samples include all of the positive environmental samples collected from wild animal stalls at the HSM (Gao et al., 2022; Worobey et al., 2022b).

Given the evident sampling focus on the Southwest corner of the HSM, it is worth noting that there are five stalls with more than one positive sample (Fig. 11; Supp data), all of which are larger than a single stall in size. Given their greater surface area, larger stalls are more likely to have multiple samples taken, and therefore have a higher chance of receiving more than one positive sample. We additionally note, one goal of market sampling discussed in Joint WHO-China Study (2021a), to sample “*doors and floors of all the stalls in the blocks where early cases were located*” was not met, as unsampled stalls with COVID-19 cases can be found in all market blocks (Fig. 3). Critically, the Joint WHO-China Study (2021b) did not specify the exact nature and number of each type of environmental sample taken at the HSM. This greatly limits the value of the dataset, since based on the considerations mentioned above, equal sampling coverage cannot be assumed.

A table of environmental positive samples (through PCR or NGS) was provided by both the CCDC (Guizhen 2020) and Gao et al. (2022) but negative samples were not tabulated (Supp data). We can infer from sample numbering that at least five negative samples were taken from West 6/29 (Q62-3, Q65-7) as these numbers were positioned in between five positive samples taken at the same stall. However, as the number of negative samples per stall was not reported, it is impossible to determine the percentage positive number for any stall at the HSM. Worobey et al. (2022b) modeled the effect of 2X sampling bias, however, assuming just 2X oversampling appears to be inadequate to compensate for this bias.

The fact that the sampling at some stalls, for example, West 6/29, was heavily oversampled (we estimate at least 10 samples) relative to other stalls, which we assume mostly had one sample taken, is problematic. Because we do not know the total number of samples taken

on each stall, the fraction of positive samples per stall cannot be determined and cannot be relied upon to deduce the concentration of the virus at each stall. Additionally, we do not know the spatial distribution of sampling within stalls, if sampled stalls regularly had customers enter the stall, or if like stall West 8/25 only had a relatively small opening that customers could talk into. Furthermore, stalls at the market are approximately 2.8 m x 3.2 m for a regular stall, walled off between stalls but open within the stall. Such a layout is conducive to potential widespread contamination across the stall from an infected vendor or customer via respiratory droplets and aerosols spread (Tang et al., 2020). As such, this potentially limits inferences that can be made when multiple positive samples are found at a single stall. We expect, however, contamination across stall boundaries to be attenuated because of limited vectors (aerosol flow, vendor motion) to carry the virus across stall boundaries.

Ascertainment bias: Sample analysis methodology

Sampling by the WIV on 12 January 2020 focussed exclusively on wildlife stalls where 70 samples were taken. Six results were reported, all positive for SARS-CoV-2 using NGS, three of which were PCR-negative. As three PCR-negative samples were sequenced using NGS, we infer that the other 64 samples taken from wildlife stalls at the HSM which were PCR-negative (only 3 positive samples were reported) were also sequenced using NGS. This compares with only 3/65 PCR positive samples sequenced via NGS by the CCDC (Guizhen 2020) and NGS only conducted on PCR+ve samples by Gao et al. (2022), which we can infer as no PCR-ve and NGS positive samples were reported (Gao et al., 2022). This is indicative of an ascertainment bias in analysis whereby testing using more sensitive techniques on perceived 'high risk' stalls was selectively used.

Selection bias

Another potential bias we note is an apparent search bias introduced by Worobey et al. (2022b), who added an "Unidentified meat" category, not seen in environmental sampling maps in Joint WHO-China Study (2021b) or Gao et al. (2022). Worobey et al. describe this category as "*we identified an additional five stalls that were likely selling live or freshly butchered mammals or other unspecified meat products in the south-west corner of the western section of the market*". At the HSM, there were 160 livestock meat and 115 poultry meat stalls. Worobey et al. identified a poultry stall "刘杰家禽批发" West 7/26-28 with an environmental negative sample result as known meat. However, plucked poultry meat is difficult to identify, and we note that this stall is poorly photographed [19]. Curiously however, a stall with a positive environmental sample, "腊味香食品有限公司" West 8/19-23-West 7/20-24 sold pig carcasses and preserved livestock meat (chopped pig legs) (Supp. Figs. 27 and 28). Worobey et al. do not explain their rationale of why this stall was assigned an "Unknown meat" category. We note that of the four stalls in the Western section identified as "Unknown meat" all had environmental positive samples. While the one stall on the East side of the HSM identified as "Unknown meat" also had an

environmental positive sample result. An unknown bias may have been introduced into the “Unknown meat” category of Worobey et al. by focussing on environmental sample positive stalls.

Base rate neglect fallacy

Here we undertake a simple analysis to determine if wildlife stalls are indeed more likely to have a higher environmental positive result than non-wildlife stalls. While environmental sampling results from Joint WHO-China Study (2021a) and Gao et al. (2022) differ only slightly, more significant differences are evident in datasets in Worobey et al. (2022b), where an additional “unidentified meat” category was added. To account for this more significant difference, we undertake our analysis using datasets from both Joint WHO-China Study (2021a) and Worobey et al. (2022b). While Worobey et al. (2022b) utilize the number of environmental positive samples per stall as part of their modeling, as discussed above, we believe this introduces an inherent bias into the analysis. We therefore use a single positive or negative environmental sample result for each stall that was sampled as per maps from the Joint WHO-China Study (2021a) and Gao et al. (2022).

We notice that the average ratio of stalls with positive non-wildlife environmental samples to total amount of non-wildlife sampled stalls in the Western area of the HSM, 18/108 (17%, when unidentified meat stalls are counted as wildlife), 22/112 (20%, when unidentified meat stalls are not counted as wildlife) and 19/109 (17%, Joint WHO-China Study), is approximately comparable to the domesticated wildlife-only stall positive-to-total-wildlife-stall environmental sample ratio 2/8 (25%, when unidentified meat stalls are counted as wildlife), 2/12 (17%, when unidentified meat stalls are not counted as wildlife) and 1/8 (12.5%, Joint WHO-China Study). This indicates that there is no significant increase in the percentage of domesticated wildlife stalls with positive environmental samples compared with the background percentage of non-wildlife related environmental positive stalls within the Western area of the HSM.

Author	Non WL Env +ve	Non WL Env -ve	WL Env +ve	WL Env -ve	UM Env +ve	UM Env -ve
Worobey et al.	18 + 1 trash	90	2	6	4	0
Joint WHO-China	19	90	1	7		
Gao et al.	20 + 1 ground	90 + 2 ground	1	7		

Table 4. HSM environmental sampling PCR positive and negative results. Several differences between authors are apparent. WL: wildlife; UM: unidentified meat.

Since the percentage of wildlife-selling stalls with positive environmental samples is approximately equal to that expected from the level of background contamination by infected vendors and visitors within the HSM, we find no statistical support to the conclusion that the observed positive environmental samples at wildlife stalls are related

to animals. Such a conclusion can be categorized as an example of a base rate neglect fallacy (Tversky and Kahneman 1982).

Confounding variable bias

There is a lack of systematic environmental sampling from crowded locations across Wuhan. The only map detailing a systematic effort to conduct environmental testing for the presence of SARS-CoV-2 at the beginning of January 2020 was at the HSM. No reported sampling was conducted at the nearby Hankou Railway Station, nor was any systematic sampling of other train stations or hospitals across Wuhan published. The lack of negative controls in epidemiological studies is known to be problematic for inference, with potential for confounding external factors (Lipsitch et al., 2010; Groenwold et al., 2008). Very scant details of apparently small sampling efforts with 14 samples taken from storehouses supplying the HSM, 30 samples taken at Dongxihu market and Huanggang Center market and 51 samples from 'sewerage wells in surrounding areas' were documented in Gao et al. (2022) and Joint WHO-China study (2021a).

Conflicting data

Even at the HSM, the only location in Wuhan with documentation of any systematic sampling, as well as a lack of detailed records as discussed above, the datasets that are published are conflicting. We note multiple differences in the environmental sampling maps published by Joint WHO-China Study (2021a) and the map published by Gao et al. (2022) (Supp. Fig. 22). WHO sampling has several more of both environmental PCR-positive and PCR-negative stalls. Even more concerning, case counts at the HSM are markedly higher in Koopmans [10] compared with Joint WHO-China Study (2021a).

Lack of early data

A significant problem for tracing the early spread of COVID-19 in Wuhan is a lack of published data. The Joint WHO-China study (2021a) is lacking in detail and specifics for December 2019 (and potential earlier) cases. The detailed criterion by which each of 92 cases compatible with COVID-19 in the October-November period in Wuhan was not made available (Joint WHO-China Study 2021a). 25 of these potential cases were ruled out without testing, while blood samples on the remaining 67 were collected over a year after infection.

By mid-December case numbers appear to have been large enough to be a cause for concern with scientists in China with reports of discussions regarding the novel disease with colleagues outside China [26,27]. Another indication that case numbers in Wuhan may have been higher than officially recorded comes from stall owners at the HSM, who noted a significant decline in buyers visiting the market in late December. One vendor estimated the drop to be 20-30%, with the Beijing Times attributing this drop in traffic to

'pneumonia of unknown origin' [18,18a]. For vendors to notice such a significant decline at the market with 10,000 shoppers per day (Joint WHO-China Study 2021a) is indicative that case numbers in December in Wuhan may have been greatly under-reported.

Conclusion

Three studies, one by the WIV and HZAU (discussed in Cohen (2020b)), one by Wu et al. (2021) and a more extensive study by Gao et al. (2022) concluded that the HSM was likely a super-spreader location, and not the place SARS-CoV-2 first infected humans. We also concur with this conclusion, as the earliest case locations are spatially removed from wildlife stalls, no wildlife seller contracted COVID-19, SARS-CoV-2 positive environmental specimens are most strongly associated with human gene sequences, and no animals tested positive for the virus. Furthermore, the distribution of COVID-19 cases are not consistent with a single point source, and instead exhibit a distribution consistent with a Poisson point process model, and are more indicative of human-to-human transmission in shared communal areas, such as eating areas and toilets. Additionally, the distributions of cases and of wildlife stalls are consistent with independent Poisson point process models. This is unexpected for zoonotic spillover where a spatial relationship between cases and wildlife stalls is likely. We also find the distribution of environmental PCR-positive samples to be more spatially consistent with COVID-19 case contamination and spread from the HSM toilets, compared with the hypothesis that SARS-CoV-2 spread from wildlife stall locations. The very small quantities of potentially susceptible wild animals sold in Wuhan markets relative to other cities and towns in China where wild game is widely eaten makes an outbreak in Wuhan - and only Wuhan of all places in China - extremely unlikely from an *a priori* probability perspective. Indeed, one single market in Qingyuan, Southern China was found to trade an order of magnitude more animals than all markets in Wuhan put together. Additionally problematic for the zoonotic spillover hypothesis at the HSM, four of the earliest identifiable cases with onset in December (10th-16th) were not linked with the HSM, clearly indicating human-to-human transmission outside of the HSM prior to and simultaneously with, the first known cases at the HSM. Consequently, we find that the arguments by Worobey et al. (2022b) that SARS-CoV-2 emerged from the HSM via zoonosis and the hypothesis that at least two separate zoonotic jumps from wild animals occurred at the HSM (Pekar et al., 2022) are not supported by data. Consequently, we conclude the most likely scenario is that an infected person brought the virus to the HSM, sparking a super-spreader event.

Methods and Code

All analysis, unless otherwise indicated, was conducted using Joint WHO-China Study (2021a,b) datasets digitized and georeferenced by Worobey et al. (2022b), and digitized

and georeferenced maps from Joint WHO-China Study (2021a,b). R version 4.2.1 was used for Poisson point process simulations and Ripley's function analysis using spatstat version 2.3.4 (Baddeley and Turner 2005). Sparr version 2.2.16 (Davies et al., 2018) was used for risk analysis based on an adaptation of the code provided in Worobey et al. (2022b).

Geopandas version 0.11 was used for plotting case distribution and KDE plots.

QGIS Desktop version 3.26.2 was used for generating HSM layout plots using geojson data from Worobey et al. (2022b).

Code to reproduce environmental sample plots and analysis can be found here: [https://github.com/bioscienceresearch/Huanan Seafood Market Zoonosis Critique](https://github.com/bioscienceresearch/Huanan_Seafood_Market_Zoonosis_Critique)

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