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Zoonosis at the Huanan Seafood Market: A Critique

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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 of 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, the distribution of cases at the HSM is consistent with a Poisson point process model (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, as compared with 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, 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 superspreader location, with only tenuous evidence to support a zoonotic spillover there. Consequently, we conclude there is insufficient evidence to indicate the HSM as the source of the pandemic.

Introduction

On the 22nd of January 2020, the Chinese CDC 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 the 23rd of January 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 China CDC, ruled out the HSM as the origin of the pandemic on the 26th of May 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 wild animals at the HSM (Worobey et al. 2022a). After peer-review, the final paper softened the conclusion, only claiming the HSM was the epicenter, not necessarily the source of the COVID-19 pandemic (Worobey et al. 2022b). In addition, Pekar et al. claim 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 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 the 3rd of 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 Pneumonia of Unknown Etiology (PUE) surveillance system appears to have been little known to or understood by clinicians (Xiang et al. 2019). Of 335 cases analyzed at 2 hospitals in Anhui province that met the criterion for reporting PUE, none were reported (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 from the HSM, notified the Jianhan District CDC on the 29th of December to report a cluster of 4 viral pneumonia cases with links to the HSM (Joint WHO-China Study 2021a). An earlier family cluster of 3 viral pneumonia cases with first case (62M, IME-WH01, lineage A) onset December 1st (Huang et al. 2020) or 12th (Zhou et al. 2020), however, was not linked with the HSM. Although this cluster reported to the Jianghan District CDC on the 27th of December, it was only after a cluster of cases linked to the HSM was reported by Xinhua Hospital on the 29th 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 superspreader 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 750m from the Hankou railway station, one of the three main railway stations in Wuhan.

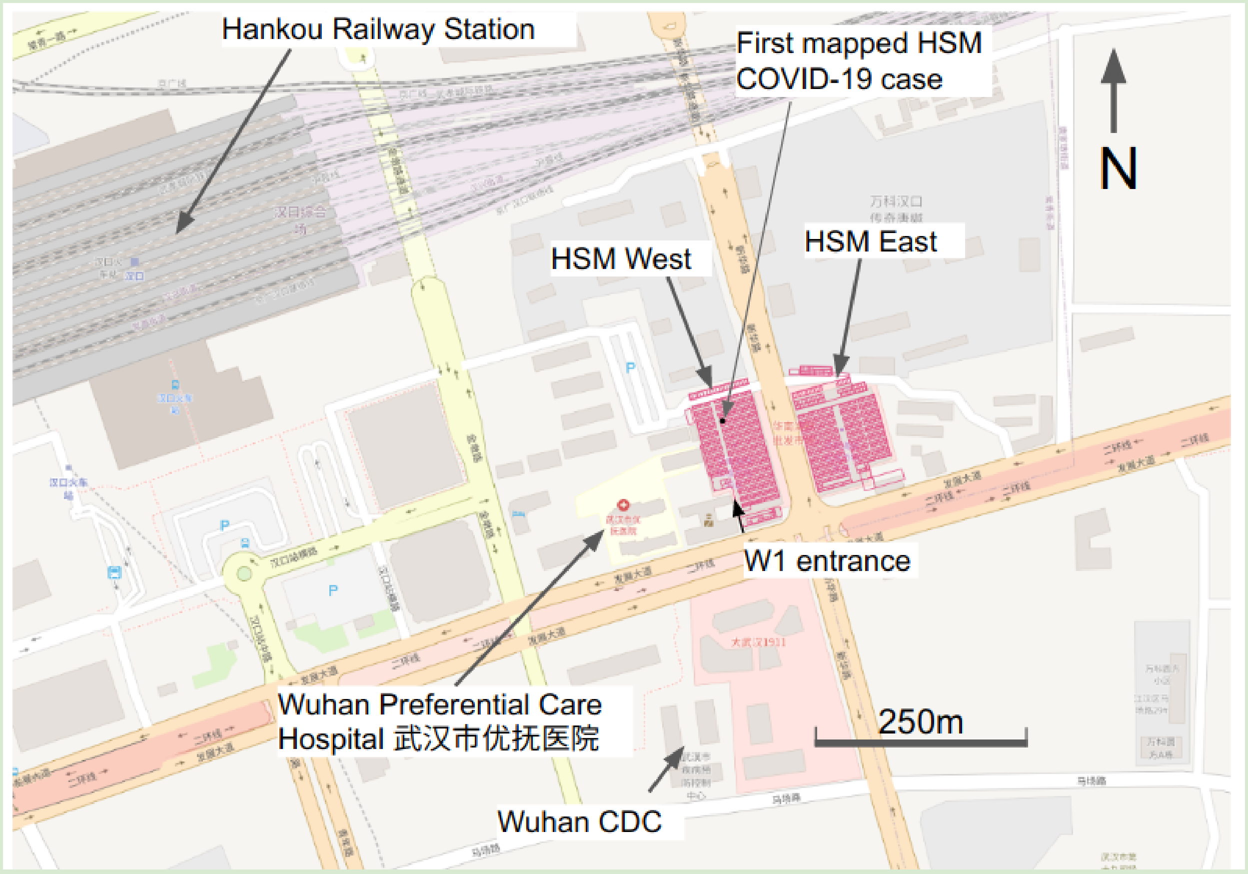


Fig. 1. Map of Huanan Seafood Market location in Wuhan, location of the Hankou railway station and Wuhan Preferential Care Hospital and Southwestern entrance 'W1'.

COVID-19 has a demonstrated high transmission risk for train passengers, with distance from an infected patient a key factor (Hu et al. 2021) and enclosed space 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 are potential entry vectors 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 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, is 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.

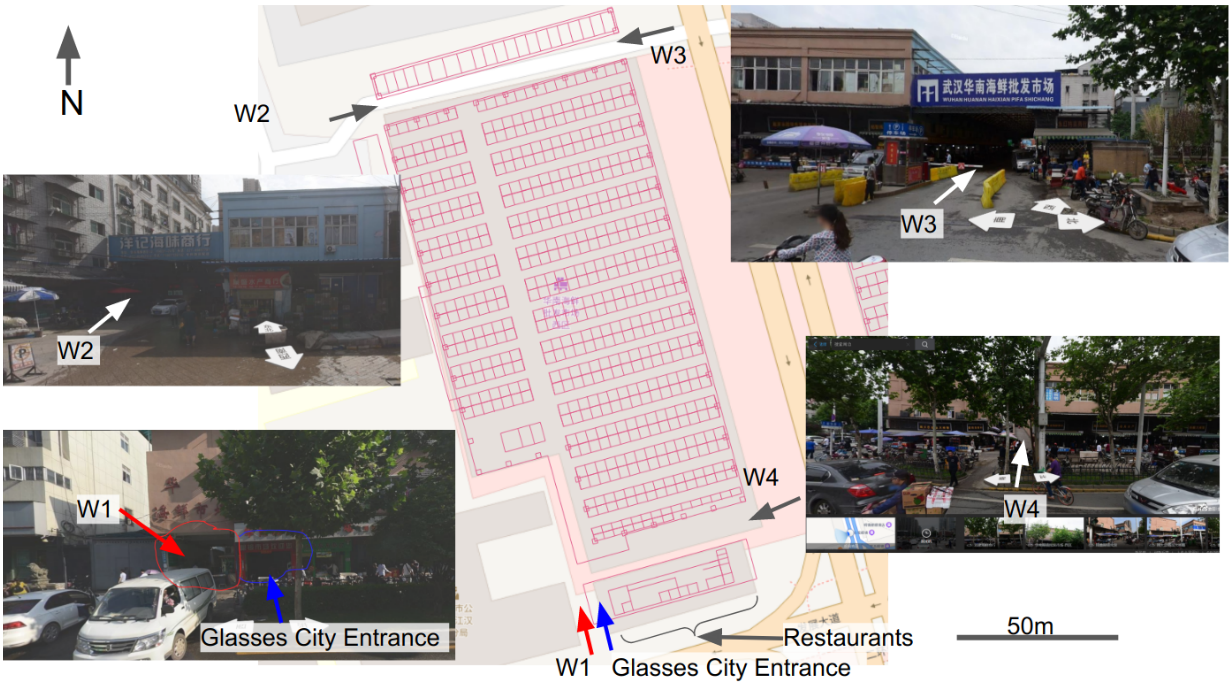


Fig. 2. Location of entrances to the Western section of the Huanan Seafood Market.

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. 2,3). 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 discussed by Gao et al., 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. Map rotated 15.2 degrees clockwise with respect to North.

As can be seen in the spatial map of cases over time for the period of 13/12/2019 to 31/12/2019, there is no clear relationship between the location of either of the two wildlife sections (West and East parts of the market) and case clusters (Fig. 4). In particular, the earliest COVID-19 case maps showing cases on the 13/12/1019 and 20/12/2019 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).

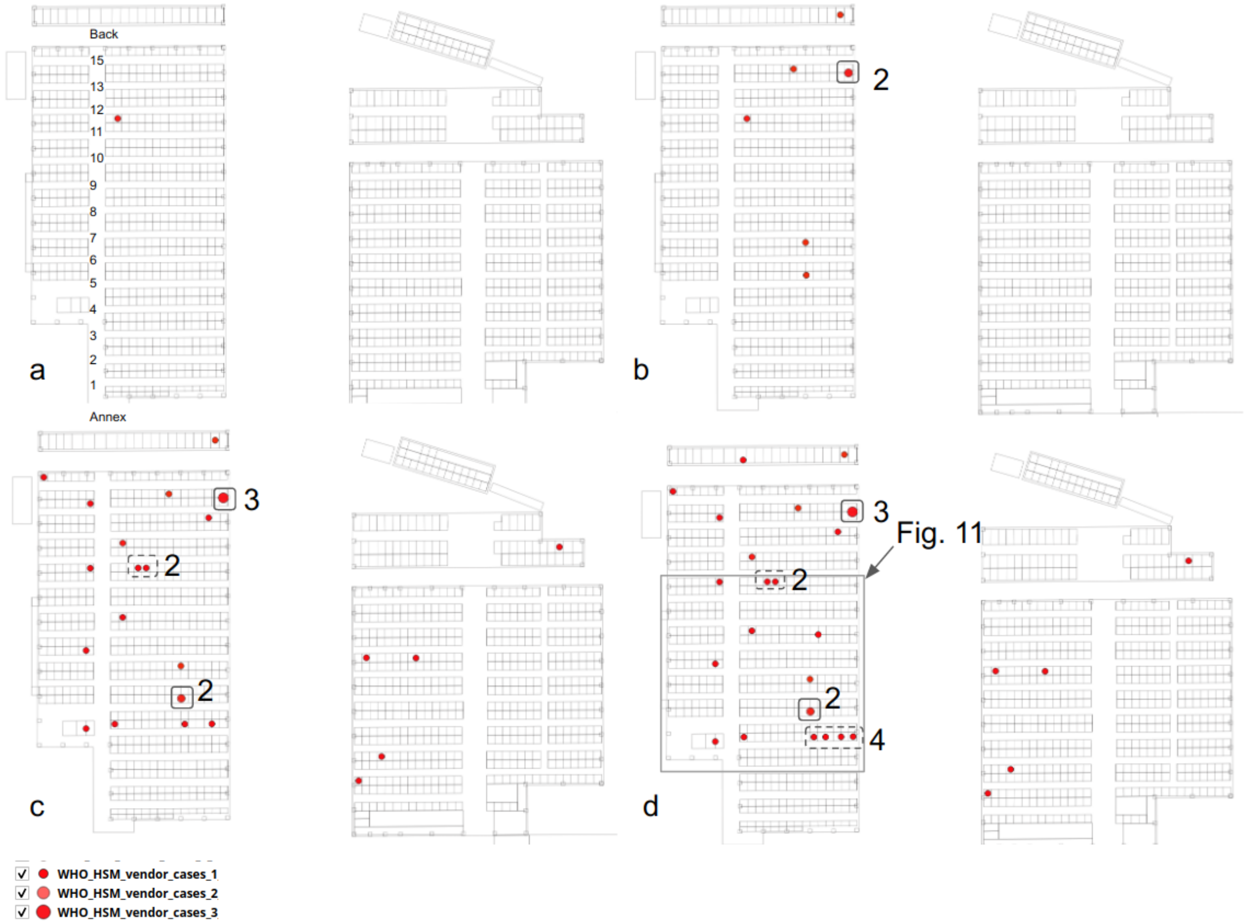


Fig. 4. Partial distribution of cases on a) 13/12/1019 (1 case), b) 20/12/2019 (7 cases), c) 27/12/2019 (26 cases) and d) 31/12/2019 (30 vendor cases). After Joint WHO-China Study (2021b). Multiple cases at the same stall indicated by solid boxes, multiple cases in close proximity across stalls indicated 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 cases locations at the HSM as at the 31st 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/λ 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 and observed point relationships plotted with and envelope of simulations and its mean (Fig. 5). The observed case distribution falls within a randomly simulated envelope of nearest-neighbor distances, except for distances 0-1m, 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, while 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.

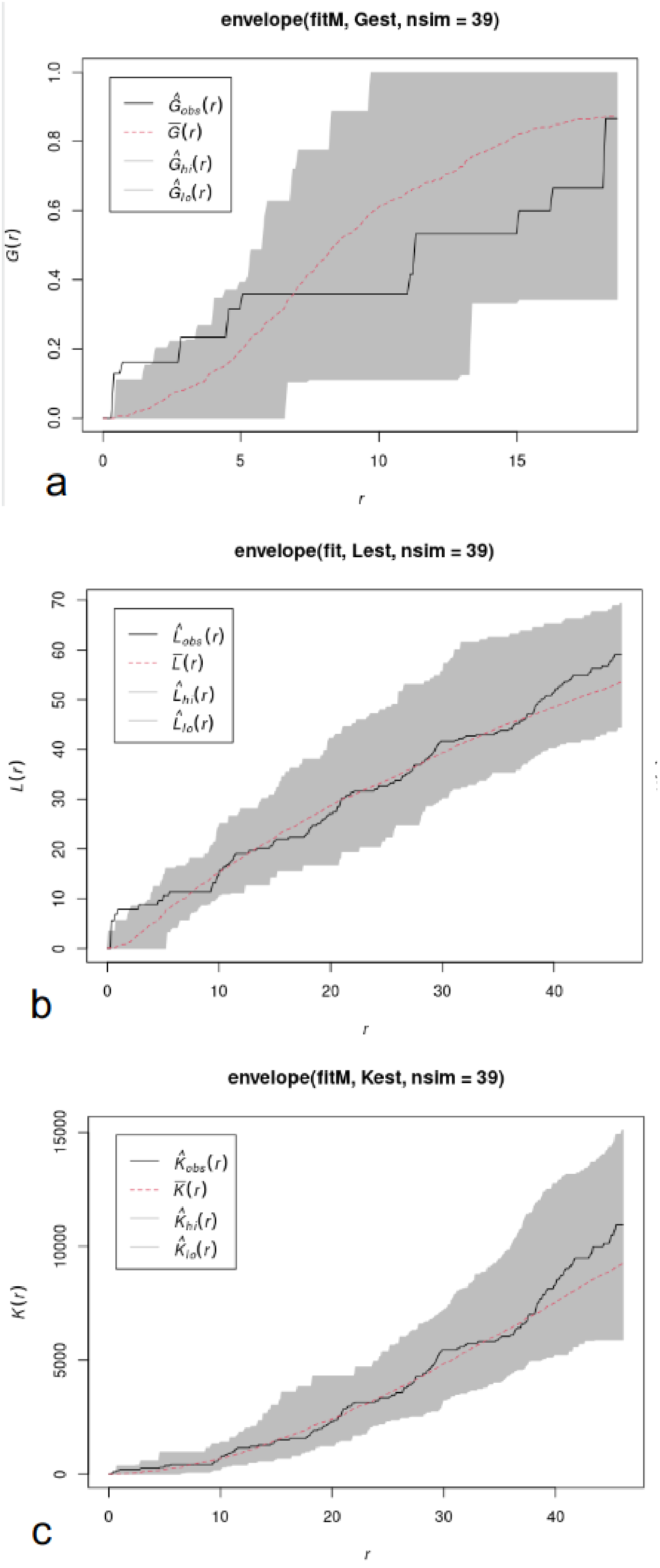


Fig. 5. Ripley's G, L and K function plots with simulated poisson models using Matérn cluster process (a-c) showing the distribution of distances for all COVID-19 cases at the 31st December at the HSM.

COVID-19 transmission is dominantly 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 transmission (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 likely (Greenhalgh et al. 2022; Peng et al. 2022). While there is some indication of <3 m scale transmission 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 the 31st December is consistent with that expected from a spatial Poisson point process model. That is, it can be considered essentially random (Figs. 4, 5). Indeed, Courtier-Orgogozo and de Ribera (2022) find that the 20-40m distance between the week 2 and the week1 COVID-19 cases and distance between week 2 cases (Figs. 4a,b) is not consistent with direct infection from a unique source, and suggest that HSM cases may have infected each other in shared areas at the HSM, such as shared eating/gambling areas and toilets (Courtier-Orgogozo and de Ribera 2022). Plots with a 3m radius around each case for the four time periods provided in the Joint WHO-China Study (2021b) and KDE plots further show some possible local transmission on the order of 3m or less between cases, but otherwise no clear point source for cases (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 any relationship of case locations as at 31st December 2019 to wildlife stalls 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 noticeable deviation (repulsion) from expected below 10m (no COVID-19 cases occur within 10m of a wildlife stall), and indication of possible clustering at >50m which may be influenced by the separation of the West and East sections of the market.

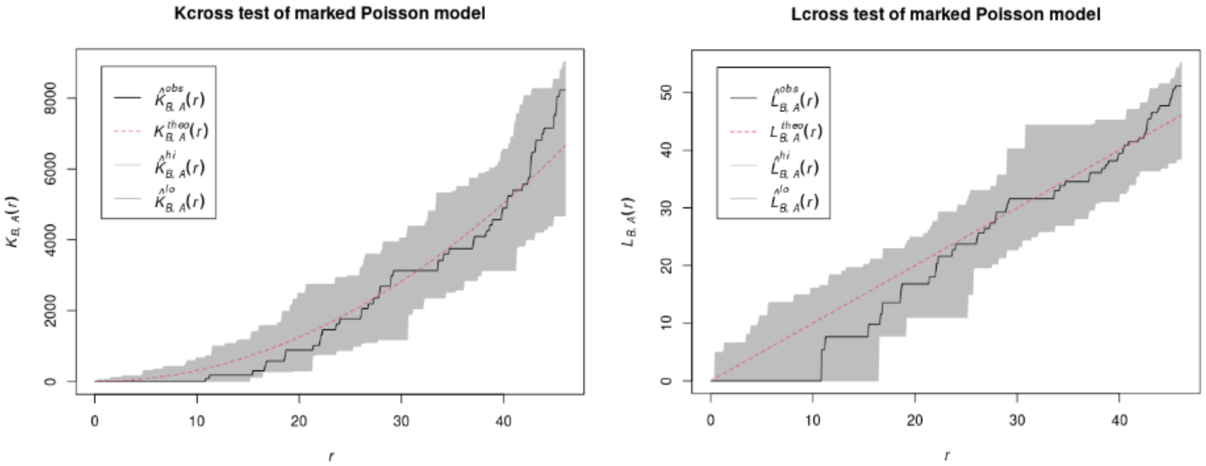


Fig. 6. Ripley's K and L cross-distance function plots with simulated poisson point process distances for all COVID-19 cases (as at the 31st December at the HSM) relative to the position of wildlife stalls. $K_{B,A}(r)$ is $1/\lambda_A$ times the expected number of points of type A (case) within a distance r of a typical point of type B (Wildlife stall). $L_{B,A}(r)$ is a variation on the K function and defined by Sqrt($K_{B,A}(r)$/pi). $K^{theo}{}_{B,A}(r)$ 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>10m for 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 the 20th of December to wildlife stalls on the West side of the market (Supp. Fig. 8). Cases to wildlife stall locations are more separated than would be expected from independent Poisson point processes (null hypothesis) and again, do not support a zoonosis hypothesis whereby some clustering of cases near wildlife stalls is expected.

Additional cases

On Jun 14, 2021, two and a half months after the publication of the Joint WHO-China Study (2021a) on 30 March 2021 a separate set of HSM case maps was provided by M. Koopmans [10]. 61 cases were shown (compared with 30 official cases in the Joint WHO-China Study (2021a)) 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 are clustered at the same stall whereas 50% of cases in Koopmans [10] are located at the same stall.

Koopmans			WHO		
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 (2021a).

We analyzed the spatial distribution of COVID-19 cases as per Koopmans [10] against the distribution of wildlife stalls (Supp. Fig. 11) assuming independent Poisson point processes. 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, they do 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 western-most block of the market where wildlife stalls were located until the week from the 21st of December to the 27th of December 2019, more than one to two weeks after the first case, and in the week when cases became widely spread across the market (Figs. 3,4) (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 W7/26-28 in Joint WHO-China Study (2021b) appears in the 21st of December to the 27th of December 2019 map, but is one of two cases on the 15th 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 the 15th December 2019 but this case is not reported in 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 W2/14, 44m from nearest wildlife stall) who experienced symptom onset on the 11th of 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 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 (2021a) market maps was 65M of 武汉市江汉区昌盛海鲜食品批发部 Wuhan Jianghan District Changsheng Seafood Wholesale Department (Fig. 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 (Fig. 3; Supp. Fig. 12). An earlier case, 48F had no documented link with the HSM, and presented on December 10th with a raised temperature (38 °C), soreness and fatigue [15,15a](Li et al. 2020). She was a patient at Tongji Hospital on December 27th but 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 the 12th (Zhou et al. 2020). 62F, the wife of 62M experienced COVID-19 onset 3 days later on the 15th. The infection date of their son is unknown and infection only identified after a CT scan at Xinhua hospital [5,5a]. Three other HSM linked cases had onset on 12th 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 the 15th); 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; Babarlelephant et al. 2022). A intriguing possible COVID-19 case '69M0', was a HSM merchant who visited Youfu outpatient clinic on the 12th 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 grey. 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 (Babarlelephant et al. 2022); 48F2 (Li et al. 2020); 62F (Joint WHO-China Study 2021a); 41M1 (Worobey et al. 2021; Babarlelephant et al. 2022). Where known, lineage (lin.) is indicated. * lineage inferred.

That 4 of 10 of the earliest identifiable cases, including 48F with onset on December 10th, prior to the first identifiable HSM market case 57F (Joint WHO-China Study 2021a) [11,12,13] clearly indicates human to human transmission was occurring outside the HSM in early December, prior to an outbreak on December 12th identified here and prior to the large outbreak at the HSM between December 20th and 27th (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 1st 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 the 12th of January, with multiple additional restricted sampling events continuing through to the 2nd of March 2020 (Gao et al. 2022).

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

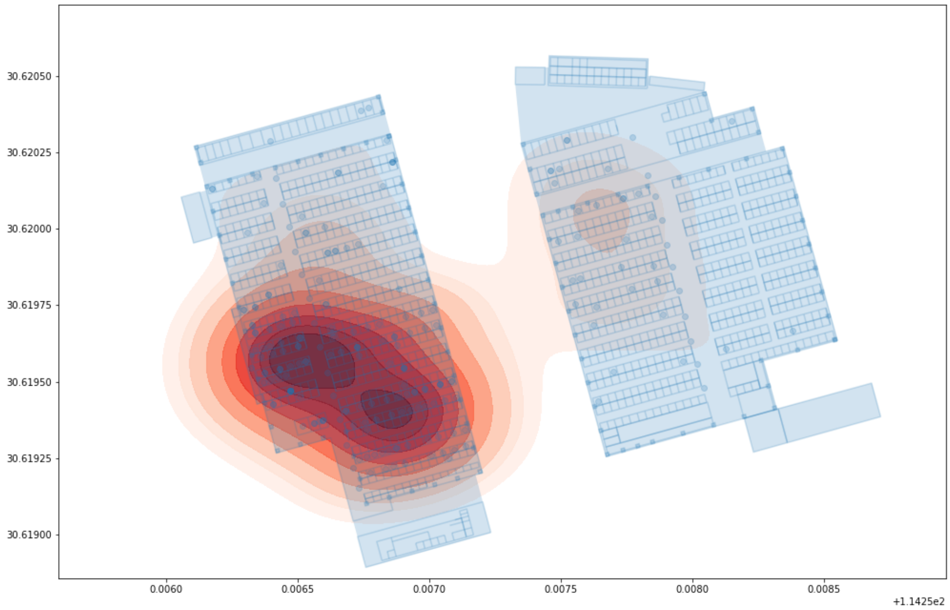


Fig. 7. Kernel density estimation (KDE) of total environmental samples taken at the Huanan Seafood Market. Data sourced from Worobey et al. (2022b).

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 MiSeq are located within a 45m radius of the HSM toilets.

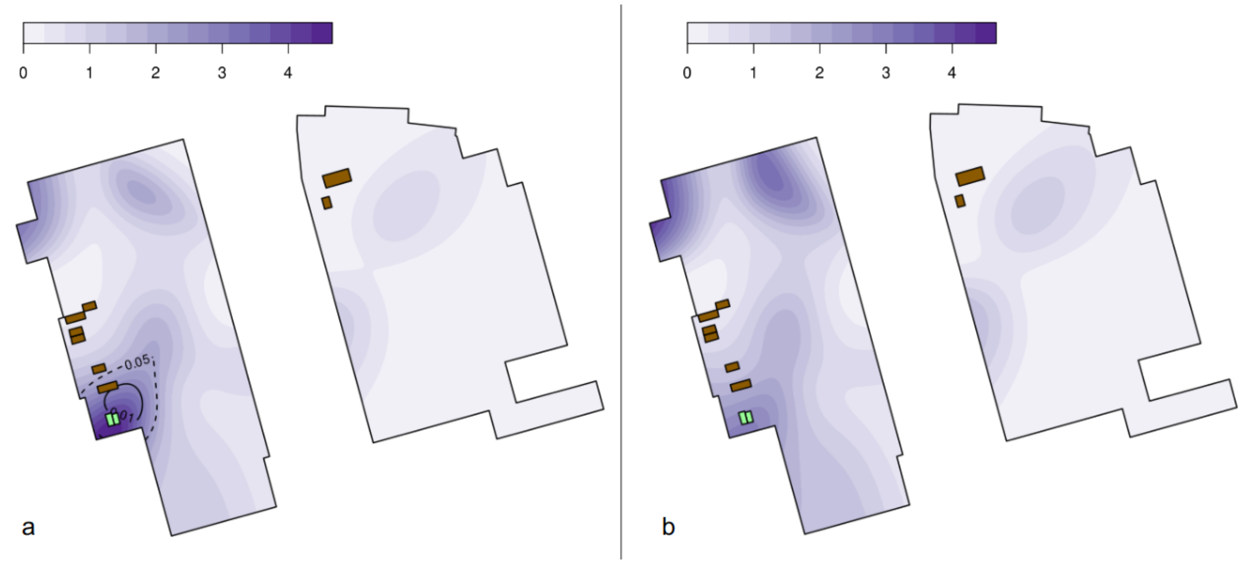


Fig. 8. Relative risk analysis of environmental positive samples using sparr (Davies, Marshall, and Hazelton 2018). a) Ratio of the environmental positive density to control density (environmental positive+negative) using the same dataset and methodology as Worobey et al. (2022b); b) Ratio of the environmental positive density to control density (environmental positive+negative), where, in stalls with multiple positive environmental samples, a single positive only is used, and environmental negative datasets have been de-duplicated. See Supp. Fig. 18 for plots of environmental positive to a control using environmental negative samples only.

We repeated this process where for stalls with multiple environmental positive samples, only a single environmental positive sample was used. This addresses one potential 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 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.

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*".

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 SW corner were linked with transmission.

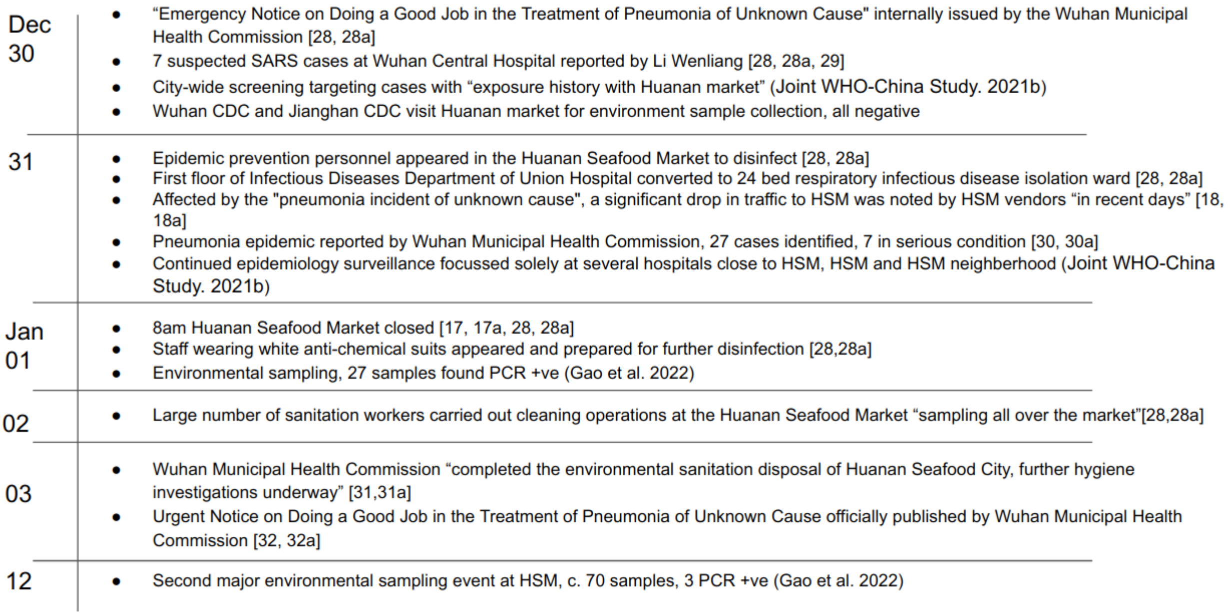
When the HSM map is divided into a grid, and the percentage of environmental samples which showed positive PCR tests is calculated per cell, the Western side of the market shows more cells with a higher percentage positive, regardless of grid size (Supp. Figs. 19-21). However both the Northern part of 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 it is likely a result of SARS-CoV-2 shedding by infected human cases.

We 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 South-western section where wildlife stalls were located (Supp. Fig. 35).

Worobey et al. (2022b) overlooked 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. First sampling occurred on the 30th of December with all environmental samples testing negative. Over 500 environmental samples were collected on the 1st of January, and a second round of environmental sampling was conducted on the 12th of January (Gao et al. 2022)



Dec 30	• “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 Jianghan CDC visit Huanan market for environment sample collection, all negative
31	• 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	• 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	• Large number of sanitation workers carried out cleaning operations at the Huanan Seafood Market “sampling all over the market”[28,28a]
03	• 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	• 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 30/12/2019 and12/01/2020. Key HSM related events in late December 2019 through early January 2020.

Six SARS-CoV-2 positive environmental samples were sampled on the 12th January, in the second major sampling event (Gao et al. 2022). Unlike other samples, these 6 samples lacked a PCR Ct (PCR cycle threshold crossover) value, and instead were identified as “PCR+” or “PCR\”, and were only confirmed through Next Generation Sequencing (NGS). We note that 3 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 3 samples where RT-PCR testing was negative amongst all the samples that were confirmed through NGS (Gao et al. 2022). 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%) than other Illumina platforms (Stoler and Nekrutenko 2021). This raises the possibility that these 3 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 widespread infection of animals. Only a single wildlife stall, W6 29-33 tested PCR-positive in the entire HSM (Joint WHO-China Study 2021b; Gao et al. 2022) (Fig. 3). 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 zoonotic jump from animal to human 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 was actually 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 vegetable and poultry (Fig. 10).

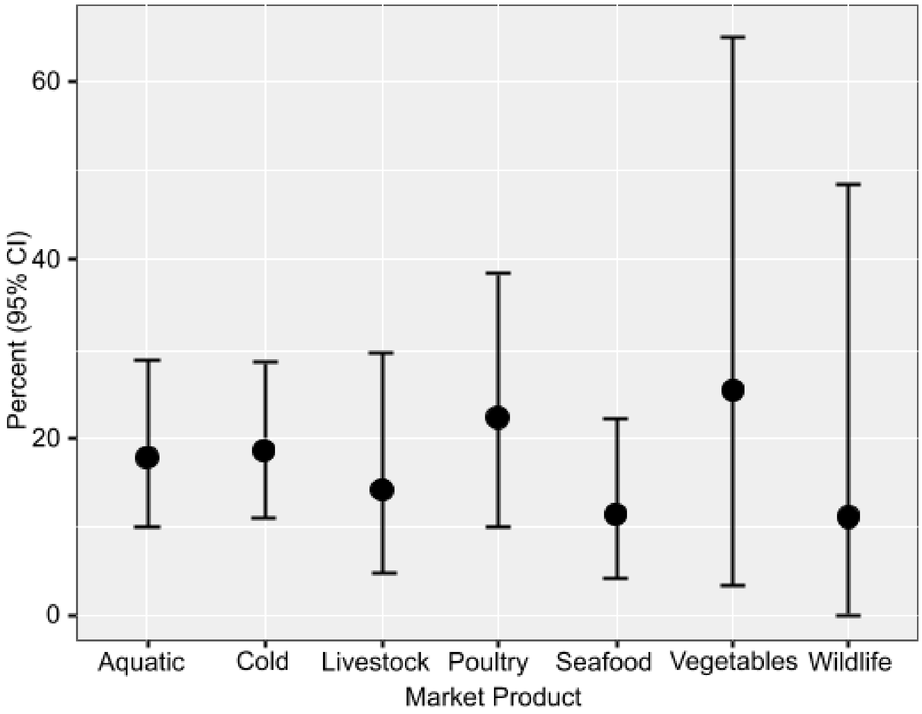


Fig. 10. Percentage positive environmental samples associated with different products in the Huanan Seafood Market. Data from (Joint WHO-China Study 2021a) p. 97. 9 of the 10 stalls selling farmed wildlife products were sampled.

Case numbers by type of goods sold show 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. 11, Table 3). The 95% confidence interval for wildlife products is the only category to include a zero prevalence in its range.

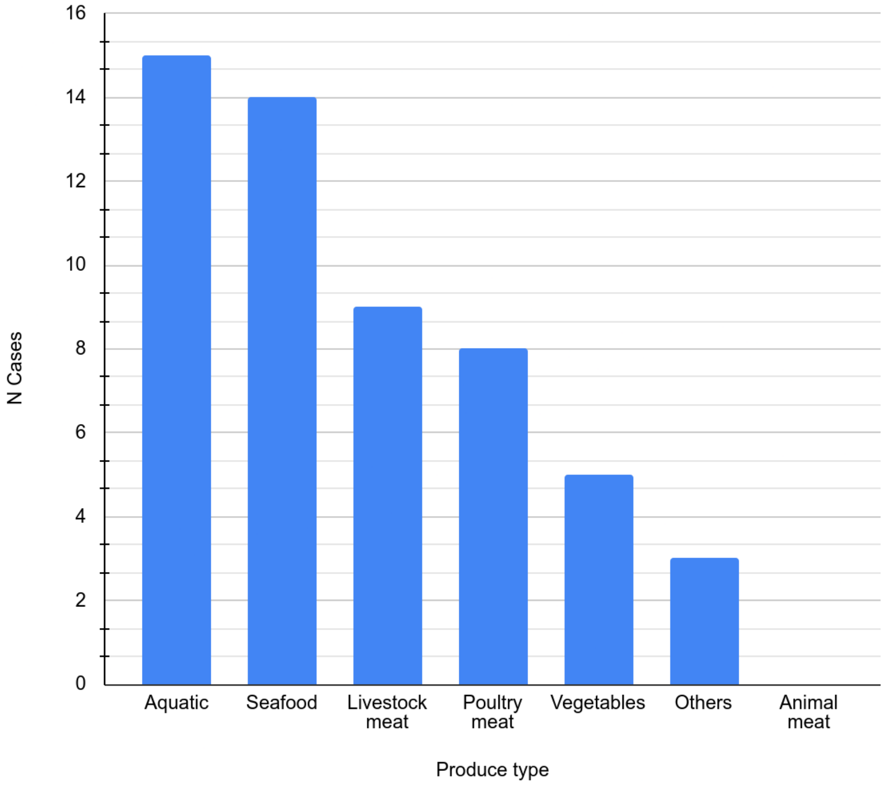


Fig. 11. Case numbers by vendor type. Note, there were 30 cases in total, with several vendors selling more than one produce type and counted more than once. Data from Joint WHO-China Study (2021b), p181.

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 prod.	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)**.**

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. 12) [19]. Stall W/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 is owned by 宋法保 with the business name 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, it is plausible that after being found to commit this offense, the owner may not actually have been undertaking further illegal wildlife trade, which would risk a second, more serious fine. 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. 22-25).

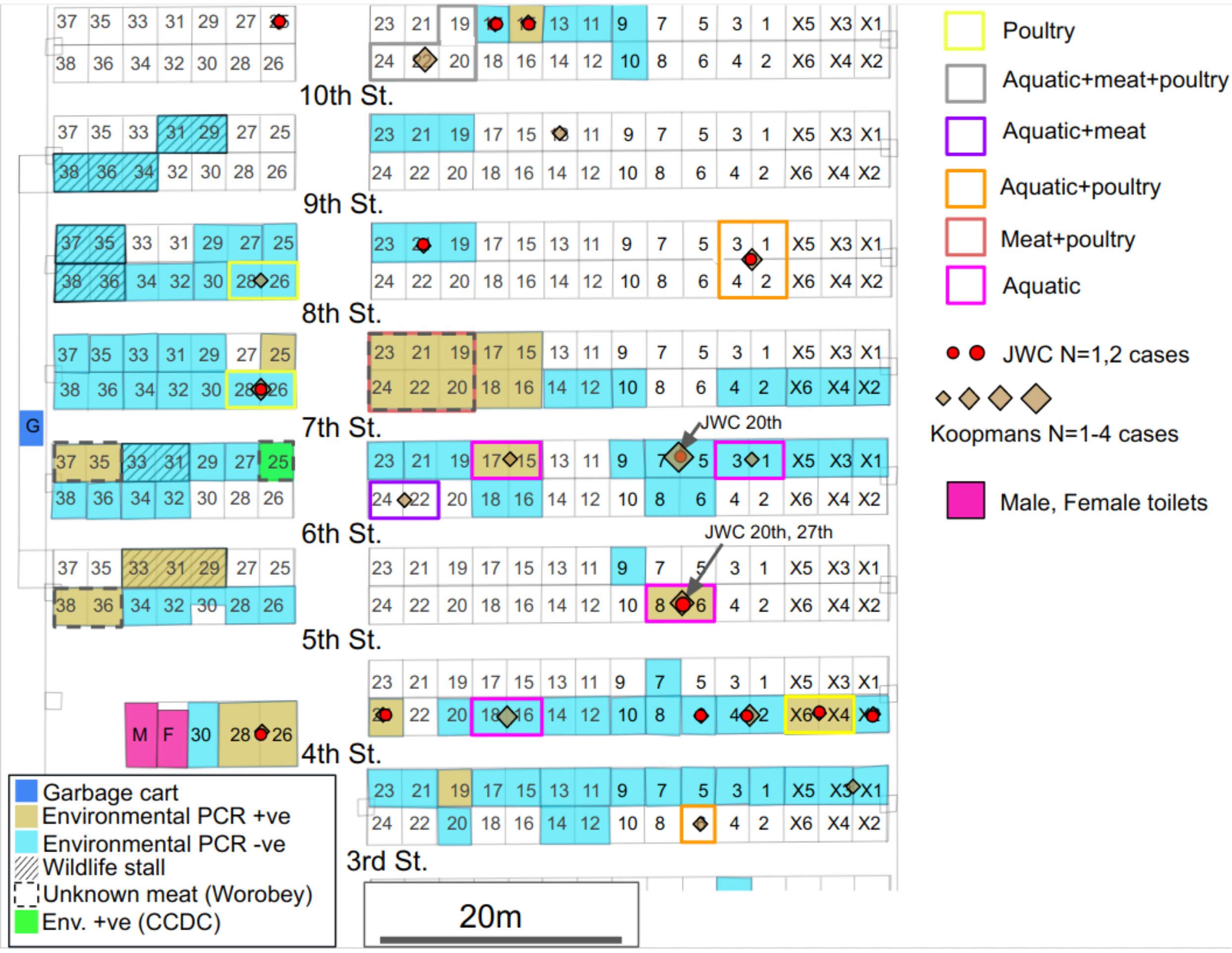


Fig. 12. Southern and Central portions of the Western section of the HSM showing wildlife stalls, environmental PCR tested stalls and COVID-19 cases. A stall fined for illegally trading hedgehogs is located at West 6 29-33.Stall West 7 25 (green) was noted in a CCDC report as an environmental positive (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 20th-27th December except two cases in the week of 13-20/12/2019 as indicated. Koopmans [10] cases shown as diamonds.

We note that hedgehogs are an implausible intermediate host for SARS-CoV-2. Hedgehog ACE2 has been found to have low affinity with the RBD of SARS-CoV-2, and no records of infection of hedgehogs with SARS-CoV-2 have been reported to date (Andy 2021; Niu et al.

2022)[21]. Hedgehog ACE2 has also been found to be unable to support SARS-CoV-2 pseudotyped virus entry (Xiong et al. 2022, extended data figure 6).

Stall W8/19-23 W7/20-24 “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. 12). The stall sold frozen, packaged and cured livestock meat (Supp. Fig. 26-28) [19]. The stall was categorized by Worobey et al. (2022b) as ‘Unknown meat’, yet there appears to be no indication that any meat other than livestock meat was sold at this stall.

Stall W7-25 “荣昌冻品” was classified by Worobey et al. (2022b) as ‘Unknown meat’, inferred from photographic evidence. However on review, we find the stall is a frozen food stall, with no evidence for meat sales [19] (Supp. Figs. 29,30).

Stall W/7 31-33, is categorized as a wildlife stall in both Joint WHO-China Study (2021b) and Gao et al. (2022), but found to have environmental sample testing 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. 30,31).

Stall West/6 29-33 was photographed selling caged raccoon dogs in 2014 by Prof. Eddie Holmes, and was suggested by Holmes on August 2nd 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 the 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 wild animal cages in China, zoonotic spillover coincidently happened to occur spillover 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) previously photographed that exact stall years previously. The second problem is the hidden variable fallacy. The whole 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 the 31st December 2019 with a closed roller-door (Supp. Fig. 32). However no evidence for cages (which are generally placed outside stalls) was found. The business owner was fined for illegally selling hedgehogs on May 7 2019, along with two other stall owners [20,20a]. We believe it is more likely than not that the owner would not have wanted to risk being caught selling wildlife without a valid certificate of origin again, and potentially incur a more serious penalty. 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 31/12/2019, before the initial sampling on 01/01/2020. As such the stalls may have been unsampled on 01/01/2020, and potentially not decontaminated the following day on 02/01/2020.

Environmental samples at stalls W5/36 and W5/38 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 the 13th February 2020, the stall had no sign and as such it is not clear if the stall was occupied in December 2019 (Supp. Fig. 33).

Seafood stall W7/15-17 was found to have 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 the 15th 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. 34).

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 December 29 2019-January 4 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 1st (Huang et al. 2020) or the 12th (Zhou et al. 2020), was also infected by the lineage A strain.

A lineage A genome was recovered from environmental sampling on January 1st 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 high-throughput sequencing with anomalous Ct to read depth ratio (Supp. Info.). We also note the lineage A genome recovered contains 2 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.).

We also note that the description of the sampling 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 surface in each vending booth, public areas, 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℃), 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 the 10th 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 tested both environmental samples and frozen animal samples from the HSM on January 12th 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).

In summary:

- The location of COVID-19 infections at the market were all in stalls at a greater than 10m distance from the closest wildlife stall (Fig. 3). With the earliest cases (up to Dec 20th) located >20m from nearest wildlife stall (Joint WHO-China Study 2021b) and >10m away in Koopmans maps [10].
- No SARS-CoV-2 was detected in animal samples, and environmental specimens were best correlated with human rather than animal genetic material, suggesting the specimens were from infected people and not infected animals (Gao et al. 2022).
- COVID-19 case distribution is fairly random and is consistent with human to human 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 is found supporting the hypothesis for sustained transmission from wild animals to humans.
- The highest relative risk for environmental positive samples relative to the null hypothesis is centered on the HSM toilets.
- Only a single wildlife stall out of 6 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 environmental positive samples are related to animals at wildlife stalls.
- No animal samples from cold storage were found to be positive for SARS2r-CoVs (Wu et al. 2020; Cohen 2020b; Joint WHO-China Study (2021a) and no samples from knives or chopping blocks at wildlife stalls were found to be positive for SARS-CoV-2 (Wu et al. 2021).
- That 4 of the 10 earliest cases were unrelated to the market shows that human to human transmission was occurring in Wuhan outside the HSM at the same time that the first cases were detected 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 60nt of position 28144. We can't 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 evident in a 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 in the HSM in November / December 2019. We consider the following wild animals possible intermediate hosts: Siberian Weasel; Mink; Raccoon dog; Red fox, and the following unknown potential intermediate hosts: Pallas squirrel; Marmot; Coypu; Chinese bamboo rat; Red squirrel; Complex tooth flying squirrel (Supp. Table 2). For these animals, for the four Wuhan markets with animal trade, a total monthly mean of 190 sales is estimated by Xiao et al (2022). We expect 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 lower than the minimal dose required for infection and sustained transmission between animals is unlikely (Mykytyn et al. 2021). We estimate approximately 60 Chinese hares were sold per month in November/December at the HSM. Considering all potential host animals and animals of unknown SARS-CoV-2 susceptibility sold at the HSM, such a caged animal population is small, and is difficult to reconcile with an animal introduction leading to human adaptation at the animal-human interface in the market. The reservoir of animals is simply too limited, and given their low numbers, the number of humans in contact with them were 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 more numerous.

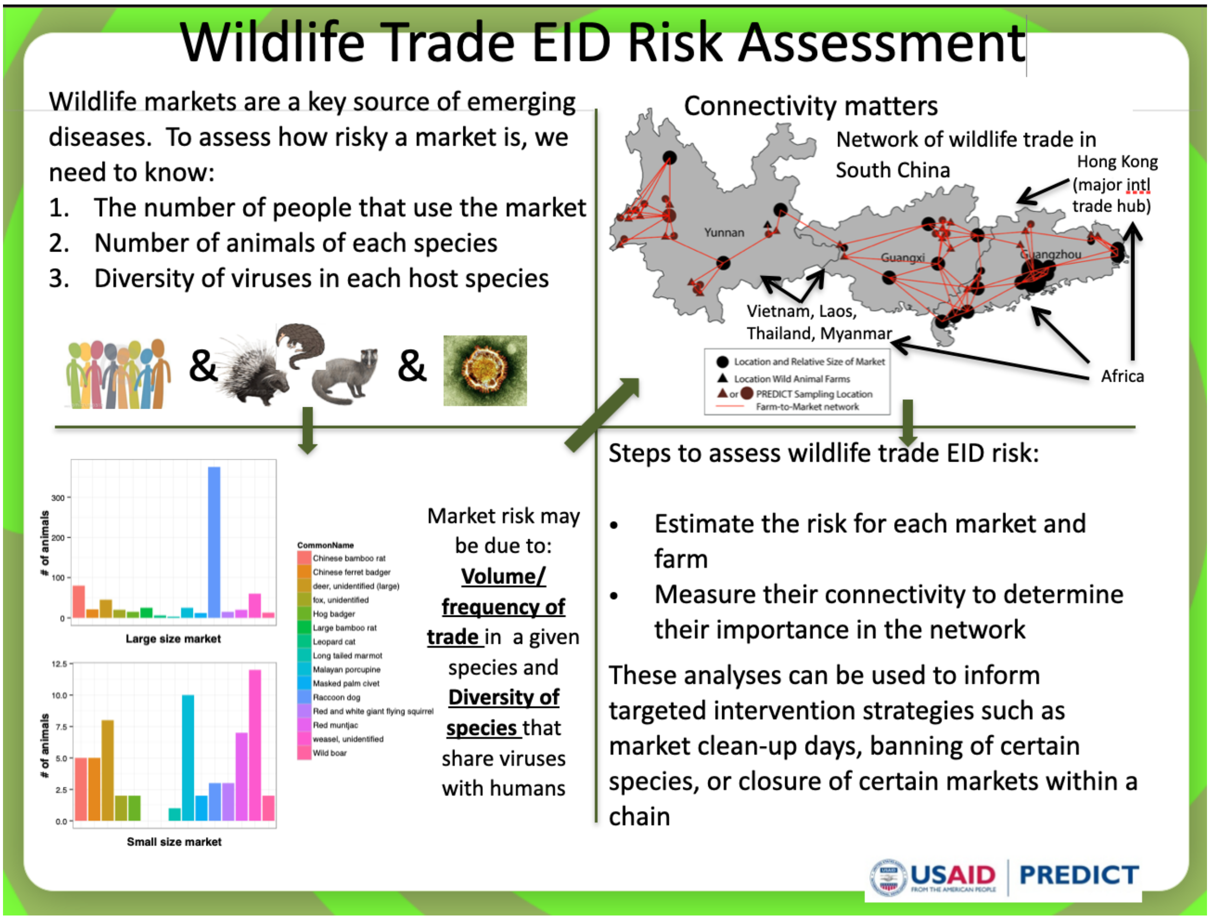
CNN footage (Stout 2020) showed a market in Qingyuan, a city of 4 million people in Southern China several hundred kilometers South of Wuhan, that had far more intense live mammal and wild animal trade. Indeed, it can be considered tens to hundreds of times larger than the wild animal trade in Wuhan. 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 far 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 are 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 100 (200 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 RBD or RdRp closely related to those found in SARS-CoV-2 was 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 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-like BatCovs 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).



Wildlife Trade EID Risk Assessment

Wildlife markets are a key source of emerging diseases. To assess how risky a market is, we need to know:

1. The number of people that use the market
2. Number of animals of each species
3. Diversity of viruses in each host species

Connectivity matters

Network of wildlife trade in South China

Market risk may be due to: **Volume/ frequency of trade** in a given species and **Diversity of species** that share viruses with humans

Steps to assess wildlife trade EID risk:

- Estimate the risk for each market and farm
- Measure their connectivity to determine their importance in the network

These analyses can be used to inform targeted intervention strategies such as market clean-up days, banning of certain species, or closure of certain markets within a chain

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 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.

Raccoon dogs have been shown to be susceptible to the more transmissible but non-ancestral G614 MUC-IMB-1 strain of SARS-CoV-2 (Freuling et al. 2020). 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 Joint WHO-China Study (2021a), documents that no raccoon dogs (or minks of 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]. Yet no evidence of the fundamentally illegal trade of live wild animals, many of which are on the nationally endangered and protected species list of China as indicated by (Xiao et al. 2021), was found on the enforcement records of the Wuhan Park and Forestry Bureau in 2019 [20,20a]. Although we assume yearly stationarity and estimate of approximately 30 potentially susceptible animals per month at the HSM, 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 on 38 raccoon dogs sold in Wuhan in 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. But 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 SARSr-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 animals except several pangolin and Malayan porcupines were sampled between February 2020 and 2021. No SARSr-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, none were SARS-CoV-2 nucleic acid test positive (Joint WHO-China Study 2021a)(Supp. Table 3). These results are consistent with extensive sampling between May and September 2020 where 27,000 wild animals across China were sampled for SARSr-CoVs will all results negative (Joint WHO-China Study 2021a).

We argue that raccoon dogs are an unlikely cause of the outbreak for three reasons: 1) They were sold in Wuhan in very small numbers relative to their overall trade, making the likelihood that a raccoon dog would be the culprit in Wuhan, of all places, and *only* Wuhan, exceedingly small; 2) 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); 3) No epidemiological evidence yet exists to indicate raccoon dogs were the intermediate hosts or are capable of supporting animal-to-animal transmission of any strain of SARS-CoV-2 in a non-laboratory setting.

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 (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 with 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 improvement of infectivity of the G614 SARS-CoV-2 S 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 very poor susceptibility to SARS-CoV-2 Wuhan-Hu-1, with a similar binding affinity as 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. 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 immunoprecipitation (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 a level with 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).

In summary:

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

- ○ The temporal signal of human cases in the market did not begin in the stalls with animals or even near those stalls.
- ○ The late December spatial signal near the animal stalls overlaps with market toilets, a known source of prior coronavirus transmission.
- ○ Potential intermediate hosts were sold in small numbers (although records are likely incomplete). For example, raccoon dogs (a likely host for SARS-CoV-1) were only sold in small numbers and likely originated from Hubei Province, where SARS-CoV-2-related coronaviruses have not been detected
- ○ 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.
- ○ 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 assumed to be unproven.
- ○ There have been no reports of natural infection of raccoon dogs anywhere in the world (World Organization for Animal Health 2022).

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 the "illegal wildlife sales" within the market may have been the origin of the virus, as indicated by large sampling bias in the southwestern corner and even more so, by a focussed sampling of wildlife stalls within the HSM on the 12/01/2020 (Gao et al. 2022) [23,23a]. In addition, some of the stated goals of the sampling efforts specified in the methods of the Joint WHO-China Study (2021b) (such as the sampling of "doors and floors of all the stalls in the blocks where early cases were located") were clearly not fulfilled, as unsampled stalls with COVID-19 cases can be found in all market blocks (white boxes in 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.

We note that the only stalls with more than one positive sample were stall vendors that had occupied more than one address number on the HSM floor plan. We also note that stalls that are larger in size have a greater probability of having multiple samples taken, and therefore have a higher chance of receiving more than one positive sample. Using supplemental table S6 from Worobey et al. (2022b) and Table 1 of Gao et al. (2022), we infer that all of the positive environmental samples collected from wild mammal stalls were taken on 12/01/2020, and not during the main sampling event on 01/01/2020, indicating non systematic sampling at the HSM.

A table of environmental positive samples (through PCR or NGS) was provided by the CDC (Guizhen 2020) but not negative samples. We can infer from sample numbering that at least 5 negative samples were taken from West 6/29 (Q62-3, Q65-7) as these numbers were positioned in between 5 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 2X oversampling appears to be inadequate to compensate for this bias.

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 would allow respiratory droplets and aerosols to spread thoroughly within each stall with the potential to contaminate all surfaces, but the spread of virions and droplets across stall borders is suppressed due to separating walls. Larger stalls would also allow air mixing within the stall, but again, with more limited cross-stall spread. The fact that the stalls were relatively enclosed spaces where visitors to the stall talk to the vendors facing the inside of the stall also indicates that individual stalls may function as well-mixed traps of aerosols - with potential for widespread contamination across the stall from an infected vendor or customer, while contamination across stall boundaries is attenuated because of limited vectors (aerosols, vendor motion) to carry the virus across stall boundaries.

Many stalls have airflow-blocking curtains in addition to their rolling shutter doors, and visitors have to either physically enter the stall and go to the inside of the curtain (where contamination is efficiently mixed and contained within the stall boundary), or in case of stalls that had walls walling off the bottom section of their openings, have to move into the enclosed space in order to talk to the vendor, again potentially facilitating efficient spread of contaminated aerosols within the enclosed space (Tang et al. 2020). 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 thus 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 the stall regularly had customers enter the stall, or if like stall West 8/25 only had a relatively small opening that customers could talk into.

In addition, a possible source of ascertainment bias relates to selective instrumentation. Knowledge of the previously documented enforcement records for illegal wildlife sales by environmental samplers appears to have led to a collection focus on these stalls. It is possible that testing using more sensitive techniques (such as nested PCR and viral metagenomics) may have been selectively used on perceived ‘high risk’ stalls compared to those used on samples taken from other stalls.

Selection bias

Another potential bias we note is an apparent search bias introduced by (Worobey, Levy, Serrano, et al. 2022), who added an “Unidentified meat” category, not seen in environmental sampling maps in Joint WHO-China Study 2021b; 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" W7/26-28 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" W8/19-23-W7/20-24 sold pig carcasses and preserved livestock meat (cut-up pig legs) (supp. Figs. 22,23). 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) datasets. 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), 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). This indicates that, given the small sample size of wildlife stalls, there is no significant increase in domesticated wildlife stalls in positive environmental samples compared with the overall ratio of positive to total 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	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, there is no statistical support to a 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).

We note the only environmental samples positive by PCR in stall West 6/29-33 were found on surfaces that are located in the outer, customer-facing room of the stall-ground, a cart and a “feather removal machine”, but not the “iron container in inner room” (“cage”) that is located in the inner, non-customer-facing room of the stall, which is consistent with respiratory droplet and aerosol contamination from an infected person.

Given that stall West 4/26-28 was located at the Southwestern entrance of the market, another possible reason for oversampling this area is that samplers may have passed this area in and out of the market. As stall West 6/29-33 was the southernmost stall that sold “domesticated wildlife products” within the HSM and the only such stall that contained samples that are positive for PCR, an oversampling bias could have lead to a higher likelihood of positive environmental samples and more positive environmental samples at this stall compared to other stalls.

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 in the beginning of January 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. 35). 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 source of SARS-CoV-2. We also concur with this conclusion, as the earliest case locations are 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 consistent with human to human transmission in shared communal areas such as eating areas and toilets. The distribution of cases and distribution of wildlife stalls are consistent with independent Poisson point process models and zoonotic spillover cannot be inferred. Additionally, 4 of the earliest identifiable cases with onset in December (10th-16th) were unlinked to the HSM clearly indicating human to human transmission outside of the HSM pre/syn what we infer to be a superspreader event at the HSM. The distribution of environmental PCR positive samples is more spatially consistent with COVID-19 case contamination and spread from the HSM toilets, than to wildlife stall locations. Furthermore, 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 a 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. We find that the arguments by Worobe et al. (2022b) that SARS-CoV-2 emerged from the Huanan Seafood Market 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 superspreader 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 simulation and Ripleys 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 adaptation of 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

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