

Corona Viruses: A Review on SARS, MERS and COVID-19

Nihala Naseefa Chathappady House, Sheeba Palissery and Honey Sebastian

Vimala College (Autonomous), Thrissur, KL, India.

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ABSTRACT: After the outbreak of SARS and MERS, the world is now in the grip of another viral disease named COVID-19 caused by a beta Coronavirus – SARS COV-2 which appears to be the only one with a pandemic potential. The case of COVID-19 was reported in the Hubei province of Wuhan city in Central China at the end of December 2019 and it is suspected that the sea food market played a role in this outbreak which was closed abruptly. Subsequently, a Public Health Emergency of International Concern was declared on 30 January 2020 by the World Health Organization. Both SARS and MERS corona viruses had its reservoir in bats and were transferred to humans from palm civets and camels respectively. This virus can be transmitted through airborne droplets. Natural reservoir and intermediate host of COVID-19 is yet to be identified. This paper reviews the occurrences of viral diseases in the recent times including SARS and MERS. As an addition to this, the paper will contain a detailed examination of the COVID-19 Pandemic.

KEYWORDS: SARS-COV, MERS-COV, COVID-19, Coronavirus

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CORRESPONDING AUTHOR: Nihala Naseefa CH, Vimala College (Autonomous), Thrissur, KL 680009, India. Email: nihalanilu05@gmail.com

Introduction

A virus is a small parasite that cannot undergo self-reproduction and once it infects a susceptible cell, the virus can direct the cell machinery to produce more viruses.¹ The Coronaviridae family comprising the genera Corona Virus and Torovirus has been classified as members of the Order Nidovirales.^{2,3} They mutate and also recombine frequently. Laboratory diagnosis is best accomplished by finding viral RNA through polymerase chain reaction. These are enveloped viruses with club-like spikes projecting from their surface.⁴ Coronaviruses (COVs) commonly bring about mild but occasionally more severe community-acquired acute respiratory infections in humans. They also affect multifarious animals and several have even crossed the barrier, producing outbreaks of severe human respiratory disease. As of 10th March, 2019, 2374 laboratory cases were confirmed. The earliest isolation of this virus was from the Wuhan sea food market in China in the first week of January 2020.⁵

Community acquired Coronavirus infections cause about 15% of common cold. They are typically epidemic in the winter. There are no accepted effective antiviral drugs. Prevention is done through epidemiologic methods and the use of appropriate respiratory precautions in hospital settings. The SARS epidemic and MERS outbreaks were controlled through careful case identification, quarantine and by the use of barrier precautions. WHO advised staying away from public places and avoiding close contact with infected persons and animals in order to prevent the rapid spread of the disease.⁶

Dromedary camels in Saudi Arabia encamp for 3 different HCOV species including the MERS HCOV.⁷ The spread of MERS-COV from dromedary camels, the high case-casualty rates, emphasize the need for preventive and therapeutic measures.⁸

The structure of this virus holds a helical nucleocapsid with 30 kb, plus-sense RNA genome coiled within an envelope that contains the S, M and E glycoproteins. Some coronaviruses have an additional membrane glycoprotein HE in them.

The name Corona viruses (COVs) was derived from the Greek word meaning Crown referring to the crown or corona like appearance of COV viruses when observed under an electron microscope.¹⁰ The Coronaviridae and Arteriviridae are viruses with monopartite plus-stranded RNA genomes that replicate using a nested (nido) set of overlapping sub genomic mRNAs.¹¹

The spikes of coronaviruses, typically described as club-like or petal-shaped, emerge from the virion surface as stalks with bulb-like distal termini. Some of the variation in particle size and shape was likely attributable to stresses exerted by virion purification or distortions introduced by negative staining of samples for electron microscopy. Through sequencing and antigenicity, the pioneer divisions of the animal and human coronaviruses discovered were as follows: group 1, containing HCOV-229E; group 2, enclosing HCOV-OC43; group 3, including the infectious bronchitis virus. The family Coronaviridae, is divided into 4 genera *alpha*-, *beta*-, *gamma*- and *deltacoronavirus* (α -, β -, γ - and δ -COV).¹²

During the winter of 2002 to 2003, there was an outbreak of a new disease, severe acute respiratory syndrome (SARS), where the intermediate hosts, were probably the Palm civet (*Paguma larvata*) and the Raccoon dog (*Nyctereutes procyonoides*).^{13,14}

The last known case of the SARS epidemic occurred in mid-2004. More recently there was an outbreak of a related but different COV, the Middle East respiratory syndrome coronavirus (MERS-COV).¹⁵ A total of 2374 individuals were infected – a majority with acute respiratory symptoms – that were arduous in most and fatal in 823 (as of 10th March,



2019).^{16,17} The dromedary camels are the reservoir of MERS COV, although evidence suggests that bats may be infected with related viruses.¹⁸

Betacoronavirus genus consists of 4 lineages: A, B, C and D.^{19,20} Alpha and Beta coronavirus descend from the bat gene pool.²¹⁻²³ The group 2 coronavirus has a smaller protein called hemagglutinin esterase (HE) which is functionally similar to S protein.²⁴ In humans, COV infections include mild diseases, such as the common cold, to more severe manifestations, like bronchitis and pneumonia with renal involvements.²⁵ The first human coronavirus (HCOV) was isolated from the nasal discharge of patients with common cold.²⁶ Currently, 6 different COV strains are known to infect humans.²⁷

229E and OC43 are the 2 main HCOVs (from lineage Alpha and Beta) that cause 15% to 29% of all common colds.²⁸ SARS-COV caused the outbreak of severe respiratory disease in China during 2002 to 2003²⁹ and MERS-COV is responsible for an ongoing outbreak of severe respiratory disease in the Middle East since 2012.³⁰ The epidemiology and pathogenesis of HCOVs are discussed in the following sections and are summarized in Table 1.

In general, 229E, OC43 and NL63 are distributed globally, transmitted predominantly during the winter season in temperate countries,³¹ while NL63 showed a spring–summer peak of activity.³² Today n-COVs are recognized as one of the most rapidly evolving viruses moving to its higher genome nucleotide substitution rates and recombination.³³ The distribution of n-COVs varies according to its geographical area and season.³⁴ Although the corona virus was identified 60 years ago, they received attention at the time of the SARS outbreak.

Severe Acute Respiratory Syndrome (SARS)

SARS is a viral disease associated with an outbreak of a typical pneumonia in Guangdong Province, China. A newly identified group of coronavirus, the SARS Coronavirus, was the causative agent of this life threatening pneumonia in humans.³⁵⁻³⁹ Typical clinical presentations of SARS are viral pneumonia with rapid respiratory deterioration, fever, chills, myalgia, malaria and non-productive cough being the major presentations showing symptoms, whereas sore throats are less the frequently seen one, with an incubation period of 2 to 7 days.^{40,41} SARS like viruses were isolated from a few Himalayan palm civets (*Paguma larvata*) and the Raccoon dog (*Nyctereutes procyonoides*) at Shenzhen sea food market.^{42,43}

It has been discovered that humans were introduced to this epidemic with the spread of a closely related bat virus among palm civets or other animals that were for sale in the live wild game markets and then to humans. The virus then adopted itself through wild action and recombined until it transmitted readily among humans. RT-PCR method was adopted for the diagnosis of this viral disease.⁴⁴ Ribavirin Drug; Interferon and Lopinavir/ritonavir are the antiviral agents used in the therapy of SARS. Ribavirin is a ribonucleoside analogue that prevents the replication of a large number of RNA and DNA Viruses.^{45,46}

Table 1. CoV-2019 cases reported (as per the information collected on 18-05-2020).

COUNTRY	TOTAL CASES	TOTAL DEATHS
USA	7 637 066	214 615
India	6 626 291	102 746
Brazil	4 915 289	146 375
Russia	1 225 889	21 475
Colombia	855 052	26 712
Peru	828 169	32 742
Spain	810 807	32 086
Argentina	798 486	21 018
Mexico	761 665	79 088
South Africa	681 289	16 976
France	619 190	32 230
UK	502 978	42 350
Iran	471 772	26 957
Chile	470 179	12 979
Iraq	379 141	9 399
Bangladesh	370 132	5 375
Saudi Arabia	336 389	4 875
Italy	325 329	35 986
Philippines	324 762	5 840
Turkey	324 443	8 441
Pakistan	315 260	6 517
Indonesia	307 120	11 253
Germany	301 571	9 602
Israel	268 175	17 19
Ukraine	230 236	4 430
Canada	166 156	9 481
Ecuador	141 034	11 647
Romania	137 491	5 048
Bolivia	136 868	8 101
Netherlands	135 892	6 454
Belgium	130 235	10 064
Poland	102 080	2 659
Oman	101 814	985
UAE	99 733	429
China	85 470	4 634
Australia	27 149	894
S. Korea	24 164	422
Croatia	17 797	300
Srilanka	3 471	13

Even though improvements were seen in some patients, some other reports failed to identify this; there were numerous adverse effects associated with ribavirin or other therapies, particularly the transaminase elevation.⁴⁷ IFN are a multigene family of inducible cytokines, possessing antiviral activity with Interferon β being far more effective against SARS.⁴⁸ Lopinavir and Ribavirin are combined and used for the treatment of human immunodeficiency virus (HIV) and have limited side effects.⁴⁹

Middle East Respiratory Syndrome (MERS)

The first case was identified in a patient with acute pneumonia and renal failure in Jeddah, Kingdom of Saudi Arabia (KSA) in June 2012.⁵⁰⁻⁵³ Sequencing was done at the Erasmus Medical Centre (EMC) in Rotterdam, the Netherlands, where the virus was named 'Human Coronavirus EMC (HCOVEMC)' and further, renamed by the International Committee on Taxonomy of Virus as the Middle East Respiratory Syndrome Coronavirus (MERS COV).⁵⁴⁻⁵⁶ The virus was propagated through African green monkeys and rhesus macaque kidney cells.^{57,58} The incubation period is 2 to 14 days [medium of approximately 5.5 to 6.5 days].^{59,60} Clinical symptoms include fever, cough, sore throat, shortness of breath, myalgia, chest pain, malaise and gastro-intestinal symptoms, such as diarrhea, vomiting and abdominal pain. A large proportion of severely ill patients required mechanical ventilation. Interestingly, many of the reported secondary cases showed mild respiratory symptoms or were even asymptomatic.⁶¹⁻⁶³

Chest radiographs of a large percentage of patients admitted to the hospital showed airspace and interstitial opacities, with subtle to extensive, unilateral to bilateral and focal to diffuse distribution; Moreover, the air space opacities vary in their distribution, as reticular or reticulonodular, and demonstrate thickening of broncho-vascular areas.⁶⁴⁻⁶⁷ Gastrointestinal symptoms such as diarrhea and vomiting are sometimes seen in patients.⁶⁸ The virus acquired by the dromedary camels subsequently spread to other animals in the Middle East region.^{69,70} No effective antiviral drug against MERS has been discovered, which is another factor contributing to the huge death rate.⁷¹

Various IFN regimens in combination with nitro viruses have been intermittently administered to severely ill patients, although typically in an ad hoc manner and in the absence of systematic evolution.⁷²

COVID-19

On 31 December 2019, the WHO China Country Office was informed about a pneumonia of unknown cause in Wuhan City, Hubei Province-China. As of 3 January 2020, a total of 44 patients with pneumonia had been reported to the WHO by the national authorities in China. The cluster was initially reported when the Chinese authorities identified a new coronavirus (COV) as the causative agent of SARS-CoV2 which was named as COVID-19 by the World Health Organization, which is an acronym of 'coronavirus disease 2019'.⁷³

SARS-COV2, designated by The International Committee on Taxonomy of Viruses (ICTV) on 11 February 2020 is the

most recent human pneumonia virus with high outbreak potential. Cases were reported in other cities, leading to a global outbreak.⁷⁴⁻⁷⁶ The first SARS related Corona virus was discovered in the horseshoe bat species (*Rhinolophus sinicus*).⁷⁷ Moreover, they belong to a large family of single-stranded RNA viruses (+ssRNA) that are isolated from different animal species.⁷⁸ There are speculations, about their animal origin.⁷⁹ Available evidence suggests that the outbreak was associated with exposures to the seafood market and hence, concerned markets in Wuhan were closed on first January 2020 for environmental sanitation and disinfection.^{80,81} In March 2020, this outbreak was characterized as a pandemic by the WHO.⁸²⁻⁸⁴ This is the first pandemic known to be caused by a new coronavirus; the third zoonotic human coronavirus (COV) of the century has features typical of the coronavirus family and was placed in the beta coronavirus 2b lineage. COVID-19 was declared as the sixth Public Health Emergency of International Concern by the WHO, following H1N1 (2009), polio (2014), Ebola in West Africa (2014) Zika (2016) and Ebola in the Democratic Republic of Congo (2019). The incubation period is the same to other known human coronaviruses, including SARS and MERS.⁸⁵ 2019 n-COV is the seventh member of the family of corona viruses that are infectious to humans.

The Common symptoms are fever, cough, myalgia sputum production, headache, haemoptysis and diarrhea.⁸⁶ In the early stages, respiratory infections in patients developed to Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure and other serious complications.⁸⁷ This disease might badly affect older patients with comorbidities and ARDS.^{88,89} Based on some studies conducted in Hong Kong, in and around Wuhan as well as Shenzhen has revealed that group O, people had more resistivity towards SARSCOV-2, because of the ABO antibodies. In fact, those with blood group A had much more risk of being affected by this virus.⁹⁰ The vital signs were stable in most cases while leukopenia and lymphopenia were common.⁹¹ Mortality has been found to be remarkably higher in patients with increased TnT (Troponium T) level. The further elevation of IP-10, MCP-3 and IL-1ra, shows the severity and the fatal outcome of this viral disease.^{92,93} Researches to identify the source of 2019 n-COV including possible intermediate animal vectors are going on.^{94,95} On January 10, the genome sequence of 2019 COV was released on Gen bank of Yong Zhen Zhang's group at Fudan University.⁹⁶

Phylogenetic analysis of viral genome uncovered the relatedness of the virus to SARS like coronavirus, genus beta coronavirus, sub genus Sarbeco virus that had previously been found in bats.^{97,98} Moreover, phylogenetic analysis of corona virus of different Species indicated that 2019 n-COV might have originated from bats.^{99,100} The viral sequence shows 79.6% identity to SARS COV and 96% identical at the whole genome level to a bat coronavirus.^{101,102} Moreover, they are closely related to a bat derived corona virus – bat SL COV ZC44, bat SL COV ZX C2.¹⁰³

The virus which causes COVID-19 most probably has its ecological reservoir in bats. Since there is a very limited close

contact between humans and bats, transmission of virus to humans might have occurred through an intermediate animal host like a domestic animal, a wild animal or a domesticated wild animal which has not yet been identified¹⁰⁴. Asymptomatic patients can still infect the other which means that COVID-19 is transmittable even during the incubation period.¹⁰⁵ The nosocomial transmission of COVID-19, facilitated by the mobile phones of health care workers and hospital equipment, cause severe problems and further accelerate the rate of transmission of this already hiking viral disease.¹⁰⁶ The vertical transmission of COVID-19; put pregnant women and fetuses at a higher risk of being infected by the virus. This is primarily due to the high expression of ACE2 receptors in the human maternal interphase. Transmission through organ transplantation and surgical operation; as the Corona viruses home in the respiratory tract and its secretions. These pose a risk to health care providers if the patients require surgery.¹⁰⁷

SARS COV-2, can remain for hours on different surfaces and was more stable and last longer on plastic as well as stainless steel which were comparatively low in copper and cardboard surfaces.¹⁰⁸⁻¹¹¹ The basic reproductive number (R0), has been used as a parameter to calculate the infectivity index. In MERS and SARS epidemic, the value was found be approximately 2, which in turn indicate that each infected person could infect 2 others in an effective contact. But for COVID-19 this index value was slightly higher. The data calculated from Wuhan was 2.2, further studies on this have had received different values (1.95-6.47).¹¹²

Ensuring early diagnosis and appropriate quarantine measures are the key factors to check the rate of transmission of the virus considerably. The current method for the diagnosis of COVID-19 includes detection of the virus by genomic techniques like polymerase chain reaction (PCR) – or deep sequencing which relies on the presence of the viral genomes in sufficient amounts.^{113,114} This method often fails to detect the viral infection, if collection procedure is not optimal or if the patient has low viral load, typically, during the early stage of the disease or if it is suppressed by host immunity. If the sample is obtained at a later stage, a supplementary 18m test can provide a better sensitivity mean of PCR based method alone.

However, new sensitive PCR essays can even further improve the detection method when combined with IgM ELISA arrays. The 2 diagnostic tests for emergency use are the Genesig real time PCR coronavirus, an open system more suitable for laboratories with moderate sample testing capacity¹¹⁵ and the cobas(R) SARS cov-2, core for use in the Cobas (R) 6800/8500 system is a closed system array for larger laboratories.¹¹⁶

Common laboratory findings include lymphopenia and bilateral ground glass opacity. At present there are no vaccines or antiviral treatments for animal coronavirus.¹¹⁷ It is observed that in more than 20% of patients, the viral RNA remained positive in feces even though it turned negative in the respiratory tract. This shows that the viral gastro intestinal infection and potential fecal, oral transmission can last even after the viral clearance in the respiratory tract of the infected person. Hence the rRT-PCR

testing from feces is also an important process to be carried out in the COVID-19 treatment plan.^{118,119}

However various research efforts are under way and number of vaccine candidates are under work which includes inactivated vaccine, adenoviral vector vaccine, recombinant subunits vaccine etc. The S protein, remains as the main factor for the vaccine development. The Cryo-EM structure of SARS COV-2 S Trimer has also accelerated the vaccine development process.¹²⁰

Patients admitted to ICUs had a high concentration of cytokines in plasma which shows that the cytokine storm is associated with the severity of this disease. In a group of patients by the end of the first week, there is a chance for the progression of the disease to pneumonia, respiratory failure and death. This step up is due to the increased inflammatory cytokines (IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A and TNFa). The GM-CSF, IL-6 CD4T cells isolated from such patients were typically high compared to the non-ICU patients. This holds that the inhibition of excessive inflammatory response might act as an adjacent therapy for COVID-19.¹²¹⁻¹²³ In most cases, it takes repeated attempts to accurately spot the presence of viral RNA from the deep oral swab samples, hence analysis of deep airway samples [like sputum, bronchoalveolar lavage, tracheal secretions] or stool, would be more effective in determining the viral presence than the prior one.^{124,125} No therapeutics and pharmaceutical products have yet been shown to be safe and effective.¹²⁶ Lopinavir and Ritonavir are licensed treatment for n-COV, evidence for COVID-19, MERS and SARS has yet to show whether it can improve clinical outcomes or prevent infection. Interferon beta Ia is used to treat multiple sclerosis. Chloroquine and hydroxychloroquine are very closely related and used to treat malaria and rheumatology conditions respectively.¹²⁷ Nucleoside analysis such as ribavirin may be potentially beneficial for the treatment of COVID-19. Ribavirin is approved for treating respiratory syncytial virus (RSV) infection and used extensively during SARS and MERS outbreak.¹²⁸ Ribavirin has been recognized as a promising antiviral drug against RNA virus infections in cultured cells in mice and non-human primates (NHP) models.¹²⁹

The new antiviral drug ribavirin as well as chloroquine at cc50 of 1 mm is found to be effective in preventing replication of this Virus.¹³⁰ Chloroquine and hydroxychloroquine are 2 of the most fascinating drugs developed in the last 60years.¹³¹ Studies have suggested that chloroquine, an immunomodulant drug traditionally used to treat malaria, is effective in reducing viral replications and other infections. COVID-19 pandemic has spread very quickly taking only 30 days to expand from Hubei province to the rest of the mainland; however rapid rate of increase in illness among people and evidence of human to human transmission suggest that 2019 n-COV is more infectious, spreading with a staggering speed.¹³²⁻¹³⁴ Immunomodulators like Baricitinib, eculizumab, interferons; multistem cell therapy, autologous adipose derived mesenchymal stem cell therapy, corticosteroids, teicoplanin, ivermectin, convalescent plasma therapy, were administered on patients with COVID-19.^{135,136}

Teicoplanin is a glycopeptide antibiotic used to treat bacterial infections caused by staphylococcus aureus and streptococcus, which has been adopted to treat COVID-19. Moreover, it is identified that teicoplanin could inhibit the entry of HIV-1-2019-NCov-S pseudoviruses with the IC50 value of 1.66 μm . They even prevent the S protein activation by directly inhibiting the enzymatic activity of cathepsin L. They are often recommended in the early stage of this viral disease.¹³⁷⁻¹³⁹ Ivermectin; belonging to the family avermectin, with a molecular weight of 870 kDa, possess strong antiviral property and has the potential to convert RT-PCR to negative quickly. It can be combined with other molecules and are safe as well as affordable.¹⁴⁰⁻¹⁴⁴ Convalescent plasma treatment; has been proposed as a principle treatment method where the CP, is obtained from a donor who has already recovered by developing a humoral immunity against SARS COV-2.¹⁴⁵ The aptamer, selected by the systemic evolution of ligands by exponential enrichment technology, are the DNA or RNA molecules that are capable of binding to a wide range of molecules with high affinity and specificity.¹⁴⁶ It seems that the aptamer molecules might be effective in treating the corona virus to some extent. They could be an effective anti-corona virus agent in both diagnosis and treatment. Aptamer-based biosensors and drugs can be used to diagnose and treat coronavirus.¹⁴⁷ The SARS COV-2 isolated from the urine and feces of infected person would then enter into the waste water treatment system. Hence analyzing virus especially in waste water would thereby help in tracking out the source of this viral disease through sewage pipe networks and determine the potential carriers in certain areas. Paper based device has emerged as a powerful tool that helps in the rapid diagnosis of pathogen as well as in the determination of infection transmission. This device is used to detect the SARS COV-2 in waste water, which would provide accurate information that can lead to timely treatment and prevent the spread of COVID-19.^{148,149}

Natural products and their derivatives have potential to treat the viral infections. Treatment carried out using Chinese, Indian as well as Iranian herbal medicine solely and in combination with western medicines had a positive impact, though their clinical trials remained to be known.¹⁵⁰ Herbal traditional medicines have been used in china since the very beginning of SARSCOV-2, (Lianhuanqingwen). Some of this have even prevented the infections of a healthy person and thereby has contributed towards the improvement in health status of patients with mild or severe symptoms.¹⁵¹ Some of the herbal agents that might be helpful in treatment of COVID-19 include, *Echinacea purpurea*, Curcumin, Cinchona SP, Xanthorrhizol etc.¹⁵²

Preventive measures have been discussed to reduce the transmission and to tackle this viral disease.¹⁵³⁻¹⁵⁶ Social distancing is imperative to run down the number of cases. Furthermore, individuals' abidance to prescriptions and reduction of social activity should be applied on all social groups for an effective result. Moreover, wearing of mask and eye protection could tackle the disease to some extent.¹⁵⁷⁻¹⁵⁹

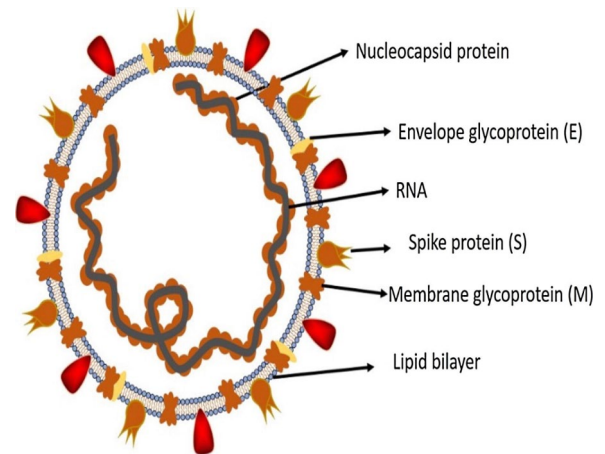


Figure 1.⁹ Structure of respiratory syndrome causing human coronavirus.

Conclusion

The spread of the novel coronavirus is declared as a pandemic by the World Health Organization (WHO). The spread of this disease is possible even during the incubation period from an asymptomatic person and this entirely poses a serious threat which can result in the death of thousands. The investigation to find the natural reservoir, intermediate host and vaccines are in progress. Further, there are many unanswered questions with regard to COVID-19 – like the root cause of outbreak, medium of transmission, effective treatment, prevention method, duration of transmission etc. MERS and SARS coronaviruses have shown that these viruses are able to cross the species barrier. In view of the new virological studies, coronaviruses are pathogens infecting a wide range of mammals that are often in contact with humans, thus providing the basis for future zoonotic outbreaks.

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