Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Review

Zoonotic evolution and implications of microbiome in viral transmission and infection

Riya Rajeev, R. Prathiviraj, George Seghal Kiran, Joseph Selvin

1 Department of Microbiology, Pondicherry University, Puducherry 605014, India
2 Department of Food Science and Technology, Pondicherry University, Puducherry 605014, India

ARTICLE INFO

Keywords: Covid-19 Zoonotic evolution Human microbiome Viral infection Zoonotic infection Synthetic virus

ABSTRACT

The outbreak and spread of new strains of coronavirus (SARS-CoV-2) remain a global threat with increasing cases in affected countries. The evolutionary tree of SARS-CoV-2 revealed that Porcine Reproductive and Respiratory Syndrome virus 2, which belongs to the Beta arterivirus genus from the Arteriviridae family is possibly the most ancient ancestral origin of SARS-CoV-2 and other Coronaviridae. This review focuses on phylogenomic distribution and evolutionary lineage of zoonotic viral cross-species transmission of the Coronaviridae family and the implications of bat microbiome in zoonotic viral transmission and infection. The review also casts light on the role of the human microbiome in predicting and controlling viral infections. The significance of microbiome-mediated interventions in the treatment of viral infections is also discussed. Finally, the importance of synthetic viruses in the study of viral evolution and transmission is highlighted.

1. Introduction

In the end of December 2019, the world witnessed its new devastating pandemic outbreak in the form of an acute respiratory illness, caused by a novel coronavirus, SARS-CoV-2, first reported in Wuhan, Hubei Province, in central China (Chan et al., 2020; Chen et al., 2020). In the absence of specific antiviral drugs and vaccines, the conventional treatment strategies seem to be less effective in controlling the virus spread which makes it an international public health emergency with a huge number of individuals being infected each day all over the globe (Sun et al., 2020). Genome sequencing of human SARS-CoV-2 reveals 96.2% match with bat SARS-related coronavirus, BatCoV RaTG13 which indicates that bats might be a natural host (Guo et al., 2020; Zhou et al., 2020). Pangolin-CoV which is 91.02% identical to SARS-CoV-2 is reported to be its next closest relative (Zhang et al., 2020). Despite the knowledge of the process of emergence of the infectious agents, it is not yet possible to predict the outbreak in the earlier stages. But now, it has become necessary for the researcher to intrude even before the pathogen infects the humans, and to develop the precautionary measures (Morse et al., 2012).

Several studies have been conducted to reveal the evolutionary basis of coronavirus (Andersen et al., 2020; Ye et al., 2020), but the exact origin, diversity and transmission of SARS-CoV-2 from animals to humans remain unclear. The host-microbiome-virus co-evolution, that has been taking place since millennia is very crucial since each element of this relationship exerts selective pressures on the others, thus affect the overall evolutionary process (Kuss et al., 2011; Zohdy et al., 2019). Viral zoonotic outbreaks can be predicted to some extent if there is a detailed understanding of the virus population associated with the key reservoir or intermediate host in the upcoming outbreak (Donaldson et al., 2010). Various studies have revealed that the human microbiome can be useful to predict the susceptibility of infectious diseases and therefore the microbiome modulation can aid in lowering the chances of infection (Unger and Bogaert, 2017).

This review focuses on phylogenomic distribution and evolutionary lineage of zoonotic viral cross-species transmission of the Coronaviridae family. Here, we also discuss the importance and involvement of the microbiome of the possible reservoir host in the study of the evolutionary aspects and epidemiology of a pathogen; and how the human microbiome can be useful in predicting and controlling infectious diseases. Finally, the importance of synthetic viruses in the study of viral evolution and transmission is discussed.
2. Zoonotic viral evolution and transmission

Based on various factors such as physiology, life history, ecology, etc., the tendency of various animals to transmit viruses to human beings vary (Mollentze and Streicker, 2020). Zoonotic viral infections emerge due to few factors such as phylogenetic similarity of the reservoir host to humans (Mollentze and Streicker, 2020; Olival et al., 2017), animal taxonomy and range overlap with human populations (Olival et al., 2017). The study of interspecific viral transmission plays key roles in comprehending the viral evolution, disease spread to humans, and the overall global change (Albery et al., 2020). Various shreds of evidence support that CoVs show higher genetic diversity, which makes them highly susceptible to adaptive mutation due to the spike protein which can easily exploit various cellular receptors and therefore helps in host jumps (Forni et al., 2020). The variations in the functional sites of the receptor-binding domain (RBD) present in the spike of SARS-CoV-2 and pangolin SARSr-CoVs is mainly attributed to natural selection apart from recombination (Tang et al., 2020). It is very important to trace the zoonotic origins of human CoVs, as it helps to comprehend the natural history, dynamics and restriction factors of species jumping along with any other possible intermediate, reservoir, or amplifying host so that any future spillovers could be avoided (Ye et al., 2020). So far several mutations and genomic variants have been reported in SARS-CoV-2 (Islam et al., 2020; Prathiviraj et al., 2020), and it is known to have very high infectivity and host specificity, which reflects the chances of increased disease transmission from animals to humans (Allocati et al., 2016; Harapan et al., 2020; Prathiviraj et al., 2020). Here, we provide a keen understanding of the origin and diversity of SARS-CoV-2 and how it has been transmitted from animals to human beings.

The phylogenomic large-scale supertree was constructed by retrieving the complete genome sequence of 53 coronavirus related isolates including the recent isolates of Wuhan-Hu-1 from different hosts from the NCBI (https://www.ncbi.nlm.nih.gov/) (Supplementary Table S1), using the MEGA X (Kumar et al., 2018) and Interactive Tree of Life (iTOL) v4 (Letunic and Bork, 2019). The phylogenomic tree is clustered into four major groups such as Alpha (α), Beta (β), Gamma (γ) and Delta (δ).
and Delta (δ) coronavirus (Fig. 1a; Supplementary Figure S1). The evolutionary tree revealed that Porcine Reproductive and Respiratory Syndrome (PRRS) virus 2, which belongs to the Beta arterivirus genus from the *Arteriviridae* family is possibly the most ancient ancestral origin of SARS-CoV-2 and other *Coronaviridae* (Fig. 1a).

PRRS was initially known as the 'Mystery Swine Disease', in the United States in the late 1980s after which it spread throughout the swine-rearing areas of North America and Europe, and eventually throughout the world (Murtough et al., 2016; Wensvoort et al., 1991). The first PRRS report in China was in 1995; and in May 2006, South China faced another highly pathogenic PRRS virus (HP-PRRSV) outbreak which rapidly spread across the country, infecting above 20 million pigs, which re-emerged again in 2009, in central China (Li et al., 2007, 2011; Tian et al., 2007). PRRSV has been transmitted to humans due to the oral consumption of infected pig's meat (Raymond et al., 2017). This virus has undergone rapid evolution and also gained the ability to overcome the host immune responses. A vaccine like strain was also reported in South China, which could be mostly due to the extensive use of the attenuated modified live PRRS vaccine which is capable of reverting to a virulent strain (Murtough et al., 2010; Karmiyuchuk et al., 2010; Li et al., 2011; Xie et al., 2014). The outbreak of PRRS as a novel swine disease has been attributed to the availability of a huge number of hosts which aided the viral recombination and evolution rapidly (Murtaugh et al., 2010).

It is also evident that Alpha coronavirus can be transmitted through bat, rat, mink, ferret, cat and camel to humans, while Beta coronavirus is transmitted from SARS, MERS, Erinaeus, bovine species, rat, and bat to humans (Fig. 1b). Alpha- and Beta-coronavirus can be transmitted via oral consumption of infected animals or direct transmission (Xu, 2020). Delta- and Gamma-coronavirus share their evolutionary lineage between birds (Wigeon, Night-heron, Moorhen, Bulbul, Munia, Sparrow and Turkey) and Beluga Whale as shown in Fig. 1 C and does not involve human as a host. Hence, there is no possibility of direct transmission of Delta- and Gamma-coronavirus to humans, and this correlates with the previous studies (Forni et al., 2020; Shereen et al., 2020). The wildlife has a huge diversity of viruses that undergoes evolution, hence, the best way to decrease the risk of future outbreaks is to minimize the exposure to animal pathogens to the maximum extent (Zhang and Holmes, 2020). Decreased consumption of raw meat and maintaining a safe distance from wildlife harboring possible pathogens could also aid in lowering the chances of zoonotic infections.

3. Implications of bat microbiome in zoonotic viral transmission and infection

There have been enough studies in the past two decades on the host-microbial interactions which has shed light on the concept of mammalian holobiont, as a consequence of the co-evolution of the eukaryotic host cells and its prokaryotic partners (Thaiss et al., 2016). The virome of few common bat species of North America (*Eptesicus fuscus*, *Perimyotis subflavus* and *Myotis lucifugus*) were analyzed and viral sequences having similarity to novel group 1 coronavirus, insect virus, plant virus and novel bacteriophages were identified, which indicates the possibility of bats being potential carriers of viruses which can infect various other organisms (Donaldson et al., 2010). As it is not feasible to study the microbiome of all the existing mammals, it becomes important to identify a particular clade, which could serve as a docile starting point for analyzing the evolution of microbiome among closely related species with various ecological habitats (Ingala et al., 2018). Since bats are a jackers et al., 2018; Henry et al., 2018; Selvin et al., 2019), and can serve as outstanding models for studying the microbiome evolution. Due to the excellent diversity, immunity, longevity and crucial roles displayed by them in the ecosystem, their microbiome can reveal the involvement and importance of microbes in host evolution and emergence of zoonotic pathogens, which could give us a better understanding of the epidemiology of such novel infections (Olival et al., 2017; Peixoto et al., 2018; Ingala et al., 2018). The majority of the SARS-CoV-2 genome is similar to SARS-Ra-Bat-CoV-RaTG13 present in intermediate horseshoe bat in Yunnan, China, while the receptor-binding domain (RBD) is very similar to the pangolin-SARS-CoV-MP789/Guangdong/2019 present in smuggled pangolins in Guangzhou, China. The pangolin SARS-CoVs could be originated from the bats, as they are known to be the main reservoir of SARS-CoVs. Hence, it could be inferred that the SARS-CoV-2 is most probably a recombinant virus which has its origin from bats (Lau et al., 2020).

Bats can harbor pathogenic microorganisms (Schountz et al., 2017; Banerjee et al., 2020), such as viruses which cause long-term persistent infections (Flowright et al., 2016), because such viruses could easily be adapted to the bat (Schountz et al., 2017), and hence are non-pathogenic to them; whereas such microbes are virulent in humans and other such hosts (Banskar et al., 2016; Halpin et al., 2011; Paweska et al., 2016; Schountz et al., 2017; Schuh et al., 2017; Gorburunova et al., 2020). This could be due to the high interferon-mediated immune response displayed by the bats, which supports the rapid cell-to-cell virus transmission rates within the host. Quickly-transmitting viruses, which have evolved with the bat immune system would display boosted virulence after its emergence into secondary hosts having different type of immune system (Brook et al., 2020).

The interspecies transmissions of such viruses from bats to other animals including human beings occur due to possible contact between the two, which causes the outbreak of serious zoonotic diseases (Allocati et al., 2016). The growing rate of bat-associated contagions is likewise supported by an increasing overlap between bat and human habitats (Chen et al., 2014). The swapping of bat microbiome with human beings and other animals can occur due to their flexible roosting behavior and their existence in close proximity (Sanderson et al., 2006; Ingala et al., 2018), consumption of fruits partially consumed by bats (Yob et al., 2001; Ingala et al., 2018) or coming in contact with bat guano (Field, 2016; Ingala et al., 2018). Hence, further studies on bat microbiome could provide better insights into zoonotic viral transmission and infection, and it could also aid in the prediction of any future outbreaks.

4. The role of human microbiome in viral transmission

The implications of the microbiome in infectious (Hanada et al., 2018) and non-infectious disease (Cryan et al., 2020) has been well documented. The theory of sterile lungs has been shifted to "lung microbiome", the resident microflora of the respiratory system (Dickson et al., 2016), however contagion specific fingerprint of lung microbiome remains to be fully established. The development and establishment of lung microbiome and lung-gut-axis play a critical role in respiratory diseases (Unger and Bogaert, 2017; Enaud et al., 2020). The usefulness of the nose/throat microbiome is being utilized in the prediction of vulnerability to influenza and also modulation of the microbiome can lower the chances of infection (Fanos et al., 2020). Tsang et al. (2019) observed that increased abundance of *Streptococcus* spp. reduced the vulnerability to influenza A(H3N2) and influenza B infection by 48 % and 25 % respectively, whereas a ten times greater abundance of *Prevotella salivae* reduced the vulnerability to influenza virus A(H3N2) by 63 % and increased the vulnerability to influenza B infection by 83 %.

SARS-CoV-2 gain access to the cell via the angiotensin-converting enzyme 2 (ACE-2) receptor (Yan et al., 2020; Zhou et al., 2020). The single-cell RNA sequencing (scRNA-seq) revealed that ACE-2 is present in various organs where they are located on specific cell types such as ileum and esophagus epithelial cells, type II alveolar cells (AT2) in lungs, proximal tubule cells in the kidney, myocardial cells and bladder urothelial cells, which indicates the vulnerability of these organs to COVID-19 infection. Individuals have reported certain clinical
symptoms such as acute cardiac injury and kidney failure along with common symptoms like dyspnea and diarrhea which could be attributed to the invasion of SARS-CoV-2 into the heart and kidney along with lung, upper respiratory tract and ileum (Zou et al., 2020). The microbiome present in the lung tissue of patients who were deceased due to COVID-19 was studied and results reveal that the most predominant bacterial members were of the genera Acinetobacter, Burkholderia, Chryseobacterium, Sphingobium, Brevundimonas and Enterobacteriaceae; and the fungal members included Aspergillus spp., Issatchenkia spp., Candida spp., Alternaria spp., and Cladosporium spp., which are well known opportunistic invasive pathogens in immunocompromised patients. Hence, a combination of bacterial and fungal infections was observed (Fan et al., 2020).

ACE-2 receptors are also present in oral cells, mainly in tongue epithelial cells as per the recent report (Xu et al., 2020), which indicates that SARS-CoV-2 could interact with the oral microbiome, hence causing co-infection between the oral microbiome and SARS-CoV-2 in the lungs of the infected individuals (Bao et al., 2020). Capnocytophaga, Veillonella (Chen et al., 2020) and potential pathogens such as Pseudomonas, Acinetobacter, Escherichia and Streplococcus were present in the Bronchoalveolar lavage fluid (BALF) of COVID-19 patients (Ren et al., 2020).

The SARS-CoV-2 could hinder the nutrient absorption by binding to ACE-2 receptors which leads to gastroenteritis-related symptoms and disturbance of gut homeostasis (Gu et al., 2020). The individuals suffering from respiratory illness also undergo gut dysbiosis which indicates the presence of gut-lung crosstalk (Fanos et al., 2020). The gut-lung axis is bidirectional because the microbial metabolites and endotoxins produced in the gut reach the lungs via blood, also any infection or inflammation in the lungs affects the gut microbiome (Dumas et al., 2018; Dhar and Mohanty, 2020). The action of ACE-2, present on the surface of the lumen of the intestine is known to be influenced by the gut microbial community in COVID-19 (Yan et al., 2020). Hence, it indicates the impact of SARS-CoV-2 infection on the gut microbiome. Also, various studies have revealed the alteration in the gut microbiome during respiratory infections (Dhar and Mohanty, 2020; Groves et al., 2020).

Viral as well as the cytokine storm-driven variations enhance the gut permeability and lead to dysbiosis, which reduces the amounts of short-chain fatty acid (SCFAs) such as butyrate, and carries lipopolysaccharide (LPS) into the circulation (Anderson and Reiter, 2020). The ‘colonization resistance’ strategy used by the host microbiome prevents the colonization of pathogens whereby the beneficial microbes occupy the pathogen’s niche or the mucosal entry points specific to the pathogen and also initiating the innate immune response (Thaisis et al., 2016). And few viruses can take over and manipulate the signaling interactions such as Lipopolysaccharide-Toll-like receptor 4 (LPS-TLR4) signaling between the microbiome and immune system, hence benefiting their own proliferation and spread (Dominguez-Diaz et al., 2019). Enteric viruses like Poliovirus, Norovirus and mouse mammary tumor virus have been found to utilize the microbial components like lipopolysaccharides to evade the host immune response (Kane et al., 2011; Robinson et al., 2014; Berger and Mainou, 2018); and the virion thermostability of reovirus was enhanced due to its interaction with bacterial cells (Berger et al., 2017; Berger and Mainou, 2018). A study revealed that allogeneic reovirus was enhanced due to its interaction with bacterial cells (Berger et al., 2018), along with hypertension and CVD (Hendriksen et al., 2014). Lowered expression of ACE-2 is closely linked with obesity (Namekawa et al., 2017), also reduces the ACE-2 levels significantly (Bundalo et al., 2016). The consumption of higher amounts of processed food increases sodium intake which leads to higher oxidative stress and reduced ACE-2 expression in kidneys (Bernardi et al., 2012), along with hypertension and CVD (Hendriksen et al., 2014). Lowered expression of ACE-2 is closely linked with higher COVID-19 severity (Alghatrif et al., 2020).

Nutritional interventions and the use of probiotics could prove beneficial in boosting the immunity of the host. Modulation and manipulation of microbiome via probiotics, prebiotics and high-fiber diet consumption may lower inflammation and dysbiosis by maintaining a healthy gut microbiome and also boosts the immune response (Toraldo and Conte, 2019). The beneficial activity of probiotics on pro-inflammatory and immune-regulatory cytokines leads to a reduction in the virus load, acute respiratory distress syndrome (ARDS) and also lowers the tissue damage caused by the cytokine storm which occurs in individuals with severe COVID-19 (Baud et al., 2020). Supplementation of combined probiotics, prebiotics, synbiotics and nutrition-enriched plant bioactives modify the bacterial composition and can protect against viral infections of the respiratory tract to some extent (Shinde et al., 2020). Due to various positive aspects of probiotics, such as anti-viral action, gut microbiome rebiosis, anti-inflammatory activity, easy availability, ease of administration, safety, and affordable nature, it could prove helpful in the treatment of COVID-19 (Angurana and Bansal, 2020). Hence, it is proposed that well documented probiotic strains should be considered and used for clinical trials to treat COVID-19 (Giannoni et al., 2020). In the coming days, the use of metabolomics could decipher the furtive dialects between the microbiome and its host (Fanos et al., 2020). Therefore, microbiome-mediated treatment strategies could be implemented to boost immunity, and also further studies in this field could support the present treatment strategies to some extent.

5. Conclusion

The extreme genetic diversity of the microbes enables them to evolve continuously to overcome host immune response and survive in new ecological niches, which leads to novel infectious outbreaks every time. Therefore, it is necessary to carefully analyze the phylogenomics of the microbe to identify the evolutionary and transmission patterns (Mortarito and Vignuzzi, 2018). To understand the evolutionary pattern in...
the laboratory condition, experimental evolution is of great importance, where evolutionary dynamics of the newly emerging mutation is studied in controlled laboratory conditions. For this purpose, synthetic viruses synthesized from non-viral protein cages mimicking the evolutionary steps of primitive viruses could be used. Such artificial viruses can be safely used to identify the evolutionary pattern of each virus in a bottom-up fashion (Terasaka et al., 2018). Such an approach can help to understand the virulence patterns, predict its immediate future, host range and response to antiviral drugs, which can possibly help us to predict future outbreaks (Moratorio and Vignuzzi, 2018). Hence, further investigations using such synthetic viruses are highly recommended to provide a better understanding of evolutionary patterns of viruses.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

Not applicable

Funding

JS is thankful to Science and Engineering Research Board (SERB), New Delhi, India for the project on Human Microbiome. PR thankfully acknowledges the NPDF scheme (Sanction No. PDF/2019/002762). Dated: 23/12/2019), SERB, New Delhi, India.

Conflicts of interest

The authors declare that they have no competing interests

Appendix A. Supplementary data

Supplementary material related to this article can be found in the online version, at doihps://doi.org/10.1016/j.viruses.2020.198175.

References

Alberca, R.W., Oliveira, I.D.M., Branco, A.C.C.C., Pereira, N.Z., Sato, M.N., 2020. Obesity as a risk factor for COVID-19: an overview. Crit. Rev. Food Sci. Nutr. http://doi.org/10.1080/10408398.2019.1705545.
Albery, G.F., Eskew, E.A., Ross, N., Olival, K.J., 2020. Predicting the global mammalian virus reservoir using phylogenetics. Nat. Commun. 11, 2260. http://doi.org/10.1038/s41467-020-16153-4.
Aguirre, D., Cingolani, O., Lakatta, E.G., 2020. The dilemma of coronavirus disease 2019 (COVID-19). Circulation Research 126 (5), 748. https://doi.org/10.1161/CIRCRESAHA.119.316545.
AlGhatrif, M., Cingolani, O., Lakatta, E.G., 2020. The dilemma of coronavirus disease 2019 (COVID-19), SERB, New Delhi, India.

Appendix B. Supplementary data

Not applicable

Availability of data and material

Not applicable

Funding

JS is thankful to Science and Engineering Research Board (SERB), New Delhi, India for the project on Human Microbiome. PR thankfully acknowledges the NPDF scheme (Sanction No. PDF/2019/002762). Dated: 23/12/2019), SERB, New Delhi, India.

Conflicts of interest

The authors declare that they have no competing interests

Appendix A. Supplementary data

Supplementary material related to this article can be found in the online version, at doihps://doi.org/10.1016/j.viruses.2020.198175.

References

Alberca, R.W., Oliveira, I.D.M., Branco, A.C.C.C., Pereira, N.Z., Sato, M.N., 2020. Obesity as a risk factor for COVID-19: an overview. Crit. Rev. Food Sci. Nutr. http://doi.org/10.1080/10408398.2019.1705545.
Albery, G.F., Eskew, E.A., Ross, N., Olival, K.J., 2020. Predicting the global mammalian virus reservoir using phylogenetics. Nat. Commun. 11, 2260. http://doi.org/10.1038/s41467-020-16153-4.
Aguirre, D., Cingolani, O., Lakatta, E.G., 2020. The dilemma of coronavirus disease 2019 (COVID-19). Circulation Research 126 (5), 748. https://doi.org/10.1161/CIRCRESAHA.119.316545.
AlGhatrif, M., Cingolani, O., Lakatta, E.G., 2020. The dilemma of coronavirus disease 2019 (COVID-19). New Delhi, India.

Appendix B. Supplementary data

Not applicable

Availability of data and material

Not applicable

Funding

JS is thankful to Science and Engineering Research Board (SERB), New Delhi, India for the project on Human Microbiome. PR thankfully acknowledges the NPDF scheme (Sanction No. PDF/2019/002762). Dated: 23/12/2019), SERB, New Delhi, India.

Conflicts of interest

The authors declare that they have no competing interests

Appendix A. Supplementary data

Supplementary material related to this article can be found in the online version, at doihps://doi.org/10.1016/j.viruses.2020.198175.

References

Alberca, R.W., Oliveira, I.D.M., Branco, A.C.C.C., Pereira, N.Z., Sato, M.N., 2020. Obesity as a risk factor for COVID-19: an overview. Crit. Rev. Food Sci. Nutr. http://doi.org/10.1080/10408398.2019.1705545.
Albery, G.F., Eskew, E.A., Ross, N., Olival, K.J., 2020. Predicting the global mammalian virus reservoir using phylogenetics. Nat. Commun. 11, 2260. http://doi.org/10.1038/s41467-020-16153-4.
Aguirre, D., Cingolani, O., Lakatta, E.G., 2020. The dilemma of coronavirus disease 2019 (COVID-19). Circulation Research 126 (5), 748. https://doi.org/10.1161/CIRCRESAHA.119.316545.
AlGhatrif, M., Cingolani, O., Lakatta, E.G., 2020. The dilemma of coronavirus disease 2019 (COVID-19). New Delhi, India.
Karniychuk, U.U., Geldhof, M., Vanhee, M., Doorsselaere, J., Van Saveleva, T.A., Letunic, I., Bork, P., 2019. Interactive Tree of Life (iTOL) v4: recent updates and new developments. Nucleic Acids Res. 47 (W1), W256–W259. https://doi.org/10.1093/nar/gkz007.

Lau, S.K.P., Luk, H.K.H., Wong, A.C.P., Li, K.S.M., Zhu, L., He, Z., Fung, J., Chan, T.T.Y., Li, Y., Wang, X., Bo, K., Wang, X., Tang, B., Yang, B., Jiang, W., Jiang, P., 2007. Probiotics and COVID-19: Gut microbiota modulating nutritional approaches to countering the effects of viral respiratory infections including SARS-CoV-2 through promoting metabolic and immune fitness with probiotics and plant bioactives. Microorganisms 8 (6), 921. https://doi.org/10.3390/microorganisms8060921.

Pawecka, J.T., Storm, N., Grobbleara, A.A., Marklottwer, W., Kemp, A., Janes van Vuren, F., 2016. Experimental inoculation of Egyptian fruit bats (Rousettus aegyptiacus) with Ebola virus. Viruses 8 (2), 29. https://doi.org/10.3390/v8020029.

Peixoto, F.P., Braga, P.H.P., Mendes, P., 2018. A synthesis of ecological and evolutionary determinants of bat diversity across spatial scales. BMC Ecol. 18, 1. https://doi.org/10.1186/s40779-018-0017-4.

Paweska, J.T., Storm, N., Grobbleara, A.A., Marklottwer, W., Kemp, A., Janes van Vuren, F., 2016. Experimental inoculation of Egyptian fruit bats (Rousettus aegyptiacus) with Ebola virus. Viruses 8 (2), 29. https://doi.org/10.3390/v8020029.

Murtagh, M.P., Stadejek, T., Abrhan, J.E., Lam, T.T.Y., Leung, F.C., 2010. The ever-expanding diversity of porcine respiratory and reproductive syndrome virus. Virus Res. 154 (1–2), 18–30. https://doi.org/10.1016/j.virusres.2009.12.014.

Murtaugh, M.P., Stadejek, T., Abrhan, J.E., Lam, T.T.Y., Leung, F.C., 2010. The ever-expanding diversity of porcine respiratory and reproductive syndrome virus. Virus Res. 154 (1–2), 18–30. https://doi.org/10.1016/j.virusres.2009.12.014.

Akter, S., Sultana, M., Crandall, K.A., Hossain, M.A., 2020. Genome-wide analysis of PRRSV variants: unparalleled outbreaks of atypical PRRS in China and molecular characterisation of the epidemic PRRSV strains circulating worldwide implicates heterogeneity. Sci. Rep. 10, 18136. https://doi.org/10.1038/s41598-020-75410-3.

Plowright, R.K., Peel, A.J., Streicker, D.G., Gilbert, A.T., McCallum, H., Wood, J., Baker, M.L., Resti, F.L., 2016. Transmission or within-host dynamics driving pulses of zoonotic virus infections in reservoir hosts. PLoS Trop. Dis. 10 (8), e0004796. https://doi.org/10.1371/journal.pntd.0004796.

Prathivari, R., Kiran, G.S., Selvin, J., 2020. Phylogenomic proximity and comparative proteomic analysis of SARS-CoV-2 Gene. Rep. 2001777. https://doi.org/10.1093/scicon/2001777.

Sanderson, K.J., Jaeger, T.A., Bonner, J.F., Jansen, L., 2006. Activity patterns of bats at the Mid-Eastern region of China. Vet. J. 174 (3), 577–584. https://doi.org/10.1016/j.tvjl.2007.07.032.

Prathivari, R., Kiran, G.S., Selvin, J., 2020. Phylogenomic proximity and comparative proteomic analysis of SARS-CoV-2 Gene. Rep. 2001777. https://doi.org/10.1093/scicon/2001777.

Sanderson, K.J., Jaeger, T.A., Bonner, J.F., Jansen, L., 2006. Activity patterns of bats at the Mid-Eastern region of China. Vet. J. 174 (3), 577–584. https://doi.org/10.1016/j.tvjl.2007.07.032.

Prathivari, R., Kiran, G.S., Selvin, J., 2020. Phylogenomic proximity and comparative proteomic analysis of SARS-CoV-2 Gene. Rep. 2001777. https://doi.org/10.1093/scicon/2001777.

Sanderson, K.J., Jaeger, T.A., Bonner, J.F., Jansen, L., 2006. Activity patterns of bats at the Mid-Eastern region of China. Vet. J. 174 (3), 577–584. https://doi.org/10.1016/j.tvjl.2007.07.032.

Prathivari, R., Kiran, G.S., Selvin, J., 2020. Phylogenomic proximity and comparative proteomic analysis of SARS-CoV-2 Gene. Rep. 2001777. https://doi.org/10.1093/scicon/2001777.

Sanderson, K.J., Jaeger, T.A., Bonner, J.F., Jansen, L., 2006. Activity patterns of bats at the Mid-Eastern region of China. Vet. J. 174 (3), 577–584. https://doi.org/10.1016/j.tvjl.2007.07.032.
dissection of the unique hallmark. PLoS One 2 (6), e526. https://doi.org/10.1371/journal.pone.0000526.

Toraldo, D.M., Conte, L., 2019. Influence of the lung microbiota Dysbiosis in chronic obstructive pulmonary disease exacerbations: the controversial use of corticosteroid and antibiotic treatments and the role of Eosinophils as a disease marker. J. Clin. Med. Res. 11 (10), 667–675. https://doi.org/10.14740/jocmr3875.

Tsang, T.K., Lee, K.H., Foxman, B., Balmaseda, A., Gresh, I., Sanchez, N., Ojeda, S., Lopez, R., Yang, Y., Xuan, G., Gordon, A., 2019. Association between the respiratory microbiome and susceptibility to influenza virus infection. Clin. Infect. Dis. 1–9. https://doi.org/10.1093/cid/ciz098.

Unger, S.A., Boggaert, D., 2017. The respiratory microbiome and respiratory infections. J. Infect. 74, S84–S88. https://doi.org/10.1016/S0163-4453(17)30196-2.

Veikkolainen, V., Vesterinen, E.J., Lilley, T.M., Pulliainen, A.T., 2014. Bats as reservoir hosts of human bacterial pathogen, Bartonella mayotimonensis. Emerging Infect. Dis. 20 (6), 960. https://doi.org/10.3201/eid2006.130956.

Wensvoort, G., Terpstra, C., Pol, J.M., Ter Laak, E.A., Blommeaard, M., De Kuyver, E.P., et al., 1991. Mystery swine disease in the Netherlands: the isolation of Lelystad virus. Vet. Q. 13 (3), 121–130. https://doi.org/10.1080/01652176.1991.9694296.

Wolkers-Rooijackers, J., Rebmann, K., Bosch, T., Hazeleger, W.C., 2018. Fecal bacterial communities in insectivorous bats from the Netherlands and their role as a possible vector for foodborne diseases. Acta Chiropt. 20 (2), 475–483. https://doi.org/10.3161/15081109ACC2018.20.2.017.

Xie, J., Cui, T., Cui, J., Chen, Y., Zhang, M., Zhou, P., Deng, S., Su, S., Zhang, G., 2014. Epidemiological and evolutionary characteristics of the PRRSV in Southern China from 2010 to 2013. Microb. Pathog. 75, 7–15. https://doi.org/10.1016/j.micpath.2014.08.001.

Xu, Y., 2020. Unveiling the origin and transmission of 2019-nCoV. Trends Microbiol. 28 (4), 239–240. https://doi.org/10.1016/j.tim.2020.02.001.

Xu, K., Cai, H., Shen, Y., Ni, Q., Chen, Y., Hu, S., Li, J., et al., 2020a. Management of coronavirus disease-19 (COVID-19): the Zhejiang experience. Journal of Zhejiang University (medical science) 49 (2), 147–157. https://doi.org/10.3785/j.issn.1008-9292.2020.02.02.

Ye, Z., Yuan, S., Yuan, K., Fang, S., Chan, C., Jin, D., 2020. Zoonotic origins of human coronaviruses. International Journal of Biological Sciences 16 (10), 1686–1697. https://doi.org/10.7150/ijbs.45472.

Yob, J.M., Field, H., Rashdl, A.M., Morrissey, C., van der Heide, B., Rota, P., et al., 2001. Nipah virus infection in bats (order Chiroptera) in peninsular Malaysia. Emerging Infect. Dis. 7 (3), 439. https://doi.org/10.3201/eid0703.010312.

Zhang, Y.Z., Holmes, E.C., 2020. A genomic perspective on the origin and emergence of SARS-CoV-2. Cell 181 (2), 223–227. https://doi.org/10.1016/j.cell.2020.03.035.

Zhang, T., Wu, Q., Zhang, Z., 2020. Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak. Curr. Biol. https://doi.org/10.1016/j.cub.2020.03.022.

Zhou, P., Yang, X., Wang, X., Hu, B., Zhang, L., Zhang, W., et al., 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579 (7798), 270–273. https://doi.org/10.1038/s41586-020-2012-7.

Zohdy, S., Schwartz, T.S., Oaks, J.R., 2019. The coevolution effect as a driver of spillover. Trends Parasitol. 35 (6), 399–408. https://doi.org/10.1016/j.pt.2019.03.010.

Zou, X., Chen, K., Zou, J., Han, P., Hao, J., Han, Z., 2020. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front. Med. 14 (2), 185–192. https://doi.org/10.3389/fmed.2020.00754.

Zuo, T., Zhang, F., Lui, G.C., Yeoh, Y.K., Li, A.Y., Zhan, H., et al., 2020. Alterations in Gut Microbiota of patients with COVID-19 during time of hospitalization. Gastroenterology 149 (3), 944–955. https://doi.org/10.1053/j.gastro.2020.05.0484 e8.