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Coronavirus in America Research Literatures

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Abstract: Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus is mainly spread during close contact and via respiratory droplets that are produced when a person talks, coughs, or sneezes. Respiratory droplets may be produced during breathing, however, current research indicates that the virus is not considered airborne. People may also contract COVID-19 by touching a contaminated surface (Fomite) and then inadvertently transfer the pathogen to a mucous membrane (such as the eyes, nose, or mouth). It is most contagious when people are symptomatic, although spread may be possible before symptoms appear. The virus can live on surfaces up to 72 hours. Time from exposure to onset of symptoms is generally between two and fourteen days, with an average of five days. The standard method of diagnosis is by reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab. The infection can also be diagnosed from a combination of symptoms, risk factors and a chest CT scan showing features of pneumonia. This article introduces recent research reports as references in the related studies.
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Key words: COVID-19; America; life; research; literature

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus is mainly spread during close contact and via respiratory droplets that are produced when a person talks, coughs, or sneezes. Respiratory droplets may be produced during breathing, however, current research indicates that the virus is not considered airborne. People may also contract COVID-19 by touching a contaminated surface (Fomite) and then inadvertently transfer the pathogen to a mucous membrane (such as the eyes, nose, or mouth). It is most contagious when people are symptomatic, although spread may be possible before symptoms appear. The virus can live on surfaces up to 72 hours. Time from exposure to onset of symptoms is generally between two and fourteen days, with an average of five days. The standard method of diagnosis is by reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab. The infection can also be diagnosed from a combination of symptoms, risk factors and a chest CT scan showing features of pneumonia. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Abolnik, C. (2015). "Genomic and single nucleotide polymorphism analysis of infectious bronchitis coronavirus." Infect Genet Evol **32**: 416-424.

Infectious bronchitis virus (IBV) is a Gammacoronavirus that causes a highly contagious respiratory disease in chickens. A QX-like strain was analysed by high-throughput Illumina sequencing and genetic variation across the entire viral genome was explored at the sub-consensus level by single nucleotide polymorphism (SNP) analysis. Thirteen open reading frames (ORFs) in the order 5'-UTR-1a-1ab-S-3a-3b-E-M-4b-4c-5a-5b-N-6b-3'UTR were predicted. The relative frequencies of missense: silent SNPs were calculated to obtain a comparative measure of variability in specific genes. The most variable ORFs in descending order were E, 3b, 5'UTR, N, 1a, S, 1ab, M, 4c, 5a, 6b. The E and 3b protein products play key roles in coronavirus virulence, and RNA folding demonstrated that the mutations in the 5'UTR did not alter the predicted secondary structure. The frequency of SNPs in the Spike (S) protein ORF of 0.67% was below the genomic average of 0.76%. Only three SNPS were identified in the S1 subunit, none of which were located in hypervariable region (HVR) 1 or HVR2. The S2 subunit was considerably more variable containing 87% of the polymorphisms detected across the entire S protein. The S2 subunit also contained a previously unreported multi-A

insertion site and a stretch of four consecutive mutated amino acids, which mapped to the stalk region of the spike protein. Template-based protein structure modelling produced the first theoretical model of the IBV spike monomer. Given the lack of diversity observed at the sub-consensus level, the tenet that the HVRs in the S1 subunit are very tolerant of amino acid changes produced by genetic drift is questioned.

Adedeji, A. O. and H. Lazarus (2016). "Biochemical Characterization of Middle East Respiratory Syndrome Coronavirus Helicase." mSphere **1**(5).

Middle East respiratory syndrome coronavirus (MERS-CoV) helicase is a superfamily 1 helicase containing seven conserved motifs. We have cloned, expressed, and purified a Strep-fused recombinant MERS-CoV nonstructural protein 13 (M-nsp13) helicase. Characterization of its biochemical properties showed that it unwound DNA and RNA similarly to severe acute respiratory syndrome CoV nsp13 (S-nsp13) helicase. We showed that M-nsp13 unwound in a 5'-to-3' direction and efficiently unwound the partially duplex RNA substrates with a long loading strand relative to those of the RNA substrates with a short or no loading strand. Moreover, the Km of ATP for M-nsp13 is inversely proportional to the length of the 5' loading strand of the partially duplex RNA substrates. Finally, we also showed that the rate of unwinding (ku) of M-nsp13 is directly proportional to the length of the 5' loading strand of the partially duplex RNA substrate. These results provide insights that enhance our understanding of the biochemical properties of M-nsp13. IMPORTANCE Coronaviruses are known to cause a wide range of diseases in humans and animals. Middle East respiratory syndrome coronavirus (MERS-CoV) is a novel coronavirus discovered in 2012 and is responsible for acute respiratory syndrome in humans in the Middle East, Europe, North Africa, and the United States of America. Helicases are motor proteins that catalyze the processive separation of double-stranded nucleic acids into two single-stranded nucleic acids by utilizing the energy derived from ATP hydrolysis. MERS-CoV helicase is one of the most important viral replication enzymes of this coronavirus. Herein, we report the first bacterial expression, enzyme purification, and biochemical characterization of MERS-CoV helicase. The knowledge obtained from this study might be used to identify an inhibitor of MERS-CoV replication, and the helicase might be used as a therapeutic target.

Aly, M., et al. (2017). "Occurrence of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) across the Gulf Corporation Council countries: Four years update." PLoS One **12**(10): e0183850.

The emergence of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infections has become a global issue of dire concerns. MERS-CoV infections have been identified in many countries all over the world whereas high level occurrences have been documented in the Middle East and Korea. MERS-CoV is mainly spreading across the geographical region of the Middle East, especially in the Arabian Peninsula, while some imported sporadic cases were reported from the Europe, North America, Africa, and lately Asia. The prevalence of MERS-CoV infections across the Gulf Corporation Council (GCC) countries still remains unclear. Therefore, the objective of the current study was to report the prevalence of MERS-CoV in the GCC countries and to also elucidate on its demographics in the Arabian Peninsula. To date, the World Health Organization (WHO) has reported 1,797 laboratory-confirmed cases of MERS-CoV infection since June 2012, involving 687 deaths in 27 different countries worldwide. Within a time span of 4 years from June 2012 to July 2016, we collect samples form MERS-CoV infected individuals from National Guard Hospital, Riyadh, and Ministry of health Saudi Arabia and other GCC countries. Our data comprise a total of 1550 cases (67.1% male and 32.9% female). The age-specific prevalence and distribution of MERS-CoV was as follow: <20 yrs (36 cases: 3.28%), 20-39 yrs (331 cases: 30.15%), 40-59 yrs (314 cases: 28.60%), and the highest-risk elderly group aged >/=60 yrs (417 cases: 37.98%). The case distribution among GCC countries was as follows: Saudi Arabia (1441 cases: 93%), Kuwait (4 cases: 0.3%), Bahrain (1 case: 0.1%), Oman (8 cases: 0.5%), Qatar (16 cases: 1.0%), and United Arab Emirates (80 cases: 5.2%). Thus, MERS-CoV was found to be more prevalent in Saudi Arabia especially in Riyadh, where 756 cases (52.4%) were the worst hit area of the country identified, followed by the western region Makkah where 298 cases (20.6%) were recorded. This prevalence update indicates that the Arabian Peninsula, particularly Saudi Arabia, is the hardest hit region regarding the emerging MERS-CoV infections worldwide. GCC countries including Saudi Arabia now have the infrastructure in place that allows physicians and scientific community to identify and immediately respond to the potential risks posed by new outbreaks of MERS-CoV infections in the region. Given the continuum of emergence and the large magnitude of the disease in our region, more studies will be required to bolster capabilities for timely detection and effective control and prevention of MERS-CoV in our region.

Badawi, A. and S. G. Ryoo (2016). "Prevalence of Diabetes in the 2009 Influenza A (H1N1) and the Middle East Respiratory Syndrome Coronavirus: A Systematic Review and Meta-Analysis." J Public Health Res **5**(3): 733.

Over the past two decades a number of severe acute respiratory infection outbreaks such as the 2009 influenza A (H1N1) and the Middle East respiratory syndrome coronavirus (MERS-CoV) have emerged and presented a considerable global public health threat. Epidemiologic evidence suggests that diabetic subjects are more susceptible to these conditions. However, the prevalence of diabetes in H1N1 and MERS-CoV has not been systematically described. The aim of this study is to conduct a systematic review and meta-analysis of published reports documenting the prevalence of diabetes in H1N1 and MERS-CoV and compare its frequency in the two viral conditions. Meta-analysis for the proportions of subjects with diabetes was carried out in 29 studies for H1N1 (n=92,948) and 9 for MERS-CoV (n=308). Average age of H1N1 patients (36.2+/-6.0 years) was significantly younger than that of subjects with MERS-CoV (54.3+/-7.4 years, P<0.05). Compared to MERS-CoV patients, subjects with H1N1 exhibited 3-fold lower frequency of cardiovascular diseases and 2- and 4-fold higher prevalence of obesity and immunosuppression, respectively. The overall prevalence of diabetes in H1N1 was 14.6% (95% CI: 12.3-17.0%; P<0.001), a 3.6-fold lower than in MERS-CoV (54.4%; 95% CI: 29.4-79.5; P<0.001). The prevalence of diabetes among H1N1 cases from Asia and North America was ~two-fold higher than those from South America and Europe. The prevalence of diabetes in MERS-CoV cases is higher than in H1N1. Regional comparisons suggest that an etiologic role of diabetes in MERS-CoV may exist distinctive from that in H1N1.

Beuttemmuller, E. A., et al. (2017). "Brazilian strain of bovine respiratory coronavirus is derived from dual enteric and respiratory tropism." Genet Mol Res **16**(2).

Bovine coronavirus (BCoV) is a pathogen related to enteric and respiratory diseases in cattle worldwide. Enteric (BECoV) strains of BCoV are predominant in South America, and genetic investigations have been conducted to identify its relationship with isolates of respiratory origin (BRCoV). In this study, we used a BRCoV strain (BR-UEL11) derived from an outbreak of respiratory disease in feedlot cattle in southern Brazil, and compared the partial sequence of the polymorphic region of Spike (which was detected and sequenced by two distinct reverse transcription-polymerase chain reactions) with those of other BCoV strains. The phylogenetic relationship of BR-UEL11 with Brazilian BCoV, which is associated with calf diarrhea and winter dysentery (enteric, BECoV; respiratory, BRCoV), and classical reference prototypes was analyzed. The analysis showed that the BRCoV strains from Brazil clustered with a clade that was distinct from most isolates associated with calf diarrhea (BECoV) and ancestral prototype strains such as Mebus, Nebraska, and LYVB. Furthermore, the BRCoV strains from Brazil clustered with a clade that contained recent strains associated with winter dysentery, showing 98-99% nucleotide identity with those strains. These results suggested that the Brazilian BCoV evolved from being solely enteric to a dual enteric and respiratory tropic virus.

Boldog, P., et al. (2020). "Risk Assessment of Novel Coronavirus COVID-19 Outbreaks Outside China." J Clin Med **9**(2).

We developed a computational tool to assess the risks of novel coronavirus outbreaks outside of China. We estimate the dependence of the risk of a major outbreak in a country from imported cases on key parameters such as: (i) the evolution of the cumulative number of cases in mainland China outside the closed areas; (ii) the connectivity of the destination country with China, including baseline travel frequencies, the effect of travel restrictions, and the efficacy of entry screening at destination; and (iii) the efficacy of control measures in the destination country (expressed by the local reproduction number R loc). We found that in countries with low connectivity to China but with relatively high R loc, the most beneficial control measure to reduce the risk of outbreaks is a further reduction in their importation number either by entry screening or travel restrictions. Countries with high connectivity but low R loc benefit the most from policies that further reduce R loc. Countries in the middle should consider a combination of such policies. Risk assessments were illustrated for selected groups of countries from America, Asia, and Europe. We investigated how their risks depend on those parameters, and how the risk is increasing in time as the number of cases in China is growing.

Bonilla-Aldana, D. K., et al. (2020). "Coronavirus infections reported by ProMED, February 2000-January 2020." Travel Med Infect Dis: 101575.

INTRODUCTION: Sources describing the global burden of emerging diseases accurately are still limited. We reviewed coronavirus infections reported by ProMED and assessed the reliability of the data retrieved compared to published reports. We evaluated the effectiveness of ProMED as a source of epidemiological data on coronavirus. METHODS: Using the keyword "coronavirus" in the ProMED

search engine, we reviewed all the information from the reports and collected data using a structured form, including year, country, gender, occupation, the number of infected individuals, and the number of fatal cases. RESULTS: We identified 109 entries reported between February 29, 2000 and January 22, 2020. A total of 966 cases were reported, with death reported in 188 cases, suggesting an overall case fatality rate (CFR) of 19.5%. Of 70 cases for which the gender was reported, 47 (67.1%) were male. Most of the cases were reported from China, the United Arab Emirates, and Saudi Arabia, with reports from other countries, including imported cases in Europe and North America. CONCLUSIONS: Internet-based reporting systems such as ProMED are useful to gather information and synthesize knowledge on emerging infections. Although certain areas need to be improved, ProMED provided useful information about coronaviruses especially during outbreaks.

Castells, M., et al. (2019). "Bovine coronavirus in Uruguay: genetic diversity, risk factors and transboundary introductions from neighboring countries." Arch Virol **164**(11): 2715-2724.

Bovine coronavirus (BCoV) is a recognized cause of severe neonatal calf diarrhea, with a negative impact on animal welfare, leading to economic losses to the livestock industry. Cattle production is one of the most important economic sectors in Uruguay. The aim of this study was to determine the frequency of BCoV infections and their genetic diversity in Uruguayan calves and to describe the evolutionary history of the virus in South America. The overall detection rate of BCoV in Uruguay was 7.8% (64/824): 7.7% (60/782) in dairy cattle and 9.5% (4/42) in beef cattle. The detection rate of BCoV in samples from deceased and live calves was 10.0% (6/60) and 7.6% (58/763), respectively. Interestingly, there was a lower frequency of BCoV detection in calves born to vaccinated dams (3.3%, 8/240) than in calves born to unvaccinated dams (12.2%, 32/263) (OR: 4.02, 95%CI: 1.81-8.90; p = 0.00026). The frequency of BCoV detection was higher in colder months (11.8%, 44/373) than in warmer months (1.5%, 3/206) (OR: 9.05, 95%CI: 2.77-29.53, p = 0.000013). Uruguayan strains grouped together in two different lineages: one with Argentinean strains and the other with Brazilian strains. Both BCoV lineages were estimated to have entered Uruguay in 2013: one of them from Brazil (95%HPD interval: 2011-2014) and the other from Argentina (95%HPD interval: 2010-2014). The lineages differed by four amino acid changes, and both were divergent from the Mebus reference strain. Surveillance should be maintained to detect possible emerging strains that can clearly diverge at the antigenic level from vaccine strains.

Cavanagh, D., et al. (2001). "Detection of a coronavirus from turkey poults in Europe genetically related to infectious bronchitis virus of chickens." Avian Pathol **30**(4): 355-368.

Intestinal contents of 13-day-old turkey poults in Great Britain were analysed as the birds showed stunting, unevenness and lameness, with 4% mortality. At post mortem examination, the main gross features were fluid caecal and intestinal contents. Histological examination of tissues was largely unremarkable, apart from some sections that showed crypt dilation and flattened epithelia. Negative contrast electron microscopy of caecal contents revealed virus particles, which in size and morphology had the appearance of a coronavirus. RNA was extracted (turkey/UK/412/00) and used in a number of reverse transcription-polymerase chain reactions (RT-PCRs) with the oligonucleotides based on sequences derived from avian infectious bronchitis virus (IBV), a coronavirus of domestic fowl. The RT-PCRs confirmed that turkey/UK/412/00 was a coronavirus and, moreover, showed that it had the same partial gene order (S-E-M-5-N-3' untranslated region) as IBV. This gene order is unlike that of any known mammalian coronavirus, which does not have a gene analogous to the gene 5 of IBV.The gene 5 of the turkey virus had two open reading frames, 5a and 5b, as in IBV and the coronaviruses isolated from turkeys in North America. The turkey/UK/412/00 also resembled IBV, but not mammalian coronaviruses, in having three open reading frames in the gene encoding E protein (gene 3). The percentage differences between the nucleotide sequences of genes 3 and 5 and the 3' untranslated region of turkey/UK/412/00 when compared with those of IBVs were similar to the differences observed when different strains of IBV were compared with each other. No sequences unique to the turkey isolates were identified. These results demonstrate, for the first time, that a coronavirus was associated with disease in turkeys outside of North America and that it is a Group 3 coronavirus, like IBV.

Chen, C. M., et al. (1995). "Cloning and sequencing of a 8.4-kb region from the 3'-end of a Taiwanese virulent isolate of the coronavirus transmissible gastroenteritis virus." Virus Res **38**(1): 83-89.

The nucleotide sequence (8396 nucleotides) was determined, from the 3'-end of the putative polymerase gene to the poly (A) tail, for a Taiwanese virulent isolate, TFI, of transmissible gastroenteritis virus (TGEV). The TFI nucleotide sequence had very high identity to the British virulent field isolate FS772/70 (98.3%), the attenuated Purdue 115 (96.7%) and from the S gene to ORF-4 gene region, to the low passaged

virulent Miller (98.3%) strains of TGEV. Comparison of the TFI S protein sequence with those determined from other TGEV strains and those of the TGEV variant, porcine respiratory coronavirus, isolated from Europe and North America showed that they had changed very little over a period of 4 decades. The two extra amino acids found to be present in the spike proteins of the virulent FS772/70 and Miller strains when compared to the avirulent Purdue strain were found to be present in the TFI strain. The genomic organisation of the TFI strain was the same as that of the other TGEV viruses.

Erles, K. and J. Brownlie (2008). "Canine respiratory coronavirus: an emerging pathogen in the canine infectious respiratory disease complex." Vet Clin North Am Small Anim Pract **38**(4): 815-825, viii.

Infectious respiratory disease in dogs is a constant challenge because of the involvement of several pathogens and environmental factors. Canine respiratory coronavirus (CRCoV) is a new coronavirus of dogs, which is widespread in North America, Japan, and several European countries. CRCoV has been associated with respiratory disease, particularly in kenneled dog populations. The virus is genetically and antigenically distinct from enteric canine coronavirus; therefore, specific tests are required for diagnosis.

Gomaa, M. H., et al. (2008). "Seroprevalence of turkey coronavirus in North American turkeys determined by a newly developed enzyme-linked immunosorbent assay based on recombinant antigen." Clin Vaccine Immunol **15**(12): 1839-1844.

Turkey coronavirus (TCoV) causes diarrhea in young turkey poults, but little is known about its prevalence in the field. To address this, the complete nucleocapsid gene was cloned and expressed in Escherichia coli. Expressed nucleocapsid gene produced two distinct proteins (52 and 43 kDa); their specificity was confirmed by Western blotting using two different monoclonal antibodies. Recombinant N protein was purified and used as an antigen to develop an enzyme-linked immunosorbent assay (ELISA) for the serological detection of TCoV that was then validated using experimentally derived turkey serum. The N-based ELISA showed (97%) sensitivity and (93%) specificity for TCoV, which was significantly higher than an infectious bronchitis coronavirus-based commercial test for TCoV. To assess the utility of this recombinant ELISA, 360 serum samples from turkey farms in Ontario, Canada, and 81 serum samples from farms in Arkansas were tested for TCoV-specific antibodies. A high seroprevalence of TCoV was found in turkeys from the Ontario farms with 73.9% of breeders and 60.0% of meat turkeys testing seropositive using the N-based ELISA. Similarly, a high field prevalence was found in the turkeys from Arkansas, for which 64.2% of the serum samples tested seropositive.

Guy, J. S. (2000). "Turkey coronavirus is more closely related to avian infectious bronchitis virus than to mammalian coronaviruses: a review." Avian Pathol **29**(3): 207-212.

Turkey coronavirus (TCoV) is the cause of an acute highly contagious enteric disease of turkeys. In recent years, TCoV has been increasingly recognized in North America as an important pathogen of young turkeys, resulting in economic loss due to impaired growth and poor feed conversion. While the epidemiology and pathogenesis of TCoV have been extensively studied, TCoV remains one of the least characterized of the known coronaviruses. Avian and mammalian coronaviruses have been subdivided into distinct antigenic/genotypic groups; however, classification of TCoV has been controversial. Previous studies indicated that TCoV was closely related to bovine coronavirus and other group 2 mammalian coronaviruses, but more recent antigenic and genome sequence analyses contradict these findings and, instead, provide evidence that TCoV is closely related to avian infectious bronchitis virus (IBV). Additionally, experimental studies have indicated that the host range of TCoV, once thought to be restricted to turkeys, includes chickens. These studies have raised additional questions regarding the classification of TCoV; particularly, whether IBV and TCoV are taxonomically distinct viruses, or whether TCoV is merely a variant of IBV. Sequence analyses of TCoV have given credence to the idea that TCoV is a variant of IBV, as these studies have shown that TCoV and IBV are very closely related. However, these studies have been limited to only three TCoV strains and relatively small portions of the TCoV genome. TCoV is readily distinguished from IBV based on antigenic and biological differences, and these differences suggest that TCoV should be considered a distinct virus species. Additional studies will be needed to better define the relationship between TCoV and IBV, and to resolve this taxonomic question. Based on our current understanding, it seems prudent to consider TCoV and IBV as distinct virus species that share a close phylogenetic relationship and together comprise group 3 of the coronavirus major antigenic groups.

Haider, N., et al. (2020). "Passengers' destinations from China: low risk of Novel Coronavirus (2019-nCoV) transmission into Africa and South America." Epidemiol Infect **148**: e41.

Novel Coronavirus (2019-nCoV [SARS-COV-2]) was detected in humans during the last week of

December 2019 at Wuhan city in China, and caused 24 554 cases in 27 countries and territories as of 5 February 2020. The objective of this study was to estimate the risk of transmission of 2019-nCoV through human passenger air flight from four major cities of China (Wuhan, Beijing, Shanghai and Guangzhou) to the passengers' destination countries. We extracted the weekly simulated passengers' end destination data for the period of 1-31 January 2020 from FLIRT, an online air travel dataset that uses information from 800 airlines to show the direct flight and passengers' end destination. We estimated a risk index of 2019-nCoV transmission based on the number of travellers to destination countries, weighted by the number of confirmed cases of the departed city reported by the World Health Organization (WHO). We ranked each country based on the risk index in four quantiles (4th quantile being the highest risk and 1st quantile being the lowest risk). During the period, 388 287 passengers were destined for 1297 airports in 168 countries or territories across the world. The risk index of 2019-nCoV among the countries had a very high correlation with the WHO-reported confirmed cases (0.97). According to our risk score classification, of the countries that reported at least one Coronavirus-infected pneumonia (COVID-19) case as of 5 February 2020, 24 countries were in the 4th quantile of the risk index, two in the 3rd quantile, one in the 2nd quantile and none in the 1st quantile. Outside China, countries with a higher risk of 2019-nCoV transmission are Thailand, Cambodia, Malaysia, Canada and the USA, all of which reported at least one case. In pan-Europe, UK, France, Russia, Germany and Italy; in North America, USA and Canada; in Oceania, Australia had high risk, all of them reported at least one case. In Africa and South America, the risk of transmission is very low with Ethiopia, South Africa, Egypt, Mauritius and Brazil showing a similar risk of transmission compared to the risk of any of the countries where at least one case is detected. The risk of transmission on 31 January 2020 was very high in neighbouring Asian countries, followed by Europe (UK, France, Russia and Germany), Oceania (Australia) and North America (USA and Canada). Increased public health response including early case recognition, isolation of identified case, contract tracing and targeted airport screening, public awareness and vigilance of health workers will help mitigate the force of further spread to naive countries.

Hirsch, H. H., et al. (2013). "Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis and treatment of human respiratory syncytial virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus." Clin Infect Dis **56**(2): 258-266.

Community-acquired respiratory virus (CARV) infections have been recognized as a significant cause of morbidity and mortality in patients with leukemia and those undergoing hematopoietic stem cell transplantation (HSCT). Progression to lower respiratory tract infection with clinical and radiological signs of pneumonia and respiratory failure appears to depend on the intrinsic virulence of the specific CARV as well as factors specific to the patient, the underlying disease, and its treatment. To better define the current state of knowledge of CARVs in leukemia and HSCT patients, and to improve CARV diagnosis and management, a working group of the Fourth European Conference on Infections in Leukaemia (ECIL-4) 2011 reviewed the literature on CARVs, graded the available quality of evidence, and made recommendations according to the Infectious Diseases Society of America grading system. Owing to differences in screening, clinical presentation, and therapy for influenza and adenovirus, ECIL-4 recommendations are summarized for CARVs other than influenza and adenovirus.

Ho, K. Y., et al. (2004). "Mild illness associated with severe acute respiratory syndrome coronavirus infection: lessons from a prospective seroepidemiologic study of health-care workers in a teaching hospital in Singapore." J Infect Dis **189**(4): 642-647.

BACKGROUND: Severe acute respiratory syndrome (SARS) is a newly recognized infectious disease that has recently emerged in East Asia and North America. Although the clinical features of acute infection have been well described, mildly symptomatic or asymptomatic infections have not been well characterized. OBJECTIVE: To assess the spectrum of illness in health-care workers (HCWs). METHODS: A prospective seroepidemiologic cohort study was conducted on 372 HCWs in a large teaching hospital in Singapore who were both exposed and not exposed to patients with SARS. Participating HCWs completed a questionnaire and provided paired serum samples, which were analyzed by 2 different laboratories blinded to clinical data, by use of an enzyme-linked immunosorbent assay based on a protocol developed by the Centers for Disease Control and Prevention and a dot-blot immunoassay, with confirmation by a viral neutralization assay. RESULTS: A total of 21 patients with SARS were treated at our hospital. They were associated with transmission to 14 staff members, patients, and visitors in our hospital. Of the 372 HCWs participating in the present study, 8 were found to have positive antibodies to the SARS coronavirus in both samples by use of both test methods, and 6 had pneumonia and had been hospitalized for either probable or suspected SARS

infection, whereas 2 had fever but did not have changes on chest radiographs. All seropositive HCWs had been exposed either directly or indirectly to patients with SARS. No asymptomatic, nonexposed staff members were found to be seropositive. There was a trend towards protection for HCWs who, while fully protected, had had contact with patients with SARS. CONCLUSIONS: Although the majority of cases of SARS are associated with pneumonia, a small number of mildly symptomatic individuals do seroconvert. HCWs who are exposed to patients with SARS can be infected with SARS, regardless of the intensity of exposure. This has implications for surveillance and infection control planning, in the event that SARS returns next winter.

Kin, N., et al. (2016). "Comparative molecular epidemiology of two closely related coronaviruses, bovine coronavirus (BCoV) and human coronavirus OC43 (HCoV-OC43), reveals a different evolutionary pattern." Infect Genet Evol **40**: 186-191.

Bovine coronaviruses (BCoVs) are widespread around the world and cause enteric or respiratory infections among cattle. The current study includes 13 samples from BCoVs collected in Normandy during an 11-year period (from 2003 to 2014), 16 French HCoV-OC43s, and 113 BCoVs or BCoVs-like sequence data derived from partial or complete genome sequences available on GenBank. According to a genotyping method developed previously for HCoV-OC43, BCoVs and BCoVs-like are distributed on three main sub-clusters named C1, C2, and C3. Sub-cluster C1 includes BCoVs and BCoVs-like from America and Asia. Sub-cluster C2 includes BCoVs from Europe. Sub-cluster C3 includes prototype, vaccine, or attenuated BCoV strains. The phylogenetic analyses revealed the monophyletic status of the BCoVs from France reported here for the first time. Moreover, BCoV exhibits a relative genetic stability when compared to HCoV-OC43 we previously described from the same region. The numerous recombination detected between HCoV-OC43 were much less frequent for BCoV. The analysis points thus to the influence of different evolutive constraints in these two close groups.

Lau, S. K., et al. (2013). "Genetic characterization of Betacoronavirus lineage C viruses in bats reveals marked sequence divergence in the spike protein of pipistrellus bat coronavirus HKU5 in Japanese pipistrelle: implications for the origin of the novel Middle East respiratory syndrome coronavirus." J Virol **87**(15): 8638-8650.

While the novel Middle East respiratory syndrome coronavirus (MERS-CoV) is closely related to Tylonycteris bat CoV HKU4 (Ty-BatCoV HKU4) and Pipistrellus bat CoV HKU5 (Pi-BatCoV HKU5) in bats from Hong Kong, and other potential lineage C betacoronaviruses in bats from Africa, Europe, and America, its animal origin remains obscure. To better understand the role of bats in its origin, we examined the molecular epidemiology and evolution of lineage C betacoronaviruses among bats. Ty-BatCoV HKU4 and Pi-BatCoV HKU5 were detected in 29% and 25% of alimentary samples from lesser bamboo bat (Tylonycteris pachypus) and Japanese pipistrelle (Pipistrellus abramus), respectively. Sequencing of their RNA polymerase (RdRp), spike (S), and nucleocapsid (N) genes revealed that MERS-CoV is more closely related to Pi-BatCoV HKU5 in RdRp (92.1% to 92.3% amino acid [aa] identity) but is more closely related to Ty-BatCoV HKU4 in S (66.8% to 67.4% aa identity) and N (71.9% to 72.3% aa identity). Although both viruses were under purifying selection, the S of Pi-BatCoV HKU5 displayed marked sequence polymorphisms and more positively selected sites than that of Ty-BatCoV HKU4, suggesting that Pi-BatCoV HKU5 may generate variants to occupy new ecological niches along with its host in diverse habitats. Molecular clock analysis showed that they diverged from a common ancestor with MERS-CoV at least several centuries ago. Although MERS-CoV may have diverged from potential lineage C betacoronaviruses in European bats more recently, these bat viruses were unlikely to be the direct ancestor of MERS-CoV. Intensive surveillance for lineage C betaCoVs in Pipistrellus and related bats with diverse habitats and other animals in the Middle East may fill the evolutionary gap.

Lescano, J., et al. (2015). "First Case of Systemic Coronavirus Infection in a Domestic Ferret (Mustela putorius furo) in Peru." Transbound Emerg Dis **62**(6): 581-585.

A domestic ferret from Lima, Peru, died after ten days of non-specific clinical signs. Based on pathology, immunohistochemistry and molecular analysis, ferret systemic coronavirus (FRSCV)-associated disease was diagnosed for the first time in South America. This report highlights the potential spread of pathogens by the international pet trade.

Leung, K. M., et al. (2008). "Development of human single-chain antibodies against SARS-associated coronavirus." Intervirology **51**(3): 173-181.

The outbreak of severe acute respiratory syndrome (SARS), caused by a distinct coronavirus, in 2003 greatly threatened public health in China, Southeast Asia as well as North America. Over 1,000 patients died of the SARS virus, representing 10% of infected people. Like other coronaviruses, the SARS virus also utilizes a surface glycoprotein, namely the

spike protein, to infect host cells. The spike protein of SARS virus consists of 1,255 amino acid residues and can be divided into two sub-domains, S1 and S2. The S1 domain mediates the binding of the virus to its receptor angiotensin-converting enzyme 2, which is abundantly distributed on the surface of human lung cells. The S2 domain mediates membrane fusion between the virus and the host cell. Hence two strategies can be used to block the infection of the SARS virus, either by interfering with the binding of the S1 domain to the receptor or by blocking the fusion of the virus with the cell membrane mediated by the S2 domain. Several antibodies against the S1 domain have been generated and all of them are able to neutralize the virus in vitro and in vivo using animal models. Unfortunately, point mutations have been identified in the S1 domain, so that the virus isolated in the future may not be recognized by these antibodies. As no mutation has been found in the S2 domain indicating that this region is more conserved than the S1 domain, it may be a better target for antibody binding. After predicting the immunogenicity of the epitopes of the S2 domain, we chemically synthesized two peptides and also expressed one of them using a recombinant DNA method. We screened a phage displaying library of human single-chain antibodies (ScFv) against the predicted epitopes and obtained a human ScFv which can recognize the SARS virus in vitro.

Lin, M. H., et al. (2018). "Disulfiram can inhibit MERS and SARS coronavirus papain-like proteases via different modes." Antiviral Res **150**: 155-163.

Severe acute respiratory syndrome coronavirus (SARS-CoV) emerged in southern China in late 2002 and caused a global outbreak with a fatality rate around 10% in 2003. Ten years later, a second highly pathogenic human CoV, MERS-CoV, emerged in the Middle East and has spread to other countries in Europe, North Africa, North America and Asia. As of November 2017, MERS-CoV had infected at least 2102 people with a fatality rate of about 35% globally, and hence there is an urgent need to identify antiviral drugs that are active against MERS-CoV. Here we show that a clinically available alcohol-aversive drug, disulfiram, can inhibit the papain-like proteases (PL (pro)s) of MERS-CoV and SARS-CoV. Our findings suggest that disulfiram acts as an allosteric inhibitor of MERS-CoV PL (pro) but as a competitive (or mixed) inhibitor of SARS-CoV PL (pro). The phenomenon of slow-binding inhibition and the irrecoverability of enzyme activity after removing unbound disulfiram indicate covalent inactivation of SARS-CoV PL (pro) by disulfiram, while synergistic inhibition of MERS-CoV PL (pro) by disulfiram and 6-thioguanine or mycophenolic acid implies the potential for combination treatments using these three clinically available drugs.

Nassar, M. S., et al. (2018). "Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: epidemiology, pathogenesis and clinical characteristics." Eur Rev Med Pharmacol Sci **22**(15): 4956-4961.

OBJECTIVE: Middle East Respiratory Syndrome Coronavirus-(MERS-CoV) infection is an evolving worldwide health crisis. The early diagnosis and management of the disease remains a major challenge. This study designed to discuss the epidemiology, pathogenesis and clinical appearances of MERS-CoV infections. MATERIALS AND METHODS: We conducted a broad search of the English-language literature in "PubMed" "Medline" "Web of knowledge", "EMBASE" and "Google Scholar" World Health Organization-WHO" using the key words "Middle East Respiratory Syndrome", "MERS", "MERS-CoV" "Epidemiology" "Transmission" "Pathogenesis" "Clinical Characteristics". We reviewed the literature on epidemiology, pathogenesis and clinical appearances of MERS-CoV infection and the required information was documented. RESULTS: The global prevalence of MERS-CoV infection from June 2012 to April 2018 is 2206 people. The number of cases reported from Saudi Arabia is 1831 (83%) with mortality rate of 787 (35.67%). The main clinical manifestations are fever, chills, generalized myalgia, cough, shortness of breath, nausea, vomiting and diarrhea. The age-allied prevalence of MERS-CoV was highest amongst elderly people with chronic debilitating diseases such as pulmonary diseases, end-stage renal illness, diabetes mellitus and malignancy. CONCLUSIONS: MERS-CoV infection is an emerging global health concern, affected people in 27 countries in the various continents. MERS-CoV infection has been identified mainly in the Middle East, Europe, Africa, Asia and North America. Early detection and management of MERS-CoV infection is of critical importance to minimize the burden of the disease.

Pavli, A., et al. (2014). "Middle East respiratory syndrome coronavirus (MERS-CoV): prevention in travelers." Travel Med Infect Dis **12**(6 Pt A): 602-608.

Middle East respiratory syndrome coronavirus (MERS-CoV), a novel coronavirus that causes a severe lower respiratory tract infection in humans, emerged in the Middle East in 2012. Since then, MERS-CoV has caused an ongoing epidemic in the Arabian Peninsula with sporadic cases imported in Europe, North Africa, Southeast Asia, and the United States of America. As of 28th May 2014, 636 laboratory-confirmed cases of infection with MERS-

CoV have been reported to World Health Organization including 14 cases imported by travelers. The epicenter of the current MERS-CoV epidemic is located in Saudi Arabia, where millions of pilgrims travel for two mass gatherings annually. In this review we summarize MERS-CoV cases in relation to travel with focus on the epidemiology and prevention in travelers. It is important to increase awareness of travelers about the risks and appropriate preventive measures and for health professionals to be on alert if a patient with severe respiratory symptoms reports a recent history of travel to the region affected with MERS-CoV. Measures should be taken by local health authorities of the affected countries in order to improve hospital hygiene. Finally, it is crucial to investigate the reasons for travelers' poor compliance with rules and recommendations issued by Saudi officials and to take appropriate measures in order to improve them.

Pinto, L. D., et al. (2014). "Characterization of pantropic canine coronavirus from Brazil." Vet J **202**(3): 659-662.

Characterization of canine coronavirus (CCoV) strains currently in circulation is essential for understanding viral evolution. The aim of this study was to determine the presence of pantropic CCoV type IIa in tissue samples from five puppies that died in Southern Brazil as a result of severe gastroenteritis. Reverse-transcriptase PCR was used to generate amplicons for sequence analysis. Phylogenetic analysis of the CCoV-IIa strains indicated that they were similar to those found in other countries, suggesting a common ancestor of these Brazilian isolates. This is the first report of pantropic CCoV-II in puppies from Latin America and our findings highlight that CCoV should be included as a differential diagnosis when dogs present with clinical signs and lesions typically seen with canine parvovirus infection.

Priestnall, S. L., et al. (2006). "Serological prevalence of canine respiratory coronavirus." Vet Microbiol **115**(1-3): 43-53.

Canine respiratory coronavirus (CRCoV) has recently been detected in dogs; it is a group 2 coronavirus showing similarity to bovine coronavirus (BCoV) but is distinct from canine enteric coronavirus (CECoV). CRCoV may play an important role in canine infectious respiratory disease (CIRD) either by predisposing to further and potentially more serious viral and bacterial infections or possibly as a primary pathogen. The prevalence of serum antibodies to CRCoV, in a population of dogs in the south east of England, has been shown previously to be 30.1% on the first day of entry to a rehoming kennel [Erles, K., Toomey, C., Brooks, H.W., Brownlie, J., 2003. Detection of a group 2 coronavirus in dogs with canine infectious respiratory disease. Virology 310, 216-223]. The purpose of this study was to establish the prevalence of CRCoV in the general canine population within as well as outside the UK. An ELISA, used to test for the presence of antibodies to CRCoV in canine serum samples, identified seropositive dogs in UK, USA, Canada, Republic of Ireland and Greece. The development of an ELISA based on CRCoV antigen and immunofluorescence assay are described here. 54.7% (547/1000) of North American and 36.0% (297/824) of United Kingdom dogs were seropositive for CRCoV. The age and geographical distribution of seropositive dogs was also assessed. The cross-reactivity demonstrated between CRCoV antibodies from different countries and a UK viral isolate suggests immunological similarity. The overall prevalence of this virus in both North America and the UK suggests that CRCoV has international significance and that further epidemiological studies are required.

Quiroga, M. A., et al. (2008). "Hemagglutinating encephalomyelitis coronavirus infection in pigs, Argentina." Emerg Infect Dis **14**(3): 484-486.

We describe an outbreak of vomiting, wasting, and encephalomyelitis syndrome in piglets in Argentina, caused by porcine hemagglutinating encephalomyelitis coronavirus (PHE-CoV) infection. Diagnosis was made by epidemiologic factors, pathologic features, immunohistochemistry, reverse transcription-PCR, and genomic sequencing. This study documents PHE-CoV infection in South America.

Rabenau, H. F., et al. (2005). "Efficacy of various disinfectants against SARS coronavirus." J Hosp Infect **61**(2): 107-111.

The recent severe acute respiratory syndrome (SARS) epidemic in Asia and Northern America led to broad use of various types of disinfectant in order to control the public spread of the highly contagious virus. However, only limited data were available to demonstrate their efficacy against SARS coronavirus (SARS-CoV). We therefore investigated eight disinfectants for their activity against SARS-CoV according to prEN 14476. Four hand rubs were tested at 30s (Sterillium, based on 45% iso-propanol, 30% n-propanol and 0.2% mecetronium etilsulphate; Sterillium Rub, based on 80% ethanol; Sterillium Gel, based on 85% ethanol; Sterillium Virugard, based on 95% ethanol). Three surface disinfectants were investigated at 0.5% for 30 min and 60 min (Mikrobac forte, based on benzalkonium chloride and laurylamine; Kohrsolin FF, based on benzalkonium chloride,

glutaraldehyde and didecyldimonium chloride; Dismozon pur, based on magnesium monoperphthalate), and one instrument disinfectant was investigated at 4% for 15 min, 3% for 30 min and 2% for 60 min [Korsolex basic, based on glutaraldehyde and (ethylenedioxy)dimethanol]. Three types of organic load were used: 0.3% albumin, 10% fetal calf serum, and 0.3% albumin with 0.3% sheep erythrocytes. Virus titres were determined by a quantitative test (endpoint titration) in 96-well microtitre plates. With all tested preparations, SARS-CoV was inactivated to below the limit of detection (reduction factor mostly > or =4), regardless of the type of organic load. In summary, SARS-CoV can be inactivated quite easily with many commonly used disinfectants.

Sainz, B., Jr., et al. (2006). "Inhibition of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) infectivity by peptides analogous to the viral spike protein." Virus Res **120**(1-2): 146-155.

Severe acute respiratory syndrome-associated coronavirus (SARS-CoV) is the cause of an atypical pneumonia that affected Asia, North America and Europe in 2002-2003. The viral spike (S) glycoprotein is responsible for mediating receptor binding and membrane fusion. Recent studies have proposed that the carboxyl terminal portion (S2 subunit) of the S protein is a class I viral fusion protein. The Wimley and White interfacial hydrophobicity scale was used to identify regions within the CoV S2 subunit that may preferentially associate with lipid membranes with the premise that peptides analogous to these regions may function as inhibitors of viral infectivity. Five regions of high interfacial hydrophobicity spanning the length of the S2 subunit of SARS-CoV and murine hepatitis virus (MHV) were identified. Peptides analogous to regions of the N-terminus or the pre-transmembrane domain of the S2 subunit inhibited SARS-CoV plaque formation by 40-70% at concentrations of 15-30 microM. Interestingly, peptides analogous to the SARS-CoV or MHV loop region inhibited viral plaque formation by >80% at similar concentrations. The observed effects were dose-dependent (IC50 values of 2-4 microM) and not a result of peptide-mediated cell cytotoxicity. The antiviral activity of the CoV peptides tested provides an attractive basis for the development of new fusion peptide inhibitors corresponding to regions outside the fusion protein heptad repeat regions.

Weingartl, H. M., et al. (2004). "Susceptibility of pigs and chickens to SARS coronavirus." Emerg Infect Dis **10**(2): 179-184.

An outbreak of severe acute respiratory syndrome (SARS) in humans, associated with a new coronavirus, was reported in Southeast Asia, Europe, and North America in early 2003. To address speculations that the virus originated in domesticated animals, or that domestic species were susceptible to the virus, we inoculated 6-week-old pigs and chickens intravenously, intranasally, ocularly, and orally with 106 PFU of SARS-associated coronavirus (SARS-CoV). Clinical signs did not develop in any animal, nor were gross pathologic changes evident on postmortem examinations. Attempts at virus isolation were unsuccessful; however, viral RNA was detected by reverse transcriptase-polymerase chain reaction in blood of both species during the first week after inoculation, and in chicken organs at 2 weeks after inoculation. Virus-neutralizing antibodies developed in the pigs. Our results indicate that these animals do not play a role as amplifying hosts for SARS-CoV.

Woo, P. C., et al. (2017). "Coronavirus HKU15 in respiratory tract of pigs and first discovery of coronavirus quasispecies in 5'-untranslated region." Emerg Microbes Infect **6**(6): e53.

Coronavirus HKU15 is a deltacoronavirus that was discovered in fecal samples of pigs in Hong Kong in 2012. Over the past three years, Coronavirus HKU15 has been widely detected in pigs in East/Southeast Asia and North America and has been associated with fatal outbreaks. In all such epidemiological studies, the virus was generally only detected in fecal/intestinal samples. In this molecular epidemiology study, we detected Coronavirus HKU15 in 9.6% of the nasopharyngeal samples obtained from 249 pigs in Hong Kong. Samples that tested positive were mostly collected during winter. Complete genome sequencing of the Coronavirus HKU15 in two nasopharyngeal samples revealed quasispecies in one of the samples. Two of the polymorphic sites involved indels, but the other two involved transition substitutions. Phylogenetic analysis showed that the two nasopharyngeal strains in the present study were most closely related to the strains PDCoV/CHJXNI2/2015 from Jiangxi, China, and CH/Sichuan/S27/2012 from Sichuan, China. The outbreak strains in the United States possessed highly similar genome sequences and were clustered monophyletically, whereas the Asian strains were more diverse and paraphyletic. The detection of Coronavirus HKU15 in respiratory tracts of pigs implies that in addition to enteric infections, Coronavirus HKU15 may be able to cause respiratory infections in pigs and that in addition to fecal-oral transmission, the virus could possibly spread through the respiratory route. The presence of the virus in respiratory samples provides an alternative clinical sample to confirm the diagnosis of Coronavirus HKU15 infection. Quasispecies were unprecedentedly

observed in the 5'-untranslated region of coronavirus genomes.

Zumla, A., et al. (2016). "Taking forward a 'One Health' approach for turning the tide against the Middle East respiratory syndrome coronavirus and other zoonotic pathogens with epidemic potential." Int J Infect Dis **47**: 5-9.

The appearance of novel pathogens of humans with epidemic potential and high mortality rates have threatened global health security for centuries. Over the past few decades new zoonotic infectious diseases of humans caused by pathogens arising from animal reservoirs have included West Nile virus, Yellow fever virus, Ebola virus, Nipah virus, Lassa Fever virus, Hanta virus, Dengue fever virus, Rift Valley fever virus, Crimean-Congo haemorrhagic fever virus, severe acute respiratory syndrome coronavirus, highly pathogenic avian influenza viruses, Middle East Respiratory Syndrome Coronavirus, and Zika virus. The recent Ebola Virus Disease epidemic in West Africa and the ongoing Zika Virus outbreak in South America highlight the urgent need for local, regional and international public health systems to be be more coordinated and better prepared. The One Health concept focuses on the relationship and interconnectedness between Humans, Animals and the Environment, and recognizes that the health and wellbeing of humans is intimately connected to the health of animals and their environment (and vice versa). Critical to the establishment of a One Health platform is the creation of a multidisciplinary team with a range of expertise including public health officers, physicians, veterinarians, animal husbandry specialists, agriculturalists, ecologists, vector biologists, viral phylogeneticists, and researchers to co-operate, collaborate to learn more about zoonotic spread between animals, humans and the environment and to monitor, respond to and prevent major outbreaks. We discuss the unique opportunities for Middle Eastern and African stakeholders to take leadership in building equitable and effective partnerships with all stakeholders involved in human and health systems to take forward a 'One Health' approach to control such zoonotic pathogens with epidemic potential.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

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