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Implications of Haplotype Switching for the Origin and Global Spread of COVID-19

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Abstract

When analysed in patients at epicentres of outbreaks over the first three months of the 2020 pandemic, the virus responsible for COVID-19 cannot be classed as a rapidly mutating virus. It employs a haplotype-switching strategy most likely driven by APOBEC and ADAR cytosine and adenosine deamination events (C>U, A>I) at key selected sites in the ~ 30,000 nt positive sense single-stranded RNA genome (Steele and Lindley 2020). Quite early on (China, through Jan 2020) the main haplotype was L with a minor proportion of the S haplotype. By the time of the explosive outbreaks in New York City (mid-to late-March 2020) the haplotype variants expanded to at least 13. The COVID-19 genomes analysed at the main sites of exponential increases in cases and deaths over a 2 week time period (explosive epicentres) such as Wuhan and New York City showed limited mutation per se of the main haplotypes engaged in disease. When mutation was detected it was usually conservative in terms of significant alterations to protein structure. The coronavirus haplotypes whether in Wuhan, West Coast USA, Spain or New York differ by no more than 2-9 coordinated nucleotide changes and all genomes are thus ≥99.98% identical to each other. Further, we show that the most similar SARS-like CoV animal virus sequences (bats, pangolins) could not have caused the assumed zoonotic event setting off this explosive pandemic in Wuhan and regions: zoonotic causation via a Chinese wild bat SL-CoV reservoir jumping to humans by an intermediate amplifier (e.g. pangolins) is clearly not possible on the basis of the available data. We also discuss the evidence for airborne transmission of COVID-19 as the main infection route and highlight outbreaks on certain ships at sea consistent with their hypothesised cosmic origins. We conclude that the virus originated as a pure genetic strain in a life-bearing carbonaceous meteorite which was first deposited in the tropospheric jet stream over Wuhan. Over the next month or so this viral-laden dust cloud not only descended through the troposphere to target Wuhan and its environs, but was also transported in a Westerly direction through the mid-latitude northern jet stream causing explosive in-fall events sequentially over Iran, Italy, Spain and then New York City in the early months of the pandemic to the end of March 2020.

Keywords: Coronavirus • Epidemiology • Comets • Panspermia

Introduction

The new coronavirus pandemic of 2019 causing severe acute respiratory syndrome (SARS-CoV-2) has been named COVID-19 by the World Health Organization. This newly emergent virus is related by RNA sequence similarity to the earlier pandemic SARS-CoV-1 (2002-2003). However, the genetic distance between the causative viruses is considerable, with sequence similarity of just 79.45%. This is equivalent to a difference of about 6000 single nucleotide variants accruing over a short evolutionary time period to account for the re-emergence of SARS-CoV-1 leading to the origin of the observed explosive outbreak of COVID-19 in the central China Wuhan region in December 2019.

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Cosmic Origin Hypothesis for COVID-19

We have reviewed the range of evidence [1] consistent with the hypothesis that the virus arrived via a presumed life-bearing cometary bolide possibly, though not necessarily, linked to a fireball event seen over North-Central China on the night of 11 October 2019. A few weeks later a viral-laden dust cloud entered the tropospheric jet stream, thus leading to the explosive disease outbreaks in Wuhan city and surrounds in Hubei province China [1,2]. We can argue that this viral in-fall settling on property, people and animals (domestic and wild) was on a region-wide scale, thus igniting an almost synchronous epidemic epicentre over the ensuing weeks extending well into late January 2020 (Note : A report that COVID-19 emerged in Barcelona in March 2019 was in our view based on false positive evidence, Supplementary File A).

In this paper we review the evidence and critical arguments for and against theories of terrestrial origin (animal-to-human jump and also bioweapon release models) versus the wider array of evidence supporting a cosmic origin. We argue that our proposed model is compatible with all the known facts, genetic and immunological [3], epidemiological, temporal and geophysical [2,4-6]. It is also consistent with all previously documented astrophysical and astrobiological evidence which supports the idea of a spatially interconnected cosmic biology extending to the earliest origins of the known universe [7,8,9,10,11,12,13].

The fact that pathogenic viruses including SARS-CoV-2 are genetically adapted so as to attack particular evolved host species is often cited as evidence against their extraterrestrial origins. This criticism ceases to be valid if we take account of an interconnected cosmic biosphere with genetic exchanges taking place over astronomical distances and timescales. In such a schema the host-parasite adaptation becomes an artefact of a cosmically connected evolutionary process [10,11,13].

We next focus attention on the recently reported genetic data of COVID-19 which shows that the virus does not "rapidly mutate" as is popularly believed but displays a clear haplotype switching genetic strategy in adapting to and spreading between human hosts [3]. We assume the same type of haplotype-switching spread could also occur if the virus were to infect susceptible animal hosts. Thus, initially in Chinese hosts, the numbers of complete genome sequences show the relevant haplotypes are mainly L (Hu-1, dominant) and some developed as S (minor). As the viral-laden cometary dust spread globally in the tropospheric jet streams [4,5,6] it has now become diversified via haplotype switching, displaying infections in populations with diverse genetic backgrounds across the globe. In our view the diverse haplotypes emerge as a consequence of the diversity of the host-parasite interaction via the Innate Immune response of APOBEC and ADAR deaminase-mediated C>U and A>I(G) mutagenesis at key sites in the COVID-19 RNA genome (Table 1).

Thus, haplotypes diversified from 2 (in China) to another 11 emerging in Europe (Spain, France) and New York City. We confirmed that we had captured most haplotypes emerging during this period by showing they were recovered in the airplane travelers into Victoria, Australia, between January 24 and March 15, and also for all COVID-19 sequences collected in the month of March 2020 in France [3]. This n≥13 haplotype diversity evidently occurred between January-March 2020 culminating in the explosive epidemic in New York City from March 14-March 22 [3]. However, it should be pointed out that the difference between the original Wuhan L haplotype sequence (Hu-1) and any other haplotype ranges from 2 (S haplotype) to 9 (L-241a.1) apparently coordinated single nucleotide variant (SNV) differences (Figure 1). "Thus, each of the SNV-defined haplotypes identified comprises approximately 0.02% difference from the Hu-1 reference sequence. On average there are approximately 5 SNV differences from Hu-1 defining each haplotype. There is ≥99.98% identity between any haplotype and the Wuhan reference sequence whether that sequence is collected in China, Spain, the US West Coast or New York City" [3]. It needs to be stressed at this point that the same spread of sequence similarity (≥ 99.98%) in geographically dispersed sequences was observed also in the more limited 2002-2003 coronavirus outbreak caused by the SARS-CoV-1 virus [14].

Genomic Structure of COVID-19

Figure 1 is the comparative genomic structure of SARS-CoV-1 (2002-2003) and SARS-CoV-2 (2019-2020) illustrating the SNV site positions of the two main haplotype series (L-241, S) as shown in Table 1 where site combinations defining different haplotypes can be referenced.

The two coronavirus genomes are similar at the nucleotide sequence level at 79.45% (Table 2). The MERS-CoV genome (2012) is strikingly very different again from these two related coronaviruses [15,16]. The key amino acid site in the Spike protein that is clearly altered in the L-241 haplotypes (D614G) now dominates the globe outside China. In China the L-241 haplotypes were not observed in the surveyed cases (Dec 2019-Jan 2020) by Steele and Lindley [3].

Thus L-241 haplotypes containing D614G appear to have replaced the Wuhan L haplotype and most other detected haplotypes at time of writing (July 2020). But this "replacement" reflects the outcome of the host-parasite relationship as we expect the Hu-1 sequence to be of the L haplotype in endogenous infections via the viral-laden dust in China. Of particular interest is the fact that the D614G change in S protein structure significantly facilitates infection/replication of COVID-19 but not disease severity [19]. This plausibly explains the apparent ease of spread via fomites and person-to-person spreads in contaminated environments (hospital and nursing home clusters, cruise ships, airplane environments etc).

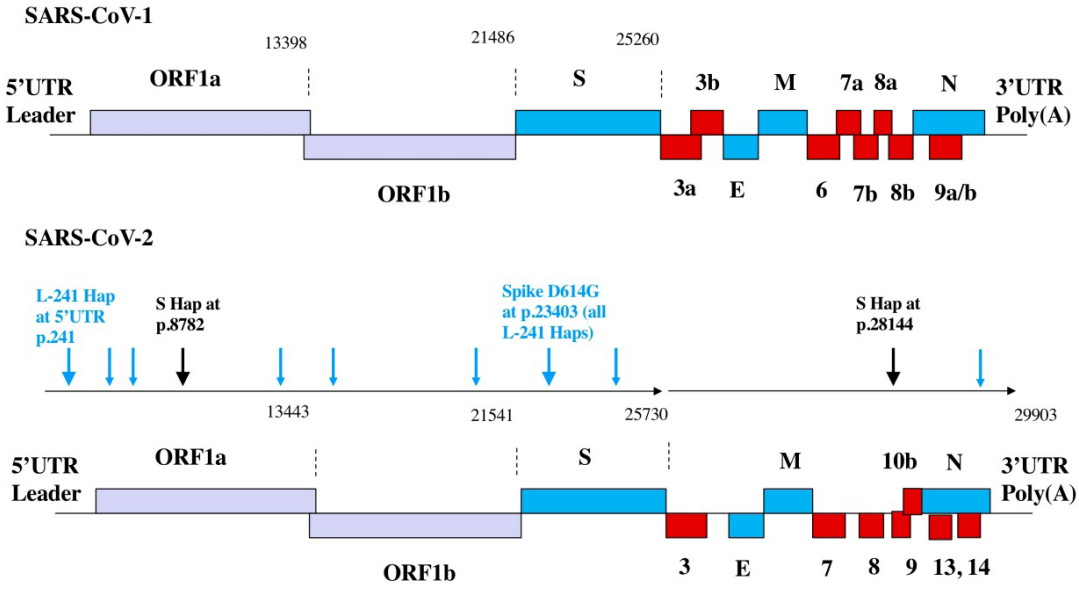
Early COVID-19 Origins and Explosive Epicentres

The COVID-19 pandemic began with the first Chinese cases of severe acute respiratory pneumonia-like diseases in late November to early December 2019 in Wuhan, Hubei province China. Of the first 41 COVID-19 patients 27 were connected and 14 were not connected at all to the Wuhan Meat and Seafood market [20,21]. So even at this early stage the clear evidence showed that one third of all patients had no connections at all to animal wet markets. Yet the common belief is that the pandemic began with a jump from a SARS-like CoV infected animal, probably a bat and/or pangolin [22,23] which then triggered the explosive region-wide epidemic in central China focused on Wuhan city and its regions [1]. The animal jump model, if true, needs to explain this extensive region-wide infection in a remarkably short period of time.

After a number of explosive epidemics, the pandemic then developed further through January 2020 through to end of March 2020: first in Wuhan (first week January increasing exponentially from Jan 21 to Feb 10), next in Tehran/Qom and Italy/Lombardy (from March 1), then Spain (from the end first week March) and then New York City (March 14 – through into April) see Figure 1 [3,5]. This early temporal order of the epicentres is important to keep clearly in mind as most of the rest of the world had little or no evidence of the disease spreading at this point. Indeed, as we noted at the time, all these explosive epicentres fell on a narrow latitude band centred on the Latitude 40o N allowing us to predict that the next major local epidemic after Tehran, Italy and Spain would be New York City [5]. The disease has now spread extensively across the globe from the combination of infall events with person-to-person infection, as well transcontinental transport of virus-laden dust via wind/weather systems. To date some 11 million or more people in both northern and southern hemispheres have come to be infected by the virus [6]. There are also large local explosive outbreaks mainly in certain southern and south west locations in USA (Texas, Florida, Arizona and California) and to a lesser extent in nearby regions (Louisiana, Alabama, New Mexico) suggesting the possibility of a further viral-laden dust cloud in-fall directly from the troposphere or laterally by wind transport across the United States from June-into July 2020 (see charts as 18 July

HAP	AA class-> 5'UTR p.241	P<>NonP Thr<>Ile p.1059	SYN Phe<>Phe p.3037	SYN Ser<>Ser p.8782	NonP<>NonP Phe<>Tyr p.9477	NonP<>NonP Leu<>Phe p.11080/83	P<>NonP Ser<>Leu p.11916	NonP<>NonP Pro<>Leu p.14408	P<>P Tyr<>Tyr p.14805	NonP<>NonP Pro<>Leu p.17747	P<>P Tyr<>Cys p.17858	SYN Leu<>Leu p.18060	NonP<>NonP Ala<>val p.18998	Acid<>NonP Asp<>Gly p.23403	P<>Basic Gln<>His p.25563	NonP<>NonP Gly<>Val p.25979	NP<>NP Gly<>Val p.26144	P<>NonP Leu<>Ser p.28144	SYN Asp<>Asp p.28657	P<>NonP Ser<>Leu p.28863	near 3'UTR non-CDS gap p.29540
L (Hu-1)	C	C	C	C	T	G	C	C	C	C	A	C	C	A	G	G	G	T	C	C	G
Ln	C	C	C	C	T	T	C	C	T	C	A	C	C	A	G	G	T	T	C	C	G
L-241a	T	T	T	C	T	G	C	T	C	C	A	C	C	G	T	G	G	T	C	C	G
L-241a.1	T	T	T	C	T	G	T	T	C	C	A	C	T	G	T	G	G	T	C	C	A
L-241b	T	T	C	C	T	G	C	T	C	C	A	C	C	G	T	G	G	T	C	C	G
L-241c	T	C	T	C	T	G	C	T	C	C	A	C	C	G	T	G	G	T	C	C	G
L-241d/s	T	T	T	C	T	G	C	C	C	C	A	C	C	G	T	G	G	T	C	C	G
L-241e	T	C	C	C	T	G	C	T	C	C	A	C	C	G	T	G	G	T	C	C	G
L-241f	T	C	T	C	T	G	C	T	C	C	A	C	C	G	G	G	G	T	C	C	G
L-241g	T	C	C	C	T	G	C	T	C	C	A	C	C	G	G	G	G	T	C	C	G
S	C	C	C	T	T	G	C	C	C	C	A	C	C	A	G	G	G	C	C	C	G
Sa	C	C	C	T	T	G	C	C	C	T	G	T	C	A	G	G	G	C	C	C	G
Sb	C	C	C	T	A	G	C	C	T	C	A	C	C	A	G	G	G	C	C	C	G
Ss	C	C	C	T	A	G	C	C	T	C	A	C	C	A	G	T	G	C	T	T	G

Table 1. Main COVID-19 haplotypes Jan-Mar 2020. From Steele and Lindley [3].



Schematic adapted from Coleman and Frieman 2014, Lu et al 2020 – relative positions , accessary proteins in red. Arrows are approx. relative positions of the key SNV differences from Wuhan Hu-1 ref. sequence associated with L-241 and S COVID-19 haplotypes, see Table 2 in Steele and Lindley 2020. The combinations are shown for L-241 series haplotypes (blue arrows) and for the major positions at p.241, p.23403; and S haplotypes (black arrows) . Also see molecular biology and coronavirus replication strategy in Masters 2006, Yang and Leibowitz 2015.

Figure 1. Schematic comparison of the genomic structure of SARS-CoV-1 (2002-2003) and SARS-CoV-2 (2019-2020). All sources cited are in reference list [15-18,3].

	Percent Identity Matrix Multiple Clustal12.1 Alignment (date 6.7.20)						
	NC_045512.2	AY278741.1	DQ022305.1	KC881005.1	KC881006.1	MG772933.1	MG772934.1
Coronavirus	**Hu-1 (Wuhan)**	**SARS-CoV**	**Bat 1**	**Bat 2**	**Bat 3**	**Bat 4**	**Bat 5**
Hu-1 (Wuhan)	100	79.45	79.32	79.56	79.65	88	87.98
SARS-CoV (Urbani)	79.45	100	87.9	95.32	95.6	80.82	80.94
Bat 1	79.32	87.9	100	88.3	88.26	82.66	82.3
Bat 2	79.56	95.32	88.3	100	98.83	81.11	81.14
Bat 3	79.65	95.6	88.26	98.83	100	81.18	81.18
Bat 4	88	80.82	82.66	81.11	81.18	100	97.46
Bat 5	87.98	80.94	82.3	81.14	81.18	97.46	100

Coronavirus	Accession	Year Published	Ref	Bat Species
Hu-1 (Wuhan)	NC_045512.2	2019		
SARS-CoV	AY278741.1	2003	Masters 2006	
Bat 1	DQ022305.1	2005	Lau et al 2005	***Rhinolophus sinicus*** (wild Chinese horseshoe bats)
Bat 2	KC881005.1	2013	Ge et al 2013	***Rhinolophus sinicus*** (wild Chinese horseshoe bats)
Bat 3	KC881006.1	2013	Ge et al 2013	***Rhinolophus sinicus*** (wild Chinese horseshoe bats)
Bat 4	MG772933.1	2018	Hu et al 2018	***Rhinolophus pusillus*** (wild Chinese horseshoe bats)
Bat 5	MG772934.1	2018	Hu et al 2018	***Rhinolophus pusillus*** (wild Chinese horseshoe bats)

For 1% difference assume about 300 single nucleotide changes per genome (based on Hu-1 29903 nt in length)
For 10% difference assume about 3000 single nucleotide changes per genome
For 20% difference assume about 6000 single nucleotide changes per genome

Table 2. Percent Identity Matrix between COVID-19 reference sequence (Hu-1), SARS-CoV and various Bat coronavirus sequences.

in Supplementary File D). At the time of writing there have been perhaps 500,000 deaths worldwide (a death to confirmed case rate of about 5%).

The vast majority of the deaths are in vulnerable elderly already co-morbid subjects, >65 years of age, [24]. However, based on definitive (and comprehensive) data relating to an outbreak of disease on the cruise ship Diamond Princess a more accurate estimate of the COVID-19 case fatality rate emerges which varies anywhere from 0.05% to 1% [25]. And at the time of writing John Ioannidis estimates that in excess of 300 million globally may have already been infected with COVID-19, a good 10 to 20 times higher than the currently widely publicized estimates [26]. Thus, with the benefit of hindsight the disease itself, while new and striking in the speed of its global spread, should be considered at least in a figurative sense a mild common cold on a par with seasonal Influenza with vulnerabilities manifesting mainly in those with already compromised innate immune defenses.

The widely reported early induced cytokine storm and severe inflammatory sequelae has much support [27] and requires attention (via inflammation suppression) in vulnerable subjects who may also have possibly suppressed innate immunity; dysregulated interferon gene expression (suppression) as has been recently observed in COVID-19 patients [28,29,30]. This may explain why there is little or no evidence of a full innate immune response resulting in deaminase mutagenic signatures [31] in the full-length genomes of many COVID-19 patients [3]. We suspect many of the genomes examined in Steele and Lindley [3] (2020) were in fully developed diseased cases and not "asymptomatics", who may have better developed innate immunity and may thus display a higher level of APOBEC and ADAR mutagenesis in any shed viral genomes. In a Leading Edge Perspective published in Cell Netea and colleagues describe the disease thus "SARS-CoV-2 infection is mild in the majority of individuals but progresses into severe pneumonia in a small proportion of patients. The increased susceptibility to severe disease in the elderly and individuals with co-morbidities argues for an initial defect in anti-viral host defense mechanisms" and further "Epidemiological data show that the elderly and those with co- morbidities (diabetes, obesity, and cardiovascular, respiratory, renal, and lung diseases) are most susceptible to COVID-19 and more likely to suffer from the most severe disease complications. Interestingly, young children, including infants who are more susceptible to other infections, have milder symptoms and less severe COVID-19" [24]. We would further add that future research on the pathogenesis of COVID-19 in healthy versus susceptible subjects should reveal the important role of the innate immune system-in particular in contributing to a better understanding eventually as the reason for so many asymptomatic infections and for mild symptoms.

Before analyzing the COVID-19 haplotype data further in terms of its putative cosmic origin we need to review the evidence for the two widely believed popular theories of the origin of COVID-19.

The Bat to Human Jump Theory

We will briefly discuss the data on this widely accepted popular theory as it figures prominently not only in the introductory sections of all scientific papers published on the topic, but in many major newspapers around the world including articles by Wildlife Disease Surveillance groups in Science magazine [32].

The process of human infection by animal viruses is termed zoonosis. The first clear point to make is that this theory with respect to the origin of COVID-19 has no direct scientific evidence in its support (unlike the well-documented one step (yet limited) horse-to-human transmission of Hendra virus see CDC [33].

This fact is often overlooked in current public and scientific discussions [32]. Further, the same animal jump model, assumed solely on phylogenetic correlations (then further human-to-human spread) has been applied to all suddenly emergent pandemic diseases over the past 40-50 years : influenza virus epidemics come from migrating birds, domestic chicken flocks or domestic swine [7]; HIV from higher primates (e.g. chimpanzees, viz. HIV crossed from chimps to humans in the 1920s in what is now the Democratic Republic of Congo. This was probably as a result of chimps carrying the Simian Immunodeficiency Virus (SIV), a virus closely related to HIV, being hunted and eaten by people living in the area. Oct 30 2019" [34]. We should stress that there is no direct scientific evidence to support these assumed zoonotic events or animal to human transfers.

Other recent coronavirus diseases associated with acute respiratory diseases such as MERS-CoV (2012) are assumed to have arisen from camels and/or bats in combination [15] and SARS-CoV-1 (2002-2003) from bats [35-38] and/or pangolins in combination [39,40]. In all cases there are suggestive phylogenetic relationships between the putative virus sequence and the human sequence but no direct evidence that any of the major human disease pandemics have actually originated this way. The great genetic hurdles are vividly displayed in Table 2 which shows representative bat SARS-like CoV examples showing the closest sequence similarities with both SARS-CoV-1 and SARS-CoV-2 (COVID-19). These comparisons need to be taken into account when we consider the bat to human jump theory for origin of SARS-CoV-2 (2019-2020) or the more limited SARS-CoV-1 pandemic also originating in China in 2002-2003 [15]. More recently, an intermediate 'amplifying' wild host also eaten in China (pangolins) has been implicated in the explanation [39, 40, 41].

Taking the full length of Hu-1 as a reference (SARS-CoV-2, 29903 nt) the genetic distance from any bat sequence to the human SARS-CoV-1, or SARS-CoV-2 ranges from about 1300 to over 3000 single nucleotide variants (SNVs). We present the sequence similarities this way rather than in the form of a "tree" or percent sequence similarity as the mutational hurdle can be addressed directly and logically by independent observers without trying to interpret what the "tree" means (or be misled by the optimistic estimates of 90% to 96% sequence similarity). This is contrasted with the ≥ 99.98% sequence identity of the known range of COVID-19 haplotypes, despite extensive supposed human passage, during the current pandemic, Table 1 [3] – indeed the same range and stability on human passage was observed for the diversity of SARS-CoV-1 in isolates during 2002-2003 [14].

Generally speaking, many molecular evolutionists who work on these types of phylogenetic data accept our assessment that the bat-to-human genetic hurdle is too big to bridge in the time periods available. Thus, in commenting on putative jumps of this type by bat coronaviruses [35,36,42,22] state "This seriously divides the experts. Australian virologist Edward Holmes has estimated that RaTG13 would take up to 50 years to evolve the extra 4 per cent that would make it a 100 per cent match with the COVID-19 virus." Martin Hibberd, of the London School of Hygiene & Tropical Medicine, believes it might take less than 20 years to morph naturally into the virus driving the current pandemic. Others say such arguments are based on the assumption the virus develops at a constant rate. "That is not a valid assumption" asserts Richard Ebright of Rutgers University's Waksman Institute of Microbiology. "When a virus changes hosts and adapts to a new host, the rate of evolutionary change is much higher. And so it is possible that RaTG13, particularly if it entered humans prior to November 2019, may have undergone adaptation in humans at a rate that would allow it to give rise to Sars-Cov-2. I think that is a distinct possibility." Indeed Ebright believes an even more controversial theory should not be ruled out [22].

"It also, of course, is a distinct possibility that work done in the laboratory on RaTG13 may have resulted in artificial in-laboratory adaptation that erased those three to five decades of evolutionary distance." That latter comment also feeds into the Cold War conspiracy theories that claim that COVID-19 is a Chinese bioweapon that was accidently released from the Wuhan Institute of Virology, a genetically engineered upgraded version of the RaTG13 isolated from an abandoned mine in 2012-2013 below, and [23]. However, what is clear, as reported at the time on January 31 2020 by Jon Cohen of Science magazine [43]. "One of the biggest takeaway messages [from the viral sequences] is that there was a single introduction into humans and then human-to-human spread," this assertion being attributed to Trevor Bedford, a bioinformatics specialist at the University of Washington and Fred Hutchinson Cancer Research Center.

Further support of a bat origin has appeared [42] claiming that the bat SARS-like CoV, RaTG13, has 96.2% whole genome sequence similarity with SARS-CoV-2 (COVID19, the Hu-1 sequence). This virus was originally named RaBtCoV/4991, a name change itself which has fuelled the bioweapon conspiracy theory as well [23]. In any case, this close match would still require approximately 1140 SNV changes to become a COVID-19 exact match (≥ 99.98% sequence identity), a genetic hurdle we believe is too great. This however remains the mainstream view held by most workers at the present time [22].

Our view, given all of what we know on the natural haplotype switching adaptive strategy of COVID-19 coupled to its observed relatively low mutation on human passage [3] is that the genetic jumps as required by the variant distances summarized in Table 2 are impossible to bridge. If coronaviruses infecting bat colonies [35,36,38,42] are the long term "festering" endemic reservoir the sobering facts are that SARS-CoV-1 came and went rapidly in 2002-2003 and never came back [15] which also still currently applies to the more limited outbreak of MERS-CoV in the middle east in 2012.

Why many suddenly emergent epidemic viruses also go quickly and never come back is a key unsolved problem, as well as a major feature of many suddenly emerging pandemics in history [7]. It may well be a combination of natural self-limiting processes such as adaptive T/B lymphocyte "Herd Immunity", heightened and 'trained' non-specific innate immunity [24] as well as degradation of the virus in the physical environment are all involved. If bats are an 'intermediate' host/reservoir and thus a widely available endemic reservoir as suggested [35,36,42] it is a real puzzle why none of the original coronavirus diseases have ever returned if the bat to human (or via animal X?) theory is indeed the explanation for the cause of pandemics such as COVID-19.

Pangolins as an Intermediate Host from Bats then to Human?

The current orthodox theory is that if the bat to human jump is a genetic bridge too far, then perhaps bats are the primary natural reservoirs of zoonotic coronaviruses and that the actual jump occurs by an intermediate host acting as an 'evolutionary amplifier'- presumably some type of evolutionary genetic fine-tuning for the zoonotic leap? [39-41]. However, it seems the genetic distance for such pangolin-nursed SL CoVs maybe just as great as for the bat SL CoVs (Table 2). Thus, in the report by [40] "Pangolin-CoV is 91.02% and 90.55% identical to SARS-CoV-2 and BatCoV RaTG13, respectively, at the whole- genome level. Aside from RaTG13, Pangolin-CoV is the most closely related CoV to SARS-CoV-2." Using the calculator from Table 2 this constitutes a deficit of 2700 SNVs to match the current COVID-19 reference Hu-1 strain, again a genetic difference itself which is insurmountable in our view. Another recent submitted survey of six novel pangolin coronavirus complete genomes [41] gave approximately 85.5% to 92.4% similarity to the Hu-1 sequence – the number of SNV required for a full match to COVID-19 ranging from 2400 to 4350.

Even if we are generous and assume from the data in Table 2 that only about 1% of the relevant nucleotides switched were mandatory for the bat to human transition to occur (i.e. 99% similarity to COVID-19 which has yet to be observed) the probability of this happening by random mutations is 1 in 4^{300}, which is equivalent to a probability of 1 in 10^{180}. The number of protons in the entire observable universe being only 10^{84}, it is amply clear that the probabilistic resources of the entire "Big Bang" universe is already stretched beyond the limit to cope with this presumed event. (We sketch an extreme and complex hypothetical genetic mechanism that might reduce some of these odds in the Supplementary File C).

If pangolin species are indeed an intermediate natural reservoir and amplifier of SARS-CoV-2-like CoVs it seems to us that the probability of a successful bat-to-pangolin-to-human jump (and then successful human-to-human transmission of COVID-19) is the product of two exceedingly improbable events, which makes the integrated jump highly unlikely – a Panglossian just so story. Thus, the actual evidence for real-time and widespread zoonotic events, though suggestive from phylogenetic analyses does not itself add up to the direct evidence for the rampant zoonosis often implied in the overwhelming majority of the papers we have read on the topic [44, 32].

Cosmic Origins?

A plausible scientific explanation (hypothesis) is expected to account for all existing data and observations whilst also making testable predictions of hitherto unexpected observations into the future.

In our view there is a plausible alternative scientific explanation for the observed diversity of all these animal and human SL-CoV sequences. Indeed, under the cosmic dust in-fall theory which entails a connected evolutionary process over vast cosmological dimensions [13], we expect susceptible terrestrial animal hosts including humans to become infected with an appropriate coronavirus variant. Further, flocks of thousands of bats, in their nocturnal scavenging flights, are ideal samplers of in-falling cometary dust clouds, some of which may plausibly harbour viruses. Bats could therefore be ideal sentinels for incoming cosmic coronavirus variants. In some cases, an informative seasonal variation has been observed in longitudinal sampling [35]. "Twenty-seven of the 117 samples (23%) were classed as positive by PCR and subsequently confirmed by sequencing. The species origin of all positive samples was confirmed to be R. sinicus by cytochrome b sequence analysis… A higher prevalence was observed in samples collected in October (30% in 2011 and 48.7% in 2012) than those in April (7.1% in 2011) or May (7.4% in 2012)… and analysis of the S protein RBD sequences indicated the presence of seven different strains of SL-CoVs." This seasonal variation may perhaps coincide with the crossing times of the Orionid meteorite stream [45] in October-November each year as well as seasonal downdrafts from the troposphere, which we commented on in an earlier paper in this series [4].

These considerations have an important bearing on the genetic similarities and variations observed in coronaviruses isolated from animals as well as human beings. It is entirely conceivable that the primary "large distance" genetic variation in (say) the beta coronavirus family (as instanced by examples in Table 2) pre-exists in the dust in the troposphere at times of in-fall (a genetic scenario which we believe applies to all incoming cosmic viral variants whether they be coronaviruses, influenza viruses or other potential pathogens such as the more sophisticated retroviruses). According to our point of view the primary viral growth and propagation occurs in cellular sources (involving evolved eukaryotic cells) throughout a vast cosmic limitless biosphere over the aeons of cosmic time. The interiors of comets transporting these virions to Earth may well be clonally partitioned with differences thus showing up in the multitude of cometary fragments that enter the Earth [7,46,8,12]. These issues are updated and discussed further in a forth coming Advances in Genetics Elsevier volume (No. 106) on "Cosmic Genetic Evolution" which is being finalized and In Press at time of writing (Editors: E.J. Steele, N.C.Wickramasinghe).

The Chinese Bioweapon Release Theory

This theory is much discussed in the popular and serious press [22,23]. Not surprisingly both the bioweapon theory and the animal jump theory (from wet markets), have now been rejected by Chinese scientists reviewing all the data [47]. However Jon Cohen of Science magazine was clear when reporting back on Jan 30 2020 "The role of Huanan Seafood Wholesale Market in Wuhan, China, in spreading 2019-nCoV remains murky, though such sequencing, combined with sampling the market's environment for the presence of the virus, is clarifying that it indeed had an important early role in amplifying the outbreak. The viral sequences, most researchers say, also knock down the idea the pathogen came from a virology institute in Wuhan." [43].

It is therefore difficult to discuss the viability of such an engineered-origins theory in the absence of hard objective scientific evidence. In our view, the way the virus has adapted to different human populations via a host-parasite-dependent haplotype riboswitching strategy has the hallmark of a pure natural biology – a biological adaptation strategy. We believe the only re-joiner is at the cold-war political level itself through rhetorical questioning: "Why design a virus bioweapon which does not lethally target the whole span of age groups in the population? Indeed, why design a weapon that targets only vulnerable elderly co-morbid human beings?" Further, if such a weapon did escape from the Wuhan Virology Institute it would need to have escaped on such a massive scale and at high assumed dose levels to ignite the first synchronous epidemic wave over a wide region of central China centred on Hubei province.

Genetic Strategy of COVID-19 is Compatible with its Putative Cosmic Origins

In our view all the animal jump models and the bioweapon idea are flawed and scientifically implausible.

The most plausible explanation, in our view, goes as follow:

- SARS-CoV-2 came as part of the fragmented carbonaceous meteorite as we have advocated earlier, fragmenting and entering the tropospheric jet stream [1-6] and this comes in as a more or less pure 'culture' clonal variant [48,2].
- Further, we strongly suspect SARS-CoV-1 is related to SARS-CoV-2 as they are putative fragments, bearing clonal variants, of the same fragmented cometary source in the Orionid meteor stream [4,45].
- Our genetic analyses have focused on the first 2-3 months of the pandemic, and for informative explosive outbreaks in the main. We focused attention on the main epidemic explosions, and initial spreads, as viral genetic patterns in these collections would be likely to be most revealing about the viral origins and mode of spread. Thus, the putative fall-out times in temporal sequence are Wuhan, China (mainly Dec 20-30 2019, Jan 2020, Feb 2-5 2020)->West Coast USA and Grand Princess cruise ship (Jan 22- Feb 27 2020, then to Mar 4), Spain (February 26-March 10), then New York City March 5-9, then March 14-22, 2020 (see details Table 1 in Steele and Lindley 2020 [3] and Supplementary Information in that paper). In addition, so that our findings could be replicated and checked readily by other scientists, we only sourced GenBank curated SARS-CoV-2 sequences at the NCBI Virus site. At the time of writing very few Iranian and Italian complete COVID-19 sequences had been deposited at NCBI Virus Site.
- At the main epicentres (Wuhan, New York) apart from the already reported haplotype diversification in New York ($n \geq 13$) relative to Wuhan ($n = 2$) there was from low to null mutation in COVID-19 isolates from subjects swabbed for the virus and thus complete genome sequencing. This was the strong repetitive pattern that showed up in the data. Person to Person (P-to-P) spreads could be identified and it was concluded that the high numbers of unmutated haplotype sequences in epicentres (and the cruise ship) could also be a reflection of P-to-P sharing of that sequence between susceptible individuals in local environments e.g. hospitals, nursing homes and other closed centres.
- The key major difference (from other low impact zones largely experiencing only P-to-P spreads), we now surmise, accounting for the explosive outbreaks in Wuhan and New York City (as well as those others on the 40° Latitude N band in Tehran, Italy/Lombardy, Spain) would have been the expected large infective viral doses at these times in these locations- large doses indicative of in-fall of viral-laden dust transported first via the tropospheric jet streams and sequentially brought to ground in these locations via local wind patterns and weather conditions : simultaneously infecting large numbers of people over a short time period. However, on each infection cycle the sequence data suggests that the haplotype fate of the virus is determined by the biochemistry and genetics of the host-parasite relationship. Thus, an APOBEC and ADAR deaminase-driven innate immune mutagenesis response on the part of the host [31] decides the haplotype. This is mainly at the RNA level through riboswitching and thus which COVID-19 haplotype sequence will survive and thrive in a particular host genetic environment [3]. This has been our operating hypothesis. The immediately reactive innate immune response to simultaneous airborne infections in the first 24-48 hours in the expected thousands of Chinese (Dec-Jan) and New Yorkers (March) to the incoming viral laden dust bearing source Hu-1 virions (L haplotype) can assist deaminase-mediated C-to-U and A-to-I (thus G) changes in the replicating viral sequences. A range of mutated positive strand RNA quasi-species are produced in an infected host cell with changes at particular deaminase hot spots or riboswitch sites determining compatible RNA secondary structures. Coordinated changes at two or more of these sites allows rapid replication in that biochemical background. Thus "host-directed" deaminase-mediated riboswitches are expected to create adaptive options for the virus which if then selected allows more rapid replication in that particular cellular environment. This hypothesis is a great simplification conceptual tool, and it has allowed us to order the complex data sets now emerging in the pandemic in a rational way" [3] Table 1. In our view once a haplotype successfully establishes itself by replicating within a particular biochemical-genetic background it would be expected to spread quickly in those hosts sharing that particular biochemical background. This cosmic-derived genetic strategy is part and parcel of the efficient spread of viruses throughout living systems across the cosmos [10,11].

Airborne Transmission COVID-19 Formally Recognized?

It is being more formally recognized that airborne transmission of COVID-19 is the most likely "highly virulent transmission route" in the spread the disease in the explosive outbreaks in Wuhan, Italy, and New York City [49]. The authors of this paper analysed the trends and mitigation measures in Wuhan, China, Italy, and New York City, from January 23 to May 9, 2020, revealing that the differences of outcome with and without mandated face masks was the main determinant in shaping the pandemic trends in the three epicentres. This significantly reduced the number of COVID-19 infections, by over 78,000 in Italy (April 6 to May 9), and by over 66,000 in New York City (April 17 to May 9). The conclusion is that social distancing rules implemented in the United States, were woefully insufficient by themselves in protecting the public. On the other hand, the wearing of face masks in public spaces appears to be is the most effective means to limit human-to human transmission [49]. This conclusion, while agreeable to our position, has been challenged by others (Supplementary File B).

COVID-19 Outbreaks in Ships at Sea

Numerous reports of this type appeared in the media from February 2020 (Supplementary File B). They are consistent with a global airborne transmission of COVID-19 in the air and winds from above. However strong this putative evidence, it is always difficult to separate it from more conventional explanations of infectious communicable disease theory i.e. the simplest explanation being in all cases it is an imported disease to the ships by infected passengers or crew (or fomites such a luggage and supplies), and the subsequent person-to-person spread. Here we discuss two outbreaks which are not easy to explain by conventional communicable infectious disease theory.

Al Kuwait sheep ship

One of us HR (Dr Herbert Rebhan) was the Veterinary surgeon on board the Al Kuwait sheep ship and supplied these details [50]. The ship, without a sheep cargo as it was returning after delivery of a live consignment

to Kuwait, docked in Fremantle harbour on May 22, with 21 of its 48 crews testing positive for COVID-19. At sea approaching Fremantle HR, at the request of the ship's Captain (as there was no medical doctor on the ship), provided medical advice and care. What follows now is largely on the public record [51] and are HR recollections and summaries:

"HR found nearly all of the ill crew members displaying symptoms of a bacterial infection (sore throat and sinusitis). No ill crew member complained of any problems with breathing. In regards to coughing, crew members reported no or mild and infrequent coughing. HR did not expect a viral agent to be at work as all ill crew improved 48 hours after starting antibiotic medication and most were deemed fit for duty 96 hours after the start of antibiotics. HR was as surprised as anyone when these crew members tested positive for COVID-19. As the crew had no outside contact since early March, HR was at a loss to explain the source of the infecting agent."

"Although it cannot be ruled out that the virus entered the ship on supplies obtained from shore, the explanation of exposure via sailing through a "viral cloud" dispersed through sea-spray perhaps, is more plausible for several reasons. One is that the sick crew members who tested positive all fell ill within 48 hours of one another, a clear indication of near simultaneous exposure. There was no evidence of person-to-person transmission. The second objection to infection from supplies at ports of call related to the well-attested properties of the virus. Studies have shown that when the virus is exposed to environmental temperatures greater than 30^0 C, viability is greatly reduced. The supplies taken aboard the Al Kuwait were exposed to environmental temperatures much greater than 30^0 C for many hours (in Kuwait). It would be hard to imagine that the incoming provisions would have been contaminated with a great enough viral load to infect all the crew at the same time. The crew members who tested positive for COVID were deck workers and would not have had any direct contact with the goods brought on the ship. The chef, cook, and galley helpers who had the closest contact with the goods brought aboard would have had maximum exposure to any and all viral contaminated supplies – but all subsequently tested negative for COVID-19."

HR further reports as follows (after arrival in Fremantle when all crew were placed in quarantine for two weeks in a Perth hotel).

"Of the 48 crew 21 were COVID-19 positive, and were all deck crew (Phillipinos). The officers (Croatian) were unaffected by COVID-19 including HR."..."The first crew member that fell ill with flu symptoms was one working at the end of the loading ramp. He was in full PPE and the only one that came close to people other than crew. He tested negative on both PCR and serology tests. He was extensively tested by Western Australian State Health Department looking for something. He took a full seven days to recover"……."The next three crew members who fell ill within 24 hours of one another and 5 days after the first crew member became ill all tested PCR corona positive. They took three days to recover"……."The crew member who was taken to the hospital tested negative. He was hospitalized for the flu"……."The crew members who were the most poorly did not have coronavirus. Some crew members who were ill and tested positive for coronavirus had milder symptoms and a faster recovery. 75% of those that tested positive for coronavirus were asymptomatic."

This testimony is very informative, and is consistent with an airborne and/or associated sea spray exposure to COVID-19 while the ship was isolated in the Indian Ocean. The high asymptomatic rate is similar to the rate reported by [52] on the small cruise ship MV Greg Mortimer (Supplementary Information B).

Argentinian Fishing Boat Echizen Maru (Agence France-Presse (AFP), July 14 2020)

Of all the reports of COVID-19 outbreaks in ships at sea this is perhaps the most compelling and definitive in limiting the types of causal explanations. It clearly supports Dr Rebhan's observations on the Al Kuwait sheep ship and has been recently discussed by us in Howard et al [51].

"The Echizen Maru fishing trawler returned to port in Ushuaia, Argentina after some of its crew began exhibiting symptoms typical of COVID-19." 57 sailors out of 61 were infected with the coronavirus after 35 days at sea, despite the entire crew testing negative before leaving port [53]. Thus, the reports says "57 sailors, out of 61 crew members, were diagnosed with the virus after undergoing a new test…. Yet all of the crew members had previously undergone 14 days of mandatory quarantine at a hotel in the city of Ushuaia. Prior to that, they had negative results, the ministry said in a statement" As the report went further "….it's hard to establish how this crew was infected, considering that for 35 days, they had no contact with dry land and that supplies were only brought in from the port of Ushuaia," said Alejandra Alfaro, the director of primary health care in Tierra del Fuego. "The head of the infectious diseases department at Ushuaia Regional Hospital, Leandro Ballatore, said he believed this is a "case that escapes all description in publications, because an incubation period this long has not been described anywhere."

"We cannot yet explain how the symptoms appeared,"said Ballatore. Sceptical comments suggesting possible alternative explanations have been offered at the AFP online site reporting the story. Of course, there may be ways of escaping this uncomfortable conclusion but the odds are beginning to stack up against this. One might for instance assert that a Pandora's box containing the virus was opened in mid-ocean and that a surviving virus population suddenly emerged to simultaneously infect 57 individuals.

In summary we note that all "ships-at-sea"data and observations (Supplementary File B) are consistent with the airborne arrival of coronavirus-laden dust contaminating the ships and inhabitants directly or by the undoubted sea spray of already heavily contaminated ocean surface waters from earlier in-falls prior to the ship's crossing that particular patch of ocean.

Summary: Haplotype Switching as a Cosmic Viral Adaptation Strategy

In summary the COVID-19 genetic haplotype patterns are consistent with an "adaptive genetic" strategy of a new virus from space trying to fit into, and replicate within, the genetic-background and thus biochemistry of the host cells, for example, the cells in the respiratory tracts of human beings. We expect similar processes to be occurring in those species of animals that have been successfully infected by coronaviruses.

The deaminase-driven riboswitch haplotype mechanism thus allows the virus to find the best RNA haplotype for optimum replication in that host cell [3]. This is governed by a small set of approximately 2-9 coordinated changes in RNA sequence–the weighted average is 4-5 coordinated differences from the Hu-1 reference sequence per haplotype sequence. In other words, all the haplotypes are ≥ 99.98% identical in sequence to the Wuhan reference sequence (Hu-1).

In our view this is one example of a universal cosmic genetic strategy for single stranded RNA viruses seeking to find a congenial cellular niche after landing, and within which to grow and replicate. Thus, the COVID-19 genome may give the semblance of "rapidly mutating"- but that is not the case, it is actually switching haplotypes. It may also appear to have an "ethnic or genetic" preference, but only in so far as successfully replicating the haplotype it settles on. Thus, APOBEC and ADAR C-to-U /G-to-A and A-to-I(G)/U-to-C deaminase-mutagenesis generates the coordinated changes and the cell then "selects" that sequence from among the variant quasi-species to replicate in that host cell. It is a "selection" mechanism from the variant set of quasi-species of RNA genomes that appears shortly after successful initial infection. This is a general biological strategy – for example the immune system uses a similar strategy to select the best-fitting

antibodies. Thus, with COVID-19 haplotype riboswitching we are witnessing a universal biological adaptation strategy, one that we think has evolved and operates on a truly cosmic scale.

The challenge for mankind is to now systematically introduce near-Earth early warning surveillance (and mitigation) for incoming cosmic in-falls of micro-organisms and viruses from the cometary dust and meteorite streams that our planet routinely encounters as it orbits the Sun.

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Note in Proof

The role of air pollution in facilitating the global spread and severity of the COVID-19 epidemic has been reported in Coccia, M (2020) Factors determining the diffusion of COVID-19 and suggested strategy to prevent future accelerated viral infectivity similar to COVID. Science of the Total Environment 729 (2020) 138474. Further, due to the rapid developments of the pandemic many key references are either online or will remain online at time of submission. All references with active URL internet links are listed in Supplementary File E."

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