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Review on Severe Acute Respiratory Syndrome

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Abstract: Severe Acute Respiratory Syndrome (SARS), in its rapid international spread, zoonotic and seasonal epidemic forms, is a formidable public health threat throughout the world. Therefore, this seminar paper is aimed at giving an Overview of SARS-CoV. SARS is a viral respiratory syndrome caused by a newly identified *coronavirus*, named *SARS-CoV*. The virus can be transmitted via contact, droplet and airborne from human to human and non-human to human, particularly through dromedary camels. Most SARS patients acquired the infection in Asian country, which subsequently led to limited human-to-human transmission in clusters, in healthcare workers and in travel-related cases outside the region. The most frequent signs represent infection of the respiratory tract and include mild to severe respiratory signs such as fever, cough and respiratory difficulty. Diagnosis can be confirmed using reverse transcription RT-PCR on broncho-alveolar lavage, sputum and tracheal aspirates. Currently, there are no (prophylactic/prevention) vaccines or specific antiviral agents that are effective in the prevention and/or treatment of SARS. Treatment is support therapies including infection control procedures and management of complications. In conclusion, to prevent the disease general public health precautions seem to be the center of primary preventive strategy. These measures should focus on alleviating those possible non-humans to human and human-to- human risk factors.

Key words: Coronavirus · Epidemic · RT-PCR · SARS · SARS-Cov · Severe Acute Respiratory Syndrome · Zoonotic

INTRODUCTION

Severe acute respiratory syndrome (SARS) is a viral respiratory syndrome caused by a newly identified *coronavirus,* named SARS [1, 2]. The disease caused an average mortality of approximately 10% for which there is no direct remedy available. This disease was documented for the first time in Guangdong province in China at the end of 2002 and it quickly spread to 32 countries within a short period. But in July 2003 only four community acquired cases were reported in China there were three cases of laboratory-acquired infections described [3]. Although the origins of the virus are not fully understood where several studies have been conducted to explore the origin of SARS-CoV. According to the analysis of different viral genomes with a history of outbreak is proposed that palm civets are a direct source of human infection. However, they did not clarify whether animals other than civets were involved in transmission of the virus to humans or whether civets were an intermediate host or the natural reservoir host of this disease. The Sequencing of some viruses isolated from the small animals demonstrated that except for a small additional sequence, the viruses are identical to the human SARS virus [4, 5].

Six human CoVs have been identified to date they are the HCoV-229E, HCoV-OC43, HCoV-NL63, HKU1-CoV, MERS-CoV and SARS-CoV. Human CoVs were HKU1,

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NL63, 229E and OC43 predominantly cause a mild respiratory tract infection characterized by upper respiratory tract disease that includes coryza, cough and sore throat. These viruses occasionally induce lower respiratory tract disease, including bronchitis, bronchiolitis and pneumonia [6]. In contrast, two recently emerged CoVs induce a more severe lower respiratory infection that may be fatal for example Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV) [7, 8].

They occur worldwide and cause diseases of medical and veterinary significance. Generally, infections are localized to the respiratory, enteric and/or nervous systems, though some systemic diseases have been observed in several host species [9]. The SARS outbreak started in 2002 in China and, after rapid global spread through human-to-human transmission, was halted except suspected cases ended in 2004 but it is important to make aware the disease because the outbreak can occur every time in everywhere. The number of cases reported to the World Health Organization (WHO) was 8096, including 774 deaths [10]. The viruses amplify and get transmitted to new hosts including humans and this is critically important from the point of view of public health. The natural reservoir is not clear in the wild. It is conceivable that civets, raccoon dogs and ferret badgers were all infected by another, yet the true reservoir in nature is an unknown animal source [11].

Transmission of the virus particularly civets. Given the quick global expansion of this virus, many organizations such as the World Health Organization [12] have highlighted SARS health related issues as an important public health priority in high-risk populations However, there remains a great gap in the background literature and transmission of this virus. Therefore, the objective this paper was to give an overview on Severe Acute Respiratory Syndrome disease.

Severe Acute Respiratory Syndrome: Severe acute respiratory syndrome (SARS) is a serious form of pneumonia and it is caused by avirus that was first identified in 2003. Infection with the SARS-CoV produces acute respiratory distress (severe breathing difficulty) and death in both human. This disease (SARS) is caused by a member of the coronavirus family which is very a dangerous virus with an enormous impact [13]. Accumulated studies from different groups, which used a variety of approaches, the origin of the infective agent is in animals, either domestic or wild. Chlamydia pneumonia and human metapneumovirus are examples of other new pathogens causing severe acute respiratory illness in which humans have always been the likely host [1]. The first identified case of SARS-COV occurred in Guangdong province (southern china) in 2002 Witha history of high fever sex ceeding 38°C, myalgia, dry non productive cough, dyspnea, lymphopenia and in filtrate on chestradiography. In 38% of allcases, there sulting pneumonialed to acute breathing problems requiring artificial respirators [1]. When the disease moved out to southern China the outbreaks spread to Hanoi, Hong Kong, Malaysia, Canada and USA and they became the initial hot zones of these diseases characterized by a rapid increase in the number of cases, especially in health care staffs and their close contacts. In these areas, SARSfirsttookrootinhospitalsettingswherethestaffwasunawarethatanewdiseasehadsurfacedandwerebusyfightingtosavethelivesofpatientswhoexposedthemselvestotheinfectiousagentwithoutbarrierprotection.Alloftheseinitial outbreaks were subsequently characterized by chains of secondary transmission outside the healthcare environment [12].

Isolates of the virus have been identified as a *Betacoronavirus* lineage Band was described in the scientific literature, databases and popular press under various names with novel *coronavirus* as the one used most often [14]. Sequence analysis of the complete genome of SARS-COV has shown a molecule of about 29,750 bases in length, with a genome organization similar to other *coronaviruses* [15, 16].

Etiology: *Coronavirus*es (CoVs) are large, enveloped, positive-sense RNA viruses that infect birds and a wide range of mammals including humans. These viruses are composed of a few structural proteins that hold a relatively long (around 30 kb) positive-stranded genome [9]. SARS-CoV is one of 36 coronaviruses in the family *Coronaviridae* within the order *Nidovirales*. Members of the *Coronaviridae* are known to cause respiratory or intestinal infections in humans and other animals (Figure. 1). Despite a marked degree of phylogenetic divergence from other known *coronaviruses,* SARS-CoV together with bat SARS-CoV is considered group 2b *coronaviruses* [17, 18].

This genome contain genome contains five major open reading frames (ORFs) that encode the replicase polyprotein; the spike (S), envelope number of other structural proteins including Small envelope (E) and membrane (M) glycoproteins; and the nucleocapsid protein (N). Protein as well as the single stranded RNA where the S protein is the principal viral antigen that elicits neutralizing antibody on behalf of the host [14].

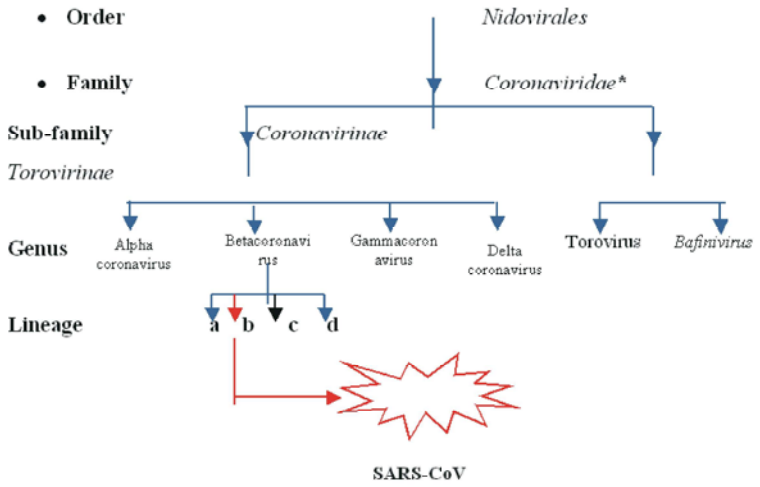

Fig. 1: Schematic representation of taxonomy of *Coronaviridae*
Source: [19].

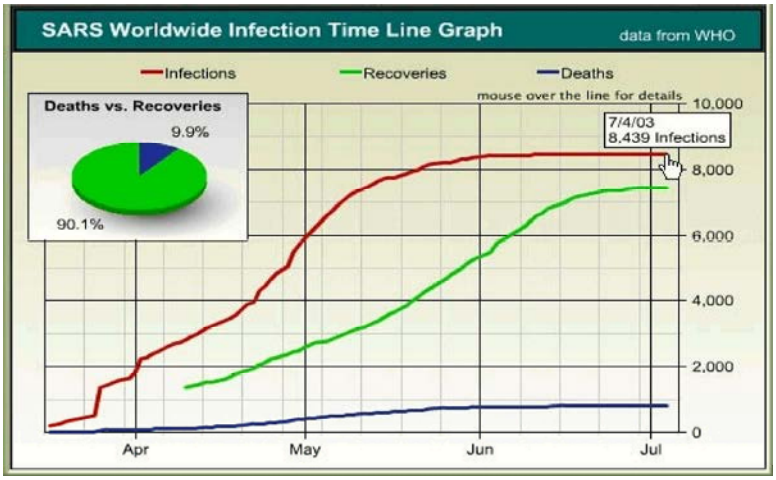

Fig. 2: Distributed confirmed cases of SARS COV
Source: [12].

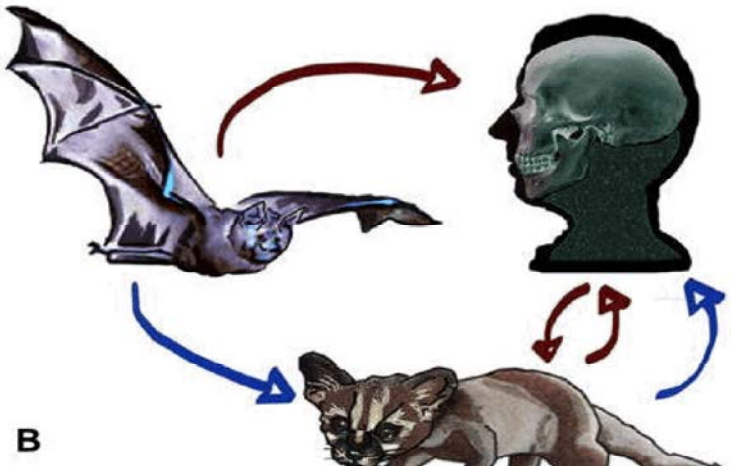

Fig. 3: Schematic representation on cycle of transmission
Source: [16].

According to the International Committee on Taxonomy of Viruses both SARS-CoV and MERS-CoV belong to the genus of *Beta coronavirus* but with different lineages. (*Coronaviridae* is together with *Arteriviridae, Mesoniviridae* and *Roniviridae*in the family) [19].

Epidemiology of SARS -COV

Temporal and Geographical Distribution: SARS- COV is a disease of worldwide distribution occurring in wild animals and humans. It has been reported mostly is a human killer wherever animals can raised all over the world, the occurrence of the disease is not fallow seasonal distribution. After investigation statistics from different countries and for different periods. The sarsnet was confirmed to automatically take care of all these conditions. The virus is most commonly distributed in China, Malaysia and Canada. The disease has been reported as a cause of respiratory disease in patients from 32 countries in the world including France, Germany, Ireland, Italy, Romania, Spain, Sweden, Switzerland and United Kingdom so SARS-CoV is possible to occur or spread everywhere in the global but until now there is not confirmed cases in Africa [12].

Host Range and Modes of Transmission: Understanding the epidemiology and transmission of SARS-CoV requires the classifications of cases into: Sporadic (community-onset), Intra-familial transmission and Health-care-related transmission. The WHO SARS-CoV Research Group defined sporadic and index cases as meeting one of the following criteria: no history of contact with other SARS-CoV cases, occurring in an area with no previous cases within the last 2 months, or the first or index case in a cluster [20].

Sporadic: Animal to Human Transmission: The acquisition of SARS-CoV in these sporadic cases could be from animal contact both domestic and wildlife. The data suggest the small wild animals are the likely source of SARS-CoV. Veterinarian studies showed a high rate of positive serology in bats, raccoon dogs and ferret badgers in multiple countries including: the China, Singapore, Vietnam, Canada and the United States [12]. A stronger evidence of the connection comes from the detection of SARS-CoV by polymerase chain reaction from bat [17]. Genome sequencing showed that the genome organization of all bat SARS Coronavirus similar other CoVs is almost identical to that of isolated from humans or civets similar with an overall sequence identity of 88% to 92% [21, 22].

Later, when the natural reservoir of the virus was found to be fruit bats, where live bats are found in wildlife wet markets and restaurants in Southern China and Asian countries for consumption, which have greatly facilitated bat-human and bat-animal interactions in the case of the infected restaurant in China and Malaysia [23]. Thefarmers could take measures to isolate their livestock from bats; this eventually led to the control of that epidemic [16].

The route of transmission from the reservoir host to the intermediate host is fully understood. However, the fecal, oral and respiratory route represents the main route of transmission among animals. Although mixing of live reservoir hosts (e.g., bats) and intermediate hosts (e.g., civets) would be an efficient means of transmission, the main source of cross-species transmission in the animal trading chain (including ware houses,vehicles and markets) may come from contaminated feces, urine, blood, or aerosols. This may also be true for civet-to-human and human-to-human transmissions as shown in the initiation of the first case which occur in bats handled in restaurants in China and Malaysia [24].

Some cases are highly contagious, have a high reproductive number and can infect more than 10 patients, on a super-spreader. For example, the five super-spreaders in Singapore have been found infecting 103 people. Such powerful infectiousness is attributable to the high viral load inside patients who could discharge abundant viruses via the respiratory tract within a short period [25].

Community Outbreaks *(*Intra-familial Outbreak): Community outbreaks of SARS-CoV have been limited to intra-familial transmission. In an initial report of a hotel cluster, there, while a resident on the ninth floor of the Metropole Hotel in China, the patient developed symptoms and was transferred to the hospital, where he died the following day. Subsequently, ten secondary infected guests in the hotel boarded planes and carried the infection to Singapore, Vietnam, Canada and the United States, making SARS the first epidemic to be transmitted by air travel [12]. Clusters of atypical pneumonia were wall reported in Malaysia and Canada, which were epidemiologically linked to outbreak of Metropole hotel in china [26].

Health-care-associated Transmission: It is known that a large proportion of SARS-CoV cases occur in the healthcare setting. From the first identified hospital outbreak in Hong Kong. This outbreak was identified retrospectively after the identification of the first

SARS-CoV in Guangdong Province in China. The Zarqa outbreak affected 305 patients and 105 of them were healthcare workers [17]. In 17 studies that reported on sero-epidemiology, the sero-prevalence varied from 0 to 1.81% for the general population, 0 to 2.92% for asymptomatic health care workers, 0 to 0.19%for asymptomatic household contacts and 12.99 to 40% for asymptomatic animal handlers so health care workers were the main risk victims in global cases [27]. *Mortality*.

A mortality rate of 20%-25% was reported in the earliest publications. the fatality ratio is less than 1% for people younger than 25, 6% for those aged 25 to 44, 15% for those aged 45 to 64 and more than 50% for people 65 so the aged man is susceptible this disease [12].

Pathogenesis: To better understand the biology of coronaviruses, timely identification of receptors could reveal important clues to its zoonotic transmission and pathogenicity and therefore important to design possible pharmacotherapy. Additionally, surface receptors play an important role in initiating virus entry into the host cells; thereby playing a major role in the tissue and host species tropism therefore the discovery characteristics of cellular receptor of SARS-CoV might provide important clues to the pathogenesis of this novel virus [28]. The exact mechanism of how the virus produces damage at cells, tissue and organs to clinical levels remains elusive. Similar to other viruses such as influenza a virus, Nipah virus, or Ebola virus, SARS-CoV must possess the ability to evade the innate antiviral response of the cells to replicate efficiently in the host [29].

Angiotensin-convertingenzyme 2(ACE2), ametal loproteinase that has previously in volved attention as are sulto fitsrolein the cardiovas cular system [30]. Concerning respect to the respiratory tract, ex vivo experiments have detected ACE2 on the luminal surface of trachea-bronchial and alveolar epithelium. Thus, Several distinct features of fatal coronaviral pneumonia have been identified [31] including epithelial cell proliferation, diffuse alveolar damage, macrophage infiltration of the lungs and haemophagocytosis which is a feature attributed to cytokine dysregulation [32]. Also it has been suggested that in SARS CoV pneumonia, pro-inflammatory cytokines released by stimulated macrophages in the alveoli have a prominent role in the pathogenesis of SARS leading to cytokine dysregulation. This idea has implications for the management of coronaviral pneumonia, as interventions with steroids might modulate this cytokine response and prevent fatal outcomes [33].

Incubation Period: The typical incubation period of SARS ranges from 2 to 10 days but may occasionally be as long as 16 days [34, 35] where the patients with severe acute respiratory syndrome were most infectious in the first 2 days of illness transmission from symptomatic SARS patients usually occurred on or after the fifth day of onset of the disease, which is in line with the rising viral load in nasopharyngeal secretions that peaked at around day 10 [1]. Currently, 10-14 days quarantine for travelers from areas with SARS outbreak is practiced by many countries. Therefore, a sensitive and accurate laboratory diagnostic test is urgently required. Most PCR-based tests using SARS-CoV-specific primers can achieve good specificity and can therefore be used as confirmatory tests [12].

Clinical and Pathological Findings: In human clinically the course may be mild or asymptomatic in some patients. The clinical course may vary in immune-suppressed individuals. The largest clinical case series report included upper respiratory tract symptoms such as rhinorrhoea, nasal obstruction, sneezing, sore throat, or hoarseness. There is usually 3-7 days from the onset of fever toexperiencing, dyspnoea [36, 37]. Physical examination of the chestwill eventually reveal crackles and dullness on percussion inmost patients.Whereas pathologically leucocytosis, leucopoenia and thrombocytopenia are uncommon, lymphopenia (1,500 cells/mm3) isalmost always seen at disease onsetTransaminases includingaspartate aminotransferase (AST) or alanine amino-transfers (ALT) are elevated slightly in 40-60% of our patients and thesetend to normalize simultaneously with clinical and radiologicrecovery [36].

In experimentally infected animalsin these animal experiments, SARS-CoV was administered intratracheally and intra-nasally to cynomolgus macaques. Intra-trachealinoculation was the most effective delivery system to the lower respiratory tract which resulted clinically in respiratory and constitutional clinical signsin cluding mildcough, sneezing, fever, lethargy, slight decreased activity and viral shedding. Soon after themonkey experiments,cats, ferrets, mice,pigs, hamsters, guineapigs, hamsters,chickens and rats were infected to studyvarious aspects of thedisease all of these animals showed the same clinical signs. However, the course of the infection in these animals was shorter than that in humans and none of these animal models replicated the human disease in all its aspects [38].

Histopathological examination of African green monkey lungsdemonstrated interstitial pneumonitis in association with SARS-CoV replication on day 2 p.i,

which was resolving byday 4 p.i. SARS-CoV antigens was present in bronchiolar epithelialcells and type I pneumocytes. The ability of primaryinfection to prevent reinfection was evaluated in African greenmonkeys by SARS-CoV challenge 2 months after the primaryinfection. These animals showed no evidence of viral replicationor enhanced disease [39].

Interestingly, the lesions in the lung,although milder than the histopathological changes observed in SARS patients were consistently observed in all animals,with hyaline membranes, lung-edema and desquamation ofalveolar lining cells in some infected macaques. This is the firststudy that follows nonhuman primates for such a long periodand it suggests that SARS-CoV infection in macaques deserves further investigation [40].

Diagnosis: Diagnosis of severe acute respiratory syndrome can usually be made based on epidemiological data, clinical signs and result of diagnosis test. Lower respiratory tract specimens (tracheal aspirate, bronchiolar lavage and pleural fluid) are the most preferred in sample collection [41]. High concentrations of viral RNA of up to 100 million molecules per milliliter were found in sputum. SARS-associated *coronavirus* RNA was detected at extremely low concentrations in plasma during the acute phase and in feces during the late convalescent phase, suggesting that the virus may be shed in feces for prolonged periods of time [14]. Viral RNA also isdetected in nasopharyngeal aspirates and urine samples by RT-PCR [1].

Diagnosis of this virus can be confirmed using Reverse transcription polymerase chain reaction RT-PCR on bronchio-alveolar lavage, sputum and tracheal aspirates [42]. The «upstream E protein, upE gene» and «ORF1a» genes are targeted for definitive diagnosis. In the event that both tests are positive, infection is regarded as present [43].

When RT-PCR was used for virus detection, tracheal aspirate and stool provided a high diagnostic yield, with an average positive rate of 66.7% and 56.5%, respectively, for the first 2 weeks. Pooled throat and nasal swabs, rectal swab, nasal swab, throat swab and nasopharyngeal aspirate provided a moderate yield with average positive rates ranging from 29.7% to 40.0% for the first 2 weeks, whereas throat washing and urine specimens provided a lower yield with an average positive rate of 17.3% and 4.5%, respectively. The yield from virus isolation was much lower than from RTPCR and no specimen was positive by culture but negativeby RT-PCR.

Antigen detection with monoclonal antibodies or monospecific polyclonal antibody against the N protein was found to be a sensitive and specific test for the diagnosis of SARS-CoV. In a large study with sera collected from 317 SARS patients at different time points of illness, EIA detection of SARS was performed using a panel of three monoclonal antibodies [44].

Treatment: Antiviral therapy: Antiviral agents used in the therapy of SARS include ribavirin, IFN-a and lopinavir, ritonavir. Ribavirin is a nucleoside analogue with in vitro activity against a number of RNA and DNA viruses, including some animal *corona-viruses* [45], *Ribavirin* is a broad-spectrum antiviral that works as a purine nucleoside analog to inhibit guanosine triphosphate synthesis and viral RNA polymerase activity. In SARS, ribavirin treatment resulted in symptom improvement of patients, but its mortality benefits were inconsistent. Ribavirin treatment also resulted in a significant prevalence of adverse events, especially hemolysis, which was reported in 68.5% of patients [46]. Ribavirinin vitro in six studies were found that described the antiviraleffect of ribavirin in vitrofourshowedAssay Type and Outcomes Measured and also Inhibition of SARS-CoV Replication. A synergistic antiviral effect between ribavirin and type I IFN (IFN-b1a or leukocytic IFN-a) was described in two studies performed in human cell lines and Vero cell lines [44, 47].

Corticosteroids also have been used widely to treat SARS-CoV,Corticosteroids significantly reduce interleukin-8 (IL-8), Monocyte Cytokine Proteine-1 (MCTP-1) and IP-10 concentrations 5-8 days after treatment. The data confirmed the Th1 cell mediated immunity and hyper innate inflammatory response in SARS through the accumulation of monocytes/macrophages and neutrophils. Another rationale for use of steroids in SARS is the necroscopic finding of features of Acute Respiratory Distress Syndrome (ARDS) [31-48]. Adverse Effects from Anti-SARS-CoV Treatment there were no major life-threatening complications. Adverse effects attributable to drug treatment included hemolytic anemia, hyperglycemia, serious secondary infections defined aspyrexia or bacteremia illness and hematemesis frank blood or coffee ground vomiting [34].

Prevention and Control: Public health decision-makers need timely access to information for action. Those responsible for the health of the public need to ensure clinical, laboratory, epidemiological and other resources

are efficiently coordinated to best respond and manage an outbreak and to evaluate these activities. This includes the undertaking of well-coordinated, priority studies to generate the information needed for public health action. Within WHO there is also a need to facilitate closer collaboration between the epidemiology, laboratory and clinical networks at policy, planning and operational levels to address public health priorities in the containment and control of SARS [49].

Vaccines already exist for animal coronaviruses; vaccine biologists are applying this expertise to SARS [50, 51]. Various techniques for vaccine development are being tried. One is targeted genetic modification of SARS virus whereby genes not needed for virus survival but required for it to cause disease are selectively deleted. Another approach uses genetically engineered harmless viruses which contain only those genetic sequences from the SARS virus that are necessary to stimulate the human immune system. This approach has been used to develop a prototype vaccine against a coronavirus that causes bronchitis in chickens [52].

Controlling the transmission of the virus is an important component of dealing with SARS-CoV epidemics. Thus, management entails early case detection, the isolation of SARS patients and the application of infection control measures. In addition to standard precautions, three infection control transmission precautions are used: contact precautions, droplet precautions and airborne precautions [12].

Contact precautions are required when patients are known or suspected to have illnesses that are easily transmitted by direct patient contact or by contact with items in the patients environment; thus, the stability of SARS-CoV in aerosol form and the presence of diarrhea in infected patients mandate the requirement of contact precaution measures [53]. Droplet precautions are required when patients are known or suspected to have illnesses transmitted by large particle droplets (droplet particle > 5 ìm in diameter) [44], airborne precautions are required during aerosol generating procedures [10]. The United States Centers for Disease Control and Prevention continues to recommend the use of airborne infection isolation precautions with all patients [28], this precautions are required when patients are known or suspected to have illnesses transmitted by airborne droplet particles (droplet particle < 5 ìm in diameter) [44]. Since most of the cases occur in the health care setting, it is prudent that all health care workers practice appropriate infection control measures when taking care of patients with suspected or confirmed SARS-CoV. Specifically, health care workers should apply standard precautions consistently with all patients. The application of droplet precautions is needed when providing care to patients with symptoms of acute respiratory infection. The addition of contact precautions and eye protection is required when caring for suspected or confirmed SARS-CoV infection [10].

CONCLUSION AND RECOMMENDATIONS

Severe Acute Respiratory Syndrome is a viral respiratory disease involving a new coronavirus. All cases to date have been directly or indirectly linked to the Asia, Europe and USA. Epidemiological data suggest that it is primarily a zoonotic disease. The disease can also be transmitted from person to person, although in a limited manner. It has also been shown to be transmitted nosocomially.

The epidemiology and the transmission pattern of SARS-CoV to date indicate that the majority of cases occur in the healthcare setting. Community-based cases are also in significant numbers and there is a real need to further prevent the animal-to-human transmission of SARS-CoV. It is also important to further delineate the transmission routes and the presence of any other animal or intermediate hosts. The remaining and ongoing SARS cases reported in many countries represent a global public health concern. Therefore based on the above conclusion the following recommendations will be forwarded:-

- Strengthening the infection control measures in the health care setting is of great importance.
- There should be a collaboration between animal and human public health organizations that would serve as a progressive step to control the spread of this zoonotic disease.
- An alliance between both fields is essential to understand the risk of transmission of SARS-CoV between animals and humans, whether there is any seasonal variation in the circulation of the virus in animals and the natural reservoir(s) of SARS- CoV.
- Frame out strategies for curbing the disease in birds by employing strict bio-security, adequate disease surveillance, timely diagnosis and suitable preventive measures.

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