SARS-Cov2 enables anaerobic bacteria (Prevotella, et al) to colonize the lungs disrupting homeostasis, causing long-drawn chronic symptoms, and acute severe symptoms (ARDS, septic shock, clots, arterial stroke) which finds resonance, with key differences, in the 'forgotten disease' Lemierre Syndrome, enabled by Epstein Barr Virus

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Abstract

Metagenomic studies of Covid19 patient sequencing data from different countries (China, Brazil, Peru, Cambodia, USA) shows a pattern that SARS-Cov2 enables anaerobic bacteria (eg *Prevotella, Veillonella, Capnocytophaga, Fusobacterium, Oribacterium and Bacteroides*) colonize the lungs, disrupting the homeostasis found in healthy patients. Long drawn symptoms in Covid19 have caused great consternation, and could be explained by persistence of biofilms. Some of these bacteria are implicated in increasing IL-6, cause ground glass opacity in lungs and are associated with cardiac injury - all symptoms associated with Covid19. Many studies also show several bacterial infection markers - like D-dimer, LDH, C-reactive protein and ferritin - being significantly high, while the viral immune response is attenuated (reported by three studies till date). This is also confirmed here in the lung sample from a 74 year old deceased patient, showing high levels of IFITM3, ferritin and S100 calcium binding protein. Anaerobic bacteria causing initial symptoms like persistent fever, chills, pain and later symptoms like ARDS, blood clots, arterial stroke and septic shock finds resonance in a "forgotten disease" - Lemierre syndrome (LS). While, LS is enabled by Epstein Barr Virus - possibly by 'a transient depression of T cell immunity', two recent studies show that IFN-λ might promote bacterial superinfection in Covid19. Also, 16S rRNA bacterial genes and endotoxins (LPS) were discovered in 18/19 severely ill pneumonia patients in one study, suggesting dissemination of endotoxins, and not actual bacteria, might suffice to cause severity. Autopsies also show foci of acute bronchopneumonia. There are key differences with LS - for example origin of LS is the jugular vein while Covid19 starts in the lungs (and this difference should result in Covid19 to be easier to treat). Co-infection of EBV and SARS-Cov2 leads to greater symptoms (fever, higher CRP) in a study of 67 patients. SARS-2003 showed a lot of similar symptoms, which did not get enough media attention. There was a specific warning issued in 2004 for 'an increased vigilance against stroke and other thrombotic complications among critically-ill SARS patients in future outbreaks'. Enhanced pathogen testing kits, which include RT-PCT for bacterial genes and endotoxin tests, could confirm this disruption in Covid19, and thus anaerobic-specific antibiotics could significantly help in therapy.

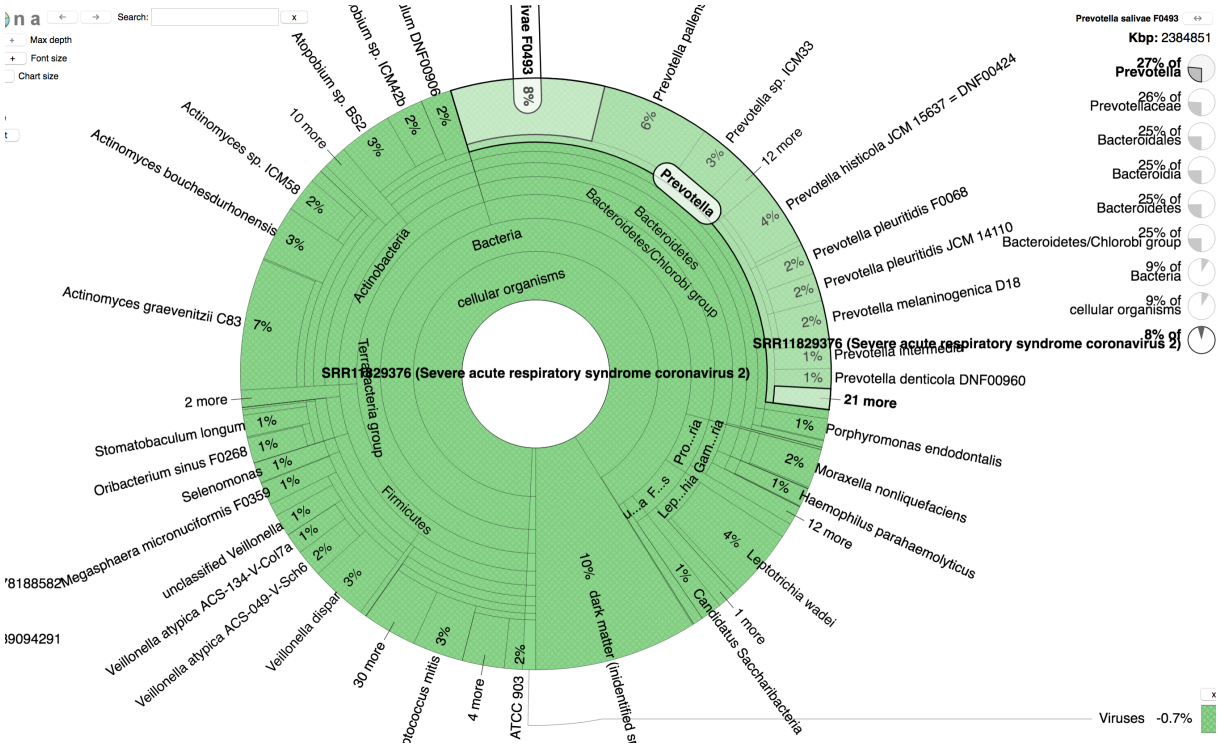

Figure 1: **Krona figure generated from the NCBI analysis of a nasopharyngeal sample from Altanta, Georgia**: The Prevotella abundance is visible (light green). Atopobium (5%) of the reads is around 11 o'clock.

Introduction

Triggered by a novel strain of a coronavirus SARS-Cov2 [1] first detected in Wuhan City, the Covid19 pandemic [2] has spread globally like a wildfire [3].

As the death toll mounts, scientists and doctors have struggled to understand the underlying mechanism of the disease. Several clinical studies have defined a pattern observed in most patients - hypoxia (lack of oxygen), high D-dimers, high LDH, low lymphocyte counts, etc [4]. Also, several studies have reported high Procalcitonin, C-reactive protein and ferritin - markers for bacterial infections [5, 6]. The success of trials using antibiotics (albeit supplemented with other therapies) indicates chances of a more prevalent bacterial role in severe cases [7]. This would not be a first - both the 1918 Spanish Flu [8] and 2003 SARS outbreak [9] had secondary infections as the primary causes of mortality.

Here, using sequencing data submitted in NCBI, I have analyzed the metagenomic composition of Covid19 patients from across the globe (the disease state remains unknown to me). Several of these have no published study on them yet. A pattern that emerges from this data is the prevalence of anaerobic bacteria, which seems to have been enabled by SARS-Cov2 to overcome homeostasis with aerobic counterparts. Some of these anaerobic bacteria are opportunistic pathogens - capable of producing the same symptoms observed in Covid19. Finally, I analyze the sequencing data from the lung sample of a 74 year deceased man, and demonstrate that markers for bacterial infections are high.

Results

Study1: China first study to publish the SARS-Cov2 genome, 29,903 nt GenBank accession number MN908947

The RNA-seq data from Wuhan, China (PRJNA603194 [10]) has significant number of reads of *Prevotella*. SI Tables in the original paper show the abundance of the bacteria (although there is no mention of this in the main paper [10]), so this is not shown here.

However, the expression of bacterial proteins are analyzed. The expression levels (Table 2) shows that the elongation factor Tu is the most expressed. Although, 'elongation factor Tu (Tuf) is a new virulence factor of Streptococcus pneumoniae that binds human complement factors, aids in immune evasion and host tissue invasion' [11], controls are needed to ascertain whether this is over-expressed here (or generally high). Leaving aside immune suppression, the abundance of Prevotella could result in a cytokine storm, since its LPS is known to 'epithelial cells to produce IL-8, IL-6 and CCL20, which can promote mucosal Th17 immune responses and neutrophil recruitment' [12].

Study2: Nanopore sequencing data from a familial cluster in Shenzhen

In this study, the patients were tested for four bacterial species - *Bordetella pertussis, Bordetella parapertussis, Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*, which gave negative results. The sequencing data (Accid:SRR10948474, Nanopore, Table 3) shows a wide range of bacterial species - *Lautropia, Cutibacterium, Haemophilus* being most abundant. The presence of Campylobacter could explain diarrhea seen in the patient [13, 14]. Also, their tests should have detected Mycoplasma - this demonstrates the sensitivity of NGS.

Study3: 2 patients in Wuhan, failure to identify pathogenic bacteria using Metaphlan2

One of the earliest studies publishing sequencing data (Illumina) from two SARS-Cov patients in Wuhan [15] wrote *'bacterial pathogen identification was carried out by using the Metaphlan2 program, which revealed Capnocytophaga sp and Veillonella sp in sample 2 and none in sample 1, and both bacteria identified were not known for their pathogenicity. Collectively, coronavirus is likely to be the main microbial pathogen'* [15]. This is clearly incorrect - Capnocytophaga and Veillonella are there, and so are many other pathogenic species (Table 4).

Study4: Very little viral load in five early patients from Wuhan

The metagenome from the BALF of five Covid19 patients from Wuhan (Accid:PRJNA605983, Table 5) shows very little viral load (in the tens/million reads). This is a very plausible reason for false negatives, as there is just not enough virus to detect. Thus, it is important to have a bigger set of RT-PCR primers to cover more of the genome.

While there are a wide range of bacteria, Pseudomonas has definitely colonized patient1, while patient5 seems to have have the least bacterial load. Here, a closely related species Alloprevotella is also abundant in one patient [16].

Study5: Patients from Peru and Cambodia - clear disruption of homeostasis:

Here, two more studies from Peru and Cambodia (Table 6) provide further corroboration to the anaerobic bacteria theory. These anaerobic bacteria have virtually colonized the metagenome - pushing other aerobic species out of the niche, disrupting the homeostasis. Around 30% and 23% of the reads from Peru and

Cambodia are bacterial, respectively. This is not observed in other patients, even when having chronic issues [17].

Study6: Brazil, very low counts, do not add upto a single genome

The metagenome from the nasopharyngeal swab of a suspected case of local transmission of Covid-19, in Brazil (Accid:PRJNA613951,reads=115933) was analyzed.

There are just 152 reads (out of 115933 reads) matching to SARS-Cov2 [18], which adds up a total of 21190 bp, much lesser than the 30000bp SARS-Cov2 genome. This is a very plausible cause for false negatives, there is just not enough virus to detect.

For eg, if the RT-PCR test was looking for a genomic fragment in the spike protein (3879bp) from 369–1174, it would not find a match. Thus, it is important to use multiple primers spread across the genome, something which the CDC test does not do.

There are a wide range of bacteria - *Lautropia*, *Prevotella*, *Haemophilus* dominating (Table 7).

Study7: Metagenome from a Covid19 patient in Bangladesh shows Lawsonella clevelandensis - hard to culture anaerobic bacteria that causes abscesses

While, bacterial load is low (and this might be due to removal of reads), it corroborates the anaerobic domination with a novel anaerobic bacteria - Lawsonella clevelandensis - being implicated (Accid:PRJNA633241, Table 8).

Lawsonella clevelandensis is a Gram-positive, partially acid-fast, anaerobic 'difficult to identify by conventional methods, leading to inappropriate treatments' [19]. The case reported is the 3-week evolution of a breast nodule in 29-year-old woman. Cultures obtained from surgical drainage of the abscess went through a prolonged incubation period of 10 days, after which colonies were observed, and Lawsonella clevelandensis was confirmed by molecular methods. The therapy was changed to amoxicillin-clavulanic acid, and the abscess was successfully resolved without recurrence. Also, recently liver abscess was reported in a patient with rheumatoid arthritis [20]. Once again, cultures failed to grow the bacteria, and 16S rRNA PCR gene sequencing analysis confirmed Lawsonella clevelandensis. Treatment was changed to amoxicillin/clavulanic acid, and abscesses went away completely in 4 weeks. Another case of a 2-year-old girl (infected spinal dermoid cyst) caused by Lawsonella clevelandensis (surgical drainage followed by prolonged course of antibiotics), which again faced culturing issues [21].

Thus, inspite of low bacterial load, metagenome of a Covid19 patient from Bangladesh (most likely a child, since it was done in Child Health Research Foundation) shows the potential of anaerobic colonization, which I hypothesize is the cause of disease severity in Covid19.

Study8: Metagenome from Atlanta, Georgia (US)

The metagenome from a Covid19 patient in Emory University School of Medicine, Georgia is analyzed (Table 9, Fig 1). Prevotella/Streptococcus and other anaerobes colonize the nasopharyngeal metagenome (Accid:SRR11829376). Another sample (Accid:SRR11827437) shows Enterococcus colonization, and although the source of the sample is mentioned as nasopharyngeal swab, most of the bacteria are gut related (Table 9). Just as the Bangladesh metagenome had a new hard-to-culture anaerobe implicated in disease (Lawsonella), here Atopobium [22, 23] is another anaerobe with significant abundance. Atopobium is implicated in bacterial vaginosis and 'around 80% of the cases and might be involved in therapeutic failure' [24]. BV biofilm formation, and antibiotic resistant A. vaginae could explain therapeutic failures and recurrences of BV [23]. Long drawn symptoms in Covid19 have caused great consternation, and could be similarly explained by persistence of biofilms [25]. Also, the synergy between Atopobium and Gardnerella Vaginalis is a key virulence factor implicated in disease, since G. vaginalis displaces protective lactobacill, and the initial colonization [26] establishes the biofilm structures to which secondary colonizers, such as A. vaginae attach.

Table 1: **Bacterial reads in sequencing data from nasopharyngeal swab (NSPH) or gut** Submitted by Emory University School of Medicine, Georgia. Prevotella/Streptococcus and other anaerobes colonize the metagenome, corroborating the hypothesis that SARS-Cov2 is enabling anaerobes. The bacterial load is quite high, the first five species comprise 70% of the load.

	PerMillion	Bacteria	Type	Diseases
NSPH	218827	Veillonella	obligateanaerobic	rare cases of meningitis, osteomyelitis, and periodontal disease [27]
	202862	Prevotella	obligateanaerobic	aspiration pneumonia, lung abscess, pulmonary empyema, etc [12, 28]
	191362	Streptococcus	FAC-ANE	pneumonia, bacteremia [29]
	66431	Schaalia	FAC-ANE	similar to Actinomyces, alimentary tract diseases [30]
	33327	Atopobium	anaerobic	Bacterial vaginosis [24]
	23896	Leptotrichia	FAC-ANE	Endocarditis [31]
	23534	Moraxella	aerobic	otitis media in infants and children [32]
	15448	Bacteroides	obligateanaerobic	'genus Bacteroides have the most antibiotic resistance mechanisms' [33]
	12172	Actinomyces	FAC-ANE	alimentary tract diseases [30]
	9603	Megasphaera	obligateanaerobic	Bacterial Vaginosis [34, 35]
	8482	Porphyromonas	obligateanaerobic	periodontal disease [36]
	7103	Campylobacter	aerobic	diarrhoea [13]
	6706	Fusobacterium	obligateanaerobic	periodontal, tonsillitis, peritonsillar abscess, etc [37]
	6689	Selenomonas	obligateanaerobic	periodontal disease [38]
	4793	Lachnoanaerobaculum	anaerobic	new genus [39]
Gut	104097	Enterococcus	FAC-ANE	urinary tract infections; intraabdominal [40]
	8612	Escherichia	FAC-ANE	cholecystitis, bacteremia, cholangitis, urinary tract infection [41]
	6383	Corynebacterium	aerobic	diphtheria toxin [42]
	3888	Klebsiella	FACANE	pneumoni [43] and intestinal colonization [44]
	3307	Salmonella	FAC-ANE	typhoid [45]
	2968	Shigella	FAC-ANE	eading cause of diarrhoeal death among children [46]
	1365	Dolosigranulum	FAC-ANE	multiple sclerosis [47]
	787	Staphylococcus	FAC-ANE	Boils, impetigo, food poisoning, cellulitis, and toxic shock syndrome
	593	Carnobacterium	anaerobic	frequently isolated from natural environments and foods [48]
	545	Bacillus	FAC-ANE	Inhalation or respiratory anthrax
	414	Lactobacillus	FACANE	mutualistic beneficial relationship with the human body, [49]
	317	Streptococcus	FAC-ANE	pneumonia, bacteremia [29]
	313	Aerococcus	aerobic	Urinary tract infection [50]
	310	Erwinia	FAC-ANE	dermohypodermitis and bactaeremia [51]
	286	Sphingomonas	aerobic	causative agent of infection in immunocompromised patients [52]

Healthy control samples

Controls using healthy samples from BALF and nasopharyngeal does not show homeostasis disruption (Table 10).

The first study (Accid:PRJNA431097) looks at children respiratory tract metagenome (BALF), while the second study (Accid:PRJNA508588) was on nasopharyngeal from children, young adults and seniors. The anaerobes implicated in Covid19 patients are almost absent here - I have highlighted Prevotella. These healthy studies are using 16S rRNA sequencing, while all Covid19 studies are not (ie they sequence everything). But rRNA is the most predominant RNA - and the correlation should hold quite well.

Another good control are the patients themselves - not all patients have anaerobes disrupting homeostasis, and that is a function of the state of the disease. Also, there will be exceptions when another pathogenic bacteria will colonize. For example, in Table 5, Pseudomonas is dominating in one patient. But, even in those five patients, one can see Prevotella more than in healthy controls - leaving aside patients where anaerobes have completely taken over.

In 2013, suggested a 'common link between microaspiration of Prevotella/Veillonella and inflammation' [53]. In 2015, a study about the analysis of the upper respiratory tract microbiotas in healthy individuals suggested that 'subclinical lung inflammation may create an environment that promotes retention of Prevotella in the lungs' or 'Prevotella may stimulate subclinical lung inflammation' [54].

Highly expressed mRNA in deceased 74 yr old Covid19 lung sample clearly shows bacterial infection

The sequencing data submitted by Mount Sinai (Accid:SRR11517739) shows high expression of several bacterial markers (Table 11). IFITM2- Interferon-induced transmembrane protein have viral roles, but also play a role "in restriction of M. tuberculosis infection" [55]. Another study found 'differences in the representation of the genus Prevotella within the Prevotellaceae family, showing significant increase in abundance' in IFITM3-deficient and knockout mice [56]. Ferritin is also high, it is a well-known marker - "lung pathogens such as H. influenza have developed strategies to acquire iron by using iron-containing human proteins such as tranferrin, lactoferrin, haemoglobin and ferritin" [57]. Also, S100 calcium binding proteins (several figure in the list), along with Procalcitonin (and CRP) which are elevated in many Covid19 patients, are used as marker for bacterial infections [58] A paper was recently published using this (and more data), which reported low Type I and III interferons and elevated chemokines, and thus "reduced innate antiviral defenses". However, they have not reported these bacterial infection markers.

Materials and methods

All sequencing data analyzed here are in NCBI. Several local programs (using C# and Perl) were used. Results were corroborated with 'Metaphlan2' a tool for enhanced metagenomic taxonomic profiling [59], and also the NCBI reported results available online.

Discussion

In the 1918 Spanish flu, where secondary infections was the primary cause of mortality [8], doctors did not have the option of administering antibiotics (discovered in 1928). Secondary infections was also implicated in deaths and hospitalizations in SARS 2003 [9].

In 2020, with a plethora of technical advancements at our disposal, it is unwise to limit ourselves to testing a limited set (18-20) of pathogens in Covid19 patients to rule out secondary infections [6]. Culturing is definitely not a good technique, as was done in Seattle, where mortality was very high [60], since many pathogens are difficult to culture.

While, it not technically or economically feasible to deploy NGS testing on a large set of patients, NGS data will help tremendously in throwing light on the mechanisms of the disease - specifically, if the disease is the result of synergy between SARS-Cov2 and a hitherto unknown set of opportunistic pathogens.

Here, I present metagenomic studies of Covid19 patient sequencing data from different countries (China, Brazil, Peru, Cambodia, US, etc.). A distinct pattern that emerges from this data is the abundance of anaerobic bacteria (eg *Prevotella, Veillonella, Capnocytophaga, Fusobacterium, Oribacterium and Bacteroides*) in comparison to aerobic bacteria. This indicates that SARS-Cov2 is enabling these anaerobes to colonize the lungs, disrupting the homeostasis found in healthy patients. The technique used to extract the sample is important as 'acellular BAL contained decreased relative abundance of Prevotella' [61].

These bacteria are known to lower lymphocyte counts [62], increase IL-6 in plasma [12, 63, 64], cause ground glass opacity in lungs [65], and associated with cardiac injury [66] - all symptoms associated with Covid19. Many studies also show several bacterial infection markers - like D-dimers, C-reactive protein and ferritin - being significantly high (somehow, Procalcitonin is not high, suggesting the calcium signalling is not effected). Although while discussing factors associated with hospitalization and critical illness in 4103 patients with COVID19 disease in New York City, it was noted "many patients with elevated Procalcitonin and critical illness were treated with antibiotics", they were unsure 'whether these patients actually had bacterial disease' [5]. Similarly, acute kidney injury in patients hospitalized with COVID-19 in Wuhan had 'higher levels of white blood cells, D-dimer, aspartate aminotransferase, total bilirubin, creatine kinase, lactate dehydrogenase, procalcitonin, C-reactive protein, a higher prevalence of hyperkalemia, lower lymphocyte counts, and higher chest computed tomographic scores' [67].

As mentioned, bacterial infection markers (CRP, D-dimer, LDH, ferritin) are all usually high, while viral immune response is attenuated. This is also confirmed here in the lung sample from a 74 year old deceased patient, showing high levels of IFITM3, ferritin and S100 calcium binding protein. The study which submitted the above data reported that the immune response to viral infection is attenuated - 'low levels of Type I and III interferons juxtaposed to elevated chemokines and high expression of IL- 6' [68]. Another study using ultra-high-throughput proteomics found CD14 and LBP (lipopolysaccharide binding protein) which recognizes bacterial LPS to be upregulated, but ascribed it to immune response dysregulation, rather than bacterial infection [69]. Another paper analyzed blood parameters patients with severe COVID-1 and concluded that the parameters resemble a bacterial rather than viral infection [70]. A third paper reported the same when compared to Influenza - 'profound suppression in type I and type II interferon signaling in COVID-19 patients across multiple clusters' [71]. Finally, doctors from a Bangkok hospital found that "bacterial DNA and toxins were discovered in virtual all severely ill COVID-19 pneumonia patients" (N=19) [72]. The endotoxin (EAA) test used above is specific for the lipid portion of endotoxin (LPS). In 19 patients, EAA was high in 8 (¿0.6) and intermediate (0.4 - 0.6) in 11. And, 18/19 patients were +ve for 16S rRNA gene amplification - although only 1 blood culture was +ve.

In the Spanish flu, many patients developed a 'post influenza pneumonia a few days after the onset of the influenza symptoms', which occurred without 'any new alarming symptoms and a prolonged duration of elevated temperature was commonly the first indication of a secondary infection' [8]. This "secondary worsening around 10 days after disease onset despite a decreasing viral load" is also being noticed in Covid19 [73]. The inability to find any viral load in severely sick patients also indicate a secondary reason for the disease [74]. Also, the analysis of 92 deceased patients in Wuhan revealed septic shock (7.6%) to be the second most common reason for mortality after ARDS (79.3%) [75]. Furthermore, among 54 non-survivors out of 191 patients, 27 (50%) had secondary infections, and 38% died of septic shock [4].

Blood (and urine) do not usually yield virus in Covid19. For example "none of 27 urine samples and none of 31 serum samples were tested positive for SARS-CoV2 RNA" [76], virus was not detected in 10 urine samples [77], only 4 urine samples were positive for viral nucleic acid out of 58 cases [78]. Finally, deep sequencing of 3 samples did not yield any virus [79]. Thus, the theory that the virus attacks hemoglobin chain does not appear to be true [80].

While the trigger of such an event is still elusive, once this happens, many features of the disease could be explained by the fact that these bacteria express hemoglobin degrading proteins [81], heme-binding proteins sequestering heme after hemoglobin degradation [82], 'plundering' iron, and thereby sequestering oxygen [83].

Hypoxia could also result from formate, the by-product of anaerobic respiration, which inhibits mitochondrial cytochrome oxidase, causing hypoxia at the cellular level [84].

Studies often ignore possible pathogens as nontoxigenic. For example, aerobic/anaerobic cultures of the lung tissue grew 'nontoxigenic Escherichia coli, Candida tropicalis, and Proteus mirabilis.' in the autopsy results of a 42-year-old obese man with muscular dystrophy, where nasopharyngeal swabs were positive and the lung parenchymal swabs were negative for SARS-Cov2 [85]. They did not find viral inclusions, while the lungs had foci of acute bronchopneumonia. Finally, there was liver cirrhosis, renal nephrosclerosis and tubular fan-shaped crystals in the kidneys. The cause of death was listed as "complications of hepatic cirrhosis" [85]. However, the facultatively anaerobic Proteus mirabilis is implicated in several of the reasons responsible for the death of the patient. Urease is an important virulence factor for Proteus mirabilis. It hydrolyzes urea, leading to stone formation [86]. Within the stones, 'COM crystals are arranged radially into fan-shaped profiles with distinct concentric laminations' [87] (see autopsy results). Proteus mirabilis has unique kidney pathology, and is an unique species that causes a large number of kidney stone formation, and greater kidney damage in rats than other similar bacteria with urease enzymes [88]. Patients with cirrhosis have a higher proportion of Proteus species compared with control,their presence in the gut are known to contribute to the pathogenesis of hepatic encephalopathy by breaking down urea into ammonia and carbonic acid [89] While, Proteus mirabilis is not associated with pneumonia very often, 13 patients with Proteus mirabilis pneumonia in Japan showed resistance for levofloxacin [90], while extended-spectrum β-Lactamase producing Proteus mirabilis was implicated in pneumonia in Korea [91]. The detection of Proteus mirabilis should have been considered more seriously as a causative agent of mortality since it is implicated in all of the reported maladies, especially in the kidneys.

Should this secondary infection by anaerobes prove to be a common occurrence in Covid19 patients, anaerobe-specific antibiotics, like doxycycline/Metronidazole, should be in the treatment regimen to supplement Azithromycin being used currently [7] since some anaerobic bacteria have resistance for Azithromycin [92].

Another intriguing question being asked is - does the BCG vaccine provide immunity against SARS-Cov2 [93]? There might be another angle to this hypothesis - does Mycobacterium tuberculosis (MTB) really do the same, since BCG is used in MTB endemic countries? A recent study note that 'MTB+ patients were enriched with Anoxybacillus,while MTB- patients were enriched with Prevotella, Alloprevotella, Veillonella, and Gemella' [94]. This observation is reiterated in another study - 'yet in pulmonary tuberculosis, contrary to expectation, Prevotella species are decreased rather than increased' [95], which goes ahead to propose a mechanism to this resistance - MTB exopolyphosphatase. In short, maybe MTB does not allow anaerobic bacteria to break the homeostasis in their favor.

SARS-2003 showed a lot of similar symptoms, which did not get enough media attention. There was a specific warning issued in 2004 for 'an increased vigilance against stroke and other thrombotic complications among critically-ill SARS patients in future outbreaks' [96]. A study including 64 male and 93 female patients showed thrombocytosis in 77 (49%), haemoglobin count in 95 (61%) and lymphopenia in 153 (98%) patients [97]. Similarly, another study noted that several organs were affected by the virus [98]. Finally, fibrinoid necrosis in the walls of small blood vessels in 'lungs, heart, liver, kidneys, adrenal glands, brain, gastrointestinal tract, and muscle tissues' confirmed widespread thrombosis associated with SARS [99].

Finally, anaerobic bacteria causing initial symptoms like persistent fever, chills, pain and later symptoms like ARDS, blood clots and septic shock finds resonance in a "forgotten disease" - Lemierre syndrome (LS) - 'characterized by an acute oropharyngeal infection, suppurative thrombophlebitis of the internal jugular vein, anaerobic sepsis, and metastatic infections' [100]. While, the most common offending pathogen in LS is the anaerobic Fusobacterium necrophorum, Prevotella was implicated in the case of a previously healthy 15-year-old admitted to the ICU because of septic shock, brain, arterial stroke and lung abscesses, and a positive blood culture for Prevotella oris [101]. In another example, a healthy immunocompetent 23-year-old male had symptoms of general malaise, difficulty in breathing, fever, and chest pain, and 'Ultrasound and CT imaging revealed internal jugular vein thrombosis with associated septic emboli reaching the lungs to form bilateral cavitations and consequently pleural effusions' [102]. Another connection to Covd19 reports the arterial stroke [103] and severe narrowing of the left cavernous carotid artery [104]. Lately, it is been reported that Covid19 is more of a vascular problem (DIC - disseminated intravascular coagulation), than

one of the lungs [105–109]. Also, antiphospholipid syndrome (APS), which leads to ARDS, could be another common feature in both these diseases [110]. It is to be noted Covid19 symptoms (mostly) does not emanate from the jugular vein, but from the lungs (though both have an oral angle, making hygiene an important consideration [111]). And the sequencing data also suggests anaerobic colonization in that region.

Just as I have postulated above that SARS-Cov2 enables anaerobes, viral infections by acute Epstein Barr Virus (EBV) can create 'conditions conducive to anaerobic growth, like a peritonsillar abscess, allow growth and penetration of the surrounding tissues by F. necrophorum' [112]. There are several such instances of Lemierre's Syndrome following EBV infection [113, 114]. The interaction between Lemierre's syndrome and EBV 'is complex and can cause diagnostic uncertainty, particularly in early infection ' [115].

EBV infection that precedes and predisposes patients to Lemierre's happens possibly 'by a transient depression of T cell immunity. and 'fusobacterium can cause false positive results in EBV rapid tests and in mycoplasma pneumoniae PCR' [115]. Type III IFN (IFN-λ) are a recent discovery [116], shown to decrease 'neutrophil motility and function in the influenza-infected lung, which increases the bacterial burden during superinfection' [117]. Recent work shows that IFN-λ may promote bacterial superinfection in Covid19 [118, 119]. Finally, co-infection with EBV and SARS-Cov2 was associated with fever, increased inflammation and higher CRP (bacterial marker) [120]. On that note, I leave this correlation of Covid19 to Lemierre syndrome.

Competing interests

No competing interests were disclosed.

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Table 2: **Human lung metagenome from a patient in Wuhan (PRJNA603194) showing most expressed proteins from** *Prevotella***.** Ribosomal proteins are not shown. These are raw read counts. Elongation factors proteins seem to be playing a key role in the virulence.

Accid	Description	Counts
WP_009012371.1	elongation factor Tu	6405
SNR97511.1	ATP-dependent Clp protease ATP-binding subunit ClpB	4960
WP_009012398.1	elongation factor G	4716
SNR93756.1	molecular chaperone DnaK	4113
WP_009012372.1	transcription termination/antitermination factor NusG	3038
SNR67224.1	hypothetical protein SAMN06265364_1044	2962
SNS04478.1	phosphoenolpyruvate carboxykinase (ATP)	2815
SNR80995.1	glyceraldehyde 3-phosphate dehydrogenase	2240
SNR91480.1	cysteine synthase A	2145
SNR94701.1	chaperonin GroEL	1984
SNR97358.1	pyruvate-ferredoxin/flavodoxin oxidoreductase	1768
WP_009012245.1	energy transducer TonB	1613
WP_004361631.1	DNA-directed RNA polymerase subunit alpha	1610
SNR93143.1	DNA-directed RNA polymerase subunit beta'	1596
SNR97473.1	Pyruvate phosphate dikinase, PEP/pyruvate binding domain	1533
SNR93835.1	Outer membrane protein OmpA	1488
WP_089365394.1	peroxiredoxin	1483
SNS00213.1	ATP-dependent Clp protease ATP-binding subunit ClpC	1437
SNR60000.1	preprotein translocase subunit SecA	1386
SNR84878.1	hypothetical protein SAMN06265364_11429	1317
WP_089366830.1	translation initiation factor IF-3	1278
SNR68043.1	Biopolymer transport protein ExbD/TolR	1242
SNR68055.1	Biopolymer transport protein ExbD/TolR	1169
WP_009010992.1	elongation factor Ts	1156

Table 3: **Bacterial secondary infections in a familial cluster of pneumonia indicating person-to-person transmission [121]** Many more species, just listed top 30 here.

NReads	Bacteria	Type	Diseases
16594	Lautropia	FAC-ANE	oral cavities of HIV-infected children [122]
14330	Cutibacterium	anaerobic	chronic blepharitis and endophthalmitis,
9618	Escherichia	FAC-ANE	
5558	Haemophilus	FAC-ANE	pneumonia, meningitis and bloodstream infection
4649	Scytonema	cyanobacteria	
3798	Hyphomicrobium	aerobic	
3289	Capnocytophaga	FAC-ANE	usually occur with dog or cat bites
2440	Burkholderia	aerobic	melioidosis [123]
2098	Variovorax	aerobic	
1811	Campylobacter	aerobic	diarrhoea [13]
1781	Pseudomonas	FAC-ANE	
1659	Staphylococcus	FAC-ANE	Boils, impetigo, food poisoning, cellulitis, and toxic shock syndrome
1604	Schaalia	aerobic	
1541	Streptococci	aerobic	pharyngitis, pneumonia, sepsis, endocarditis, etc
1174	Mycoplasma	Lack a cell wall	respiratory Mycoplasma pneumoniae [124]
1047	Phyllobacterium	aerobic	
997	Moraxella	aerobic	otitis media in infants and children [32]
940	Flavobacterium	aerobic	fish pathogens
931	Bacillus	FAC-ANE	Inhalation or respiratory anthrax
659	Neisseria	aerobic	infection and persistence in the upper respiratory tract [125]
493	Prevotella	anaerobic	aspiration pneumonia, lung abscess, pulmonary empyema, etc
463	Fusobacterium	anaerobic	periodontal, tonsillitis, peritonsillar abscess, etc
358	Veillonella	anaerobic	rare cases of meningitis, osteomyelitis, and periodontal disease
328	Cupriavidus	aerobic	Infection in 87 yr Chinese man [126]
325	Corynebacterium	aerobic	diphtheria toxin [42]
318	Sphingomonas	aerobic	
314	Micrococcus	aerobic	anaphylactoid [127]
307	Loriellopsis	cyanobacteria	
297	Calothrix	cyanobacteria	
281	Lysinibacillus		Sepsis [128]
278	Methylobacterium	aerobic	opportunistic pathogens in immunocompromised patients
277	Treponema	?	syphilis, bejel, and yaws

Table 4: **Bacterial species identified in two patients from Wuhan:** The original paper stated that 'bacterial pathogen identification was carried out by using the Metaphlan2 program, which revealed Capnocytophaga sp and Veillonella sp in sample 2 and none in sample 1, and both bacteria identified were not known for their pathogenicity' This is clearly wrong - Capnocytophaga and Lautropia are there, but there are so many other pathogenic species. Also Capnocytophaga, found in the saliva of humans, dogs and cats can be pathogenic [129]. There are many more species, just listed top 10 here.

	Patient1	Patient2
Accid: Total	SRR10903402 676694	SRR10903401 476632
	Bacteria/ Reads per million	Bacteria/ Reads per million
1	Capnocytophaga 1195.6	Prevotella 247
2	Streptococcus 694.4	Lautropia 236
3	Prevotella 578.9	Veillonella 132
4	Lautropia 512.4	Schaalia 20.5
5	Lactobacillus 161.7	Escherichia 17.5
6	Veillonella 157.5	Streptococcus 16.5
7	Mycoplasma 107.1	Campylobacter 14
8	Schaalia 81.9	Megasphaera 4.5
9	Escherichia 49	Acinetobacter 3.5
10	Rothia 37.8	Actinomyces 3.5

Table 5: **Bacterial load is much higher than SARS-Cov2 load in five patients at the early stage of the Wuhan seafood market pneumonia virus outbreak:** PM=per million. Number of reads analyzed: patient1 = 11841722, pat2 = 12882084, pat3 = 12041947, pat4 = 13333138, pat5 = 23201546. Pseudomonas is a definite secondary infection in patient1, while patient5 seems to have the least bacterial load. Patient 4 has the most viral load, otherwise viral load is quite low, just like in the patient from Brazil [130], explaining the high false negatives. As in all previous studies, Prevotella seems to be a common and abundant presence in all patients.

Patient1	PM/total	Patient2	PM/total	Patient3	PM/total	Patient4	PM/total	Patient5	PM/total
Pseudomonas	1529/18047	**Prevotella**	125/1617	Sphingomonas	351/4213	Capnocytophaga	25/333	Neisseria	11/260
Sphingomonas	1166/13766	Pseudomonas	61/790	**Prevotella**	157/1892	Veillonella	18/250	Capnocytophaga	4/113
Clostridium	400/4720	Streptococcus	30/390	Pseudomonas	141/1696	Streptococcus	5/79	Allo**Prevotella**	1/43
Sphingobacterium	326/3851	Clostridium	28/370	Clostridium	47/564	Cardiobacterium	5/72	**Prevotella**	1/38
Lactobacillus	244/2885	**Haemophilus**	18/236	Escherichia	36/440	**Prevotella**	3/51	**Haemophilus**	1/32
Anaerocolumna	217/2564	Lactobacillus	14/181	Sphingobacterium	32/386	Neisseria	3/44	Coxiella	1/26
Delftia	176/2084	Actinobacillus	12/155	Streptococcus	31/376	Schaalia	2/33	Veillonella	0/20
Paenibacillus	170/2006	Anaerocolumna	10/133	Neochlamydia	27/334	Ottowia	1/14	Streptococcus	0/17
Neochlamydia	168/1987	Escherichia	10/129	Lactobacillus	21/262	Coxiella	0/13	Nocardioides	0/16
Methylorubrum	150/1772	Neisseria	9/118	Delftia	19/232	Lautropia	0/11	Campylobacter	0/13
Lysinibacillus	148/1750	Delftia	7/101	Methylorubrum	17/206	Campylobacter	0/10	Fusobacterium	0/12
Pelomonas	123/1461	Paenibacillus	7/99	**Haemophilus**	17/204	Brachymonas	0/8	Paracoccus	0/12
Prevotella	106/1256	Sphingomonas	7/99	Anaerocolumna	16/199	Pseudomonas	0/8	Pseudomonas	0/11
Chryseobacterium	97/1155	Lysinibacillus	6/78	Paenibacillus	12/151	Eikenella	0/7	Cardiobacterium	0/10
SARS-Cov2	78/923	SARS-Cov2	30/396	SARS-Cov2	18/222	SARS-Cov2	362/4821	SARS-Cov2	19/454

Table 6: **Bacterial reads in a patient from Cambodia/Peru**: And among the first 20 such species, all, barring one or two (highlighted in bold), are either obligate-anaerobic or facultatively anaerobic (FAC-ANE). In fact, its the percentage of obligate-anaerobic that's more important, they seem to have colonized the lungs, disrupting the homeostasis with aerobic bacteria [17].

	Reads	Bacteria	Description	Disease
Cambodia	135955	Prevotella	obligateanaerobic	aspiration pneumonia, lung abscess, pulmonary empyema, etc [12, 28]
	134787	Veillonella	obligateanaerobic	rare cases of meningitis, osteomyelitis, and periodontal disease
	103875	Haemophilus	FAC-ANE	pneumonia, meningitis and bloodstream infection [131]
	95675	Neisseria	FAC-ANE	infection and persistence in the upper respiratory tract [125]
	51421	Capnocytophaga	FAC-ANE	usually occur with dog or cat bites
	45859	Streptococcus	FAC-ANE	pneumonia, bacteremia [29]
	34820	Fusobacterium	obligateanaerobic	periodontal, tonsillitis, peritonsillar abscess, etc
	23228	Leptotrichia	FAC-ANE	Endocarditis [31]
	21831	Actinobacillus	FACANE	wooden tongue disease [132]
	19160	Morococcus	**aerobic**	periodontal [133]
	15051	Campylobacter	**aerobic**	diarrhoea [13]
	11195	Parabacteroides	obligateanaerobic	[134]
	10252	Rodentibacter	FACANE	[135]
	9626	Aggregatibacter	FACANE	endocarditis, periodontal infection [136]
	9287	Bacteroides	obligateanaerobic	'genus Bacteroides have the most antibiotic resistance mechanisms' [33]
	8446	Porphyromonas	FAC-ANE	periodontal disease [137]
	6415	Pasteurella	FACANE	respiratory disease [138]
	3717	Gemella	FAC-ANE	Infective Endocarditis [139]
	3700	Kingella	weak FACANE	pneumonia, meningitis, ocular infections, pericarditis and peritonitis [140]
	3564	Bergeriella	FACANE	[141]
Peru	291478	Veillonella	obligateanaerobic	rare cases of meningitis, osteomyelitis, and periodontal disease [142]
	88835	Prevotella	obligateanaerobic	aspiration pneumonia, lung abscess, pulmonary empyema, etc [12]
	62091	Fusobacterium	obligateanaerobic	periodontal, tonsillitis, peritonsillar abscess, etc [143]
	35808	Streptococcus	FAC-ANE	pneumonia, bacteremia [29]
	25789	Oribacterium	obligateanaerobic	periodontal disease [144]
	25636	Porphyromonas	FAC-ANE	periodontal disease [137]
	25436	Selenomonas	obligateanaerobic	periodontal disease [38]
	20951	Leptotrichia	FAC-ANE	Endocarditis [31]
	15906	Megasphaera	obligateanaerobic	Bacterial Vaginosis [34]
	13417	Bacillus	FAC-ANE	Inhalation or respiratory anthrax
	13246	Campylobacter	**aerobic**	diarrhoea [13]
	10786	Haemophilus	FAC-ANE	pneumonia, meningitis and bloodstream infection
	9894	Gemella	FAC-ANE	Infective Endocarditis [139]
	6275	Streptobacillus	FAC-ANE	Rat bite fever [145]
	5697	Granulicatella	FAC-ANE	Bacterascites [146]
	4573	Bacteroides	obligateanaerobic	'genus Bacteroides have the most antibiotic resistance mechanisms' [33]
	4505	Stomatobaculum	obligateanaerobic	[147]
	4351	Centipeda	obligateanaerobic	Periodontitis Lesions [148]
	4297	Dolosigranulum	FAC-ANE	multiple sclerosis [47]
	3820	Solobacterium	obligateanaerobic	Bacteremia [149, 150]

Table 7: **Bacterial reads in a patient from Brazil** While Haemophilus, Lautropia and Prevotella are common to other metagenomes, Cellvibrio and Massilia are two unique species found in the Brazilian patient.

NReads	Bacteria	Type	Diseases
1747	Haemophilus	FAC-ANE	pneumonia, meningitis and bloodstream infection
1634	Lautropia	FAC-ANE	oral cavities of HIV-infected children [122]
1094	Prevotella	anaerobic	aspiration pneumonia, lung abscess, pulmonary empyema, etc
726	Escherichia	FAC-ANE	
714	Schaalia	aerobic	
589	Cellvibrio	aerobic	robust capacity for plant polysaccharide degradation
561	Streptococcus	aerobic	pharyngitis, pneumonia, sepsis, and endocarditis
446	Cutibacterium	anaerobic	chronic blepharitis and endophthalmitis,
434	Massilia	?	Lymphadenopathy [151]
368	Pseudomonas	FAC-ANE	

Table 8: **Bacterial reads in a patient from Bangladesh (PRJNA633241)** While, bacterial load is low (and this might be due to removal of reads), it corroborates the anaerobic domination with a novel anaerobic bacteria - Lawsonella clevelandensis - being implicated. FAC-ANE=facultatively anaerobic (aerobic, but capable of switching to fermentation if oxygen is absent).

NReads	Bacteria	Type	Diseases
57	Staphylococcus	FAC-ANE	Boils, impetigo, food poisoning, cellulitis, and toxic shock syndrome
41	Lawsonella	anaerobic	found in abscesses [152]
27	Corynebacterium	aerobic	diphtheria toxin [42]
15	Cutibacterium	obligateanaerobic	chronic blepharitis and endophthalmitis [153]
14	Pseudomonas	FAC-ANE	
10	Escherichia	FAC-ANE	
6	Haemophilus	FAC-ANE	pneumonia, meningitis and bloodstream infection [131]
5	Lautropia	FAC-ANE	oral cavities of HIV-infected children [122]
5	Nocardioides	aerobic	novel species [154]
3	Finegoldia	anaerobic	endocarditis [155]
3	Sphingomonas	aerobic	
3	Streptococcus	FAC-ANE	pneumonia, bacteremia [29]
3	Veillonella	obligateanaerobic	rare cases of meningitis, osteomyelitis, and periodontal disease [27]
2	Bacillus	FAC-ANE	Inhalation or respiratory anthrax
2	Basilea	aerobic	new genus found in lung of a parakeet in Basel,Switzerland [**?**]
2	Deinococcus	aerobic	the most radiation-resistant bacteria [156]
2	Lachnoanaerobaculum	anaerobic	new genus [39]
2	Methylovorus	aerobic	novel species [157]
2	Niveispirillum	cyanobacteria	nitrogen-fixing bacterium [158]
2	Porphyromonas	obligateanaerobic	periodontal disease [36]
2	Scytonema	cyanobacteria	
1	Prevotella	obligateanaerobic	aspiration pneumonia, lung abscess, pulmonary empyema, etc [12, 28]

Table 9: **Bacterial reads in sequencing data from nasopharyngeal swab (NSPH) or gut** Submitted by Emory University School of Medicine, Georgia. Prevotella/Streptococcus and other anaerobes colonize the metagenome, corroborating the hypothesis that SARS-Cov2 is enabling anaerobes. The bacterial load is quite high, the first five species comprise 70% of the load.

	PerMillion	Bacteria	Type	Diseases
NSPH	218827	Veillonella	obligateanaerobic	rare cases of meningitis, osteomyelitis, and periodontal disease [27]
	202862	Prevotella	obligateanaerobic	aspiration pneumonia, lung abscess, pulmonary empyema, etc [12, 28]
	191362	Streptococcus	FAC-ANE	pneumonia, bacteremia [29]
	66431	Schaalia	FAC-ANE	similar to Actinomyces, alimentary tract diseases [30]
	33327	Atopobium	anaerobic	Bacterial vaginosis [24]
	23896	Leptotrichia	FAC-ANE	Endocarditis [31]
	23534	Moraxella	aerobic	otitis media in infants and children [32]
	15448	Bacteroides	obligateanaerobic	'genus Bacteroides have the most antibiotic resistance mechanisms' [33]
	12172	Actinomyces	FAC-ANE	alimentary tract diseases [30]
	9603	Megasphaera	obligateanaerobic	Bacterial Vaginosis [34, 35]
	8482	Porphyromonas	obligateanaerobic	periodontal disease [36]
	7103	Campylobacter	aerobic	diarrhoea [13]
	6706	Fusobacterium	obligateanaerobic	periodontal, tonsillitis, peritonsillar abscess, etc [37]
	6689	Selenomonas	obligateanaerobic	periodontal disease [38]
	4793	Lachnoanaerobaculum	anaerobic	new genus [39]
Gut	104097	Enterococcus	FAC-ANE	urinary tract infections; intraabdominal [40]
	8612	Escherichia	FAC-ANE	cholecystitis, bacteremia, cholangitis, urinary tract infection [41]
	6383	Corynebacterium	aerobic	diphtheria toxin [42]
	3888	Klebsiella	FACANE	pneumoni [43] and intestinal colonization [44]
	3307	Salmonella	FAC-ANE	typhoid [45]
	2968	Shigella	FAC-ANE	eading cause of diarrhoeal death among children [46]
	1365	Dolosigranulum	FAC-ANE	multiple sclerosis [47]
	787	Staphylococcus	FAC-ANE	Boils, impetigo, food poisoning, cellulitis, and toxic shock syndrome
	593	Carnobacterium	anaerobic	frequently isolated from natural environments and foods [48]
	545	Bacillus	FAC-ANE	Inhalation or respiratory anthrax
	414	Lactobacillus	FACANE	mutualistic beneficial relationship with the human body, [49]
	317	Streptococcus	FAC-ANE	pneumonia, bacteremia [29]
	313	Aerococcus	aerobic	Urinary tract infection [50]
	310	Erwinia	FAC-ANE	dermohypodermitis and bactaeremia [51]
	286	Sphingomonas	aerobic	causative agent of infection in immunocompromised patients [52]

Table 10: **Controls using healthy samples from BALF and nasopharyngeal does not show homeostasis disruption:** Study1:Human respiratory tract metagenome (BALF) submitted by WeHealthGene Co., Ltd , Accid:PRJNA431097. Study2: To test the interaction between the human nasal microbiome shifts and human health, Renji Hosptial, China Accid:PRJNA508588. Study1 was on children. Study2 was on children, young adults and seniors. The anaerobes implicated in Covid19 are almost absent here - I have highlighted Prevotella. There is one technical detail - these healthy studies are using 16S rRNA sequencing, while all Covid19 studies are not (ie they sequence everything). But rRNA is the most predominant RNA - and the correlation should hold quite well.

Study1	1	2	3	4	5	6
	Mycoplasma-41365	Acinetobacter-23776	Mycoplasma-34316	Staphylococcus-49192	Haemophilus-37048	Acinetobacter-2404
	Acinetobacter-16545	Brevundimonas-8581	Haemophilus-5999	Mycoplasma-24481	Streptococcus-19781	Streptococcus-849
	Streptococcus-2872	Paracoccus-5864	Staphylococcus-5886	Streptococcus-963	Bergeriella-6611	Bacillus-470
	Bacillus-930	Bifidobacterium-5025	Streptococcus-4189	Haemophilus-278	Staphylococcus-3904	Haemophilus-409
	Haemophilus-742	Sphingomonas-1861	**Prevotella**-1936	Lactobacillus-210	Mycoplasma-1361	Stenotrophomonas-350
	Chlamydia-712	Bacillus-1774	Lactobacillus-1409	Bacillus-116	Lactobacillus-637	Mycoplasma-168
	Pseudomonas-674	Streptococcus-1086	Schaalia-1384	**Prevotella**-37	Pelomonas-555	Pseudomonas-123
	Staphylococcus-654	Massilia-1054	Bacillus-934	Gemella-34	Neisseria-506	Brevundimonas-119
	Bifidobacterium-426	Pseudomonas-763	Sphingomonas-573	Halomonas-33	Pectobacterium-308	Lactobacillus-90
	Rubrobacter-360	Rubrobacter-609	Pectobacterium-436	Pseudomonas-33	Bacteroides-275	Massilia-68

Study2	Child1	Child2	Young adult1	Young adult2	Senior1	Senior2
	Bacteroides-17230	Bacteroides-22948	Staphylococcus-50233	Staphylococcus-69154	Bacteroides-14501	Bacteroides-16653
	Bifidobacterium-10104	Bifidobacterium-12673	Bacteroides-11224	Corynebacterium-24903	Bifidobacterium-8604	Clostridium-10723
	Clostridium-9924	Clostridium-11092	Bifidobacterium-9080	Bacteroides-7288	Clostridium-7483	Bifidobacterium-9937
	Faecalibacterium-6294	Faecalibacterium-7055	Corynebacterium-9068	Bifidobacterium-4123	Faecalibacterium-6625	Faecalibacterium-8373
	Catenisphaera-4375	Catenisphaera-4777	Anaerococcus-6077	Anaerococcus-3214	Eubacterium-4107	Eubacterium-5585
	Eubacterium-4176	Lactobacillus-4572	Clostridium-5891	Escherichia-2942	Ruminococcus-3433	Ruminococcus-4503
	Staphylococcus-4125	Eubacterium-4489	Faecalibacterium-3739	Pseudomonas-2930	Collinsella-3142	Pectobacterium-3778
	Pectobacterium-3646	Pectobacterium-4453	Pectobacterium-2717	Clostridium-2901	Lactobacillus-2640	Collinsella-3747
	Ruminococcus-3467	Ruminococcus-3976	Eubacterium-2686	Faecalibacterium-2182	Pseudomonas-2479	Lactobacillus-3538
	Lactobacillus-3312	Staphylococcus-3386	Ruminococcus-2233	Eubacterium-1418	Flavonifractor-2456	**Prevotella**-2721

Table 11: **Highly expressed mRNA in deceased 74 yr old Covid19 lung sample clearly shows bacterial infection:** IFITM2- Interferon-induced transmembrane protein have viral roles, but also play a role "in restriction of M. tuberculosis infection" [55]. Another study found 'differences in the representation of the genus Prevotella within the Prevotellaceae family, showing significant increase in abundance' in IFITM3-deficient and knockout mice [56]. Ferritin is also high, it is a well-known marker - "lung pathogens such as H. influenza have developed strategies to acquire iron by using iron-containing human proteins such as tranferrin, lactoferrin, haemoglobin and ferritin" [57]. Also, S100 calcium binding proteins (several figure in the list), along with Procalcitonin (and CRP) which are elevated in many Covid19 patients, are used as marker for bacterial infections [58]

SL	Gene	Nreads	Accid	Description
1.	IFITM2	27374	NM_006435.2	interferon induced transmembrane protein 2
2.	FTH1	26438	NM_002032.3	ferritin heavy chain 1
3.	ACTB	25104	NM_001101.5	actin beta
4.	B2M	20225	XM_005254549.3	beta-2-microglobulin
5.	SRGN	18745	XM_024448066.1	serglycin
6.	CCL4	18665	NM_002984.4	C-C motif chemokine ligand 4
7.	SOD2	18333	NM_000636.4	superoxide dismutase 2
8.	CCL2	14536	NM_002982.4	C-C motif chemokine ligand 2
9.	FCER1G	12364	NM_004106.2	Fc fragment of IgE receptor Ig
10.	SAT1	12328	XM_024452421.1	spermidine/spermine N1-acetyltransferase 1
11.	CCL4L1	12315	NM_207007.3	C-C motif chemokine ligand 4 like 1
12.	IFITM3	11558	NM_021034.3	interferon induced transmembrane protein 3
13.	CCL3L3	10911	NM_001001437.4	C-C motif chemokine ligand 3 like 3
14.	IL1RN	10326	XM_005263661.4	interleukin 1 receptor antagonist
15.	IFI6	9119	XM_024446207.1	interferon alpha inducible protein 6
16.	HLA-A	8583	XM_024452558.1	major histocompatibility complex, class I, A
17.	FTL	8443	XM_024451447.1	ferritin light chain
18.	CD74	8346	XM_017010090.2	CD74 molecule
19.	LOC112268284	7955	XM_024452143.1	basic proline-rich protein-like
20.	SELL	7900	NM_000655.5	selectin L
21.	HLA-B	7428	NM_005514.8	major histocompatibility complex, class I, B
22.	S100A8	7340	NM_002964.5	S100 calcium binding protein A8
23.	TPT1	7008	NM_003295.3	tumor protein, translationally-controlled 1
24.	CXCL8	6434	NM_000584.4	C-X-C motif chemokine ligand 8
25.	CCL4L2	5688	NM_001291475.2	C-C motif chemokine ligand 4 like 2
26.	EEF1A1	5364	NM_001402.6	eukaryotic translation elongation factor 1 alpha 1
27.	BCL2A1	5358	NM_004049.4	BCL2 related protein A1
28.	NAMPT	5167	NM_005746.3	nicotinamide phosphoribosyltransferase
29.	CCL3	5101	NM_002983.3	C-C motif chemokine ligand 3
30.	S100A11	5008	NM_005620.2	S100 calcium binding protein A11
31.	IL1B	4896	XM_017003988.2	interleukin 1 beta
32.	PLEK	4878	NM_002664.3	pleckstrin
33.	HBA2	4652	NM_000517.6	hemoglobin subunit alpha 2
34.	IL2RG	4349	NM_000206.2	interleukin 2 receptor subunit gamma
35.	S100A9	4263	NM_002965.4	S100 calcium binding protein A9
36.	TIMP1	3933	XM_017029766.2	TIMP metallopeptidase inhibitor 1
37.	IFIT3	3918	NM_001549.6	interferon induced protein with tetratricopeptide repeats 3
38.	H3F3B	3896	NM_005324.5	H3 histone family member 3B
39.	ALOX5AP	3837	XM_017020522.2	arachidonate 5-lipoxygenase activating protein
40.	PFN1	3783	XM_017024761.1	profilin 1
41.	IFITM1	3501	NM_003641.4	interferon induced transmembrane protein 1
42.	OAS3	3429	XM_017019363.2	2-5-oligoadenylate synthetase 3
43.	CXCL10	3423	NM_001565.4	C-X-C motif chemokine ligand 10
44.	CCL8	3322	NM_005623.3	C-C motif chemokine ligand 8
45.	MARCKS	3279	NM_023009.7	MARCKS like 1