

MERS-CoV: An Epidemic Whirlwind

Ilham Qattan*, Aljohani A, Alfarsi M, Aljohani E and Alsubhi M

Taibah University (TU), AlMadenah AlMonwara, Kingdom of Saudi Arabia

*Corresponding author: Ilham Qattan, Professor of Medical Molecular Virology (MMV), Dean of the Applied Medical Sciences, AIUla Deputy University General Supervisor for PR & Conf. Board member of the Genes & Genetic Disease Center at Taibah University (TU), AlMadenah AlMonwara, Kingdom of Saudi Arabia, Tel: +966(0)148618888 Ext: 3609; E-mail: iqattan@taibahu.edu.sa

Received date: February 23, 2016; Accepted date: April 08, 2016; Published date: April 12, 2016

Copyright: © 2016 Qattan I, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Abstract

Corona virus as a Middle East Respiratory Syndrome (MERS) considered being a new complicated disease; it infects the epithelial cells in the respiratory and/or intestinal tracts, thus causing disease in epidemic proportions. The situation is exacerbated by either a short incubation period between 2-7 days or between 12-14 days. In September 2012, coronavirus was identified for the first time in a new series of infections, known as MERS-CoV. Since March 2012 and until the end of November 2015, a total of 1655 cases were reported with the number of 577 deaths and 630 recovering from the disease, while 28% of the data were analyzed throughout the world by WHO. The virus has been detected in Arabian Peninsula, European countries such as Britain, Germany, France, Italy and Middle East. However, to the idea that the Hajj season could trigger the transmission of MERSE-CoV in Saudi Arabia remained controversial.

Keywords: Coronavirus; MERS-CoV; Coronaviridae

Aim

The aim of this study is to raise a point of view on the significances of MERS-CoV statistical analysis and evaluates how the virus can furiously cause the infection.

Factors relating to patient's susceptibility to infection and variations of the virus through mutation, and integration with other species might play a role in creating a more malignant infection which leading to death. The present study is based upon global statistical analyses published online with a special focus on Saudi Arabia. All cases were compared to examine the differences between infections, recoveries and death in order to determine the significant factors that could explain how the infection spreads. Because of the lack of live sources of information, statistical reports have been monitored for data collection starting since almost the beginning of the reported on infection, and have been updated frequently. This has occurred throughout the Ministry of health (MOH) command and control centers, World Health Organization (WHO), Centers for Disease Control (CDC), European Centre for Disease Control (ECDC), and social networks such as in Twitter, Facebook and publishing the news concerning MERS-CoV infection and outbreak [1-4].

The genes of this virus were compared with genes of similar viruses from humans, pigs, cows, dogs, cats, mice, rats, camels and bats. It was clear that the genes were $\leq 70\%$ identical compared to other genes within the same family. Such data accordingly show that the new mutated virus was dormant in animals and co-existed with them for a long time. Somehow, it was isolated genetically for a long time and then suddenly a malignant virus reappeared that become harmful to humans. The recombination transition to humans occurred only once and it could be due to a doggy mixture between species rather than not as a random mutations.

Introduction

Coronavirus is a species of virus that belongs to the subfamilies Coronaviridae and Torovirinae. These viruses are enveloped with a single strand positive-sense RNA genome and have helical symmetry of their nucleocapsid. Coronavirus belongs to the Group IV ((+) ssRNA) and is in the order Nidovirales. The known species of the virus include HKU1, OC 43, 22 9E, MERS-CoV, SARS-CoV, Pipistrellus bat coronavirus HKU5, Tylonycteris bat coronavirus HKU4, and Rousettus bat coronavirus HKU9, Ba SL-CoV-WIV1, London1 novel CoV/2012 and HCov-EMC/2012. The genome size ranges from 26 to 32 kilobases which categorises it as a large RNA virus. A microscopic view of the virus is presented in Figure 1.

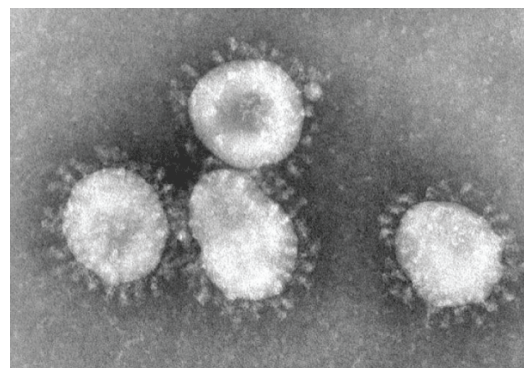


Figure 1: Coronavirus under a microscope, Wikipedia 2015.

The name comes from the Latin word for halo and is used for the appearance of virions during electron microscopy in which they have a fringe around their surface similar to the solar corona. The structure of the virus is based on the proteins that make up the spike, envelope, membrane, and nucleocapsid. A mutation in SARS affecting the

receptor binding domain and the spikes are involved in the virus. The virus was first seen in the 1960s and was seen in the nasal cavity of the patients who were diagnosed with the common cold. The virus has further been named as coronavirus 229E and OC43.

Literature Review

Past researches on coronavirus have been carried out on different aspects of it. It has always been thought that researchers have had a grasp over this virus and knew all there was to know. This paradigm has existed in the medical community and amongst different virologists for some time. In 2003, however, this paradigm went through a shift and an overhaul. With the rise of SARS to the forefront of people's minds, there was a renewed interest in coronavirus and its implications.

Peiris et al. looked at the outbreak of SARS in Hong Kong and tried to see how the viral infection spread through 50 patients [5]. The paper noted that the SARS outbreak took place in different ways with appearances of clusters of patients with pneumonia in healthcare workers and their family contacts. Testing for conventional pathogens causing pneumonia were negative and a biopsy of the lung showed a serologic reaction to the virus.

Phylogenetically, human-associated coronavirus was not related to any other known variation of coronavirus or torovirus. Peiris et al. in 2003 showed that coronavirus can undergo transmutation [6]. Further analysis of their data showed that viruses within Coronaviridae could change when they came into contact with different family groups, and genetic analysis revealed this to be within the genome. The combination of any genome changes leads to a new kind of coronavirus, and genetic or clinical data, therefore shows that the original genes can be no longer recognizable.

There are antibodies present in the human body that can counter the virus; however there is no known remedy or treatment for the disease.

Other articles on this issue are mostly concerned with novel coronaviruses and the latest articles that have been reviewed for this research are mostly concerned with the SARS outbreak that took place in 2003. The MERS related research is still in progress as the data and sampling for the disease has been limited until now. Rota et al. showed how a novel coronavirus was found in the cases researched and investigated for SARS [7]. There is an association that has been drawn based on the sequence of the genome that both share and the initial characterization of the viral genome that is discussed in their paper.

The genome of SARS-CoV is 29,727 nucleotides in length and has genome characteristics quite similar to other coronaviruses. A detailed phylogenetic analysis and sequence comparison is also carried out which showed that there is a fundamental difference between SARS-CoV and the other coronaviruses. Similar research has also been carried out by Ksiazek et al. [8]. This paper is related to the outbreak of SARS as well; however, the aspect of research to cause on was researched is the identification of the start of the outbreak.

Ksiazek suggested that the initial exposure took place in a single ill health worker in Guangdong Province of China, while trying to identify the etiologic agent that led to the outbreak [8]. In order to carry out the study, clinical specimens were gathered from seven countries and tested by virus isolation, electron microscopic and

histologic analysis in addition to molecular and serologic assays to find the range of pathogens involved.

The results of the study showed that the previously recognized respiratory pathogens were not present but there was an isolation of a novel coronavirus in patients who were diagnosed with SARS. Cytopathological features were studied based on throat swabs that were taken and the electron microscopic examination revealed some of the structural features and characteristics of the virus. Similarly, some research has examined the genome sequence of the SARS-associated coronavirus in detail. Mara et al. sequenced the 29,751 base genome of the SARS virus which is also known as Tor2 isolate [9].

The genome sequence shows that the coronavirus is moderately related to the other family of coronaviruses which includes HCoV-OC43 and HCoV-229E. A deeper analysis has shown that there are viral proteins that are very different from the other previously known coronaviruses, and that by genome analysis the medical community would be able to better diagnose the virus. The virus affects humans and animals equally and different tests and analyses like polymerase chain reaction and immunologic tests can be performed to diagnose the virus.

Further work is needed for developing antivirals and modalities of treatments. There hasn't been much progress in developing treatments for SARS. Breaking down the genome structure of the virus, an identification of efficacious vaccines that would elicit neutralising antibodies could be accomplished.

The literature evaluates SARS and how it has been identified as a novel coronavirus in patients that have shown signs of infection as infection or been diagnosed with SARS. Drosten et al. performed additional research and tried to determine SARS as a causative agent, as while the infection was thought to be caused by an unknown agent [10]. The fact that an outbreak happened and there wasn't much evidence of how it occurred or what the source of the virus was caused an alarm.

The research by Drosten et al. looked for clinical specimens from different patients with SARS and tried to breakdown the disease by trying to identify the unknown viruses [10]. This was done by using cell cultures and by applying molecular techniques to the samples collected. This study confirmed the previous research that was carried out in this field which stated that a novel coronavirus was identified in the patients with SARS. The virus was taken and isolated in cell cultures and its sequence of 300 nucleotides was determined by Polymerase chain reaction (PCR) based on random amplification procedures.

The genetic make-up showed that the virus was distantly related to other coronaviruses based on 60% similarity of the structure. On the basis of this sequence from conventional and real time PCR assays, the connection to a novel coronavirus was established. There was the virus that was detected in the SARS patients and negative controls, and there was a high concentration of viral RNA of 100 million molecules per milliliter in the sputum collected.

It is an established fact by now that the spike proteins of the coronavirus attach themselves to the target cells using angiotensin-converting enzyme 2 (ACE2). Based on this fact, studies by Li et al. showed that when the cases of SARS are considered, the major point of entry is through cellular receptors that mediate entry into the target cells [11]. This research led to the identification that metalloproteinase

isolated from the SARS patients which and ACE2 allowed the permissive cells to be exposed to the virus.

Although a connection of the soluble form of ACE2 with the viral infection was indicated, no such function was found for ACE1, which negated the association of receptor cells with ACE1. It was also concluded that anti-ACE2 and not anti-ACE1 antibodies were able to block viral replication on Vero E6 cells and that it was ACE2 which allowed the functional receptors for SARS in the patients.

In addition to research concerning humans, studies have also been carried out on animals, as the virus has had known impact on animals as well. Guan et al. concluded that there is an etiologic agent involved in SARS [12]. The virus was isolated in that study to Himalayan palm civets and concerned the farm animals living in the Guangdong Province of China. The research showed that there was evidence of the viral infection in animals like raccoon dogs and also showed transmission to humans.

The isolation of samples from humans and animals showed that the animals isolates retain a 29 nucleotide sequence which is not seen in people. The research suggested that small animals in retail markets are susceptible to the virus and there can be interspecies transmission that can be carried out in the process, although the natural animal reservoir is still not known.

Once the disease was diagnosed, the next step was to study the progression of the clinical, radiologic and virologic changes that take place with SARS infection. Peiris et al. followed 75 SARS patients for three weeks and evaluated the pattern of the disease, viral load and risk factors of the clinical conditions they had in relation to their outcome [5]. The research concluded that the consistent clinical progression, shifting infiltrates and an inverted V viral load profile showed that the worsening of patients after two weeks was not related to viral replication but was due to the immunopathological damage that occurred in the patients over time.

Known Diseases Caused by the Virus

Coronavirus primarily targets the upper respiratory tract and the gastrointestinal tract of the patient. There are six known strains of the virus that infect humans and the latest one described is the SARS-CoV which leads to SARS and has a distinct pathogenesis which affects the upper and lower respiratory tracts and can lead to gastroenteritis. The basic disease of corona caused in people is a common cold in the winter and spring months. A complication regarding diagnosis is that this virus is hard to detect and assess as it is difficult to grow in a laboratory like some of the other viruses that cause similar diseases. The acute nature of this virus can also lead to pneumonia direct the virus or as a result of secondary bacterial infection.

Coronavirus also has an impact on birds and other mammals where it manifests not only in the respiratory tract but also in the urogenital tract and is categorized as infectious bronchitis virus (IBV) as well. This virus then spreads throughout bird population over time. Many mammals and birds become infected due to the fact that there are a lot of farm animals and pets who live in close proximity. This causes an interchange of different viruses to take place and mutate into other forms causing diseases in other animals. This leads to a problem in the farming industry primarily. The viruses that have the most impact are porcine coronavirus (TGE) and bovine coronavirus which cause diarrhea in young animals.

Feline coronavirus causes minor disease in cats, but can mutate into feline infectious peritonitis (FIP) which can have drastic effects. Coronavirus has caused high fatalities in other animals, as well. The virus also impacts ferrets causing gastrointestinal consequences known as epizootic catarrhal enteritis (ECE) or can mutate into a more deadly version in the form of ferret systemic coronavirus (FSC). Dogs are also affected by this virus causing gastrointestinal complications and also some respiratory implications, while mice have also suffered rising mortality due to mouse hepatitis virus (MHV). Past *in vivo* and *in vitro* studies showed that MHV caused demyelinating encephalitis in the mice which led to multiple sclerosis.

Coronavirus is also reported to lead to illnesses like bronchitis, gastroenteritis, progressive demyelinating encephalitis, diarrhea, nasal obstruction, sneezing, cough and sore throat. Severe lower respiratory tract infection with pneumonia in children and compromised individuals can also take place. Different species of the virus lead to different diseases; for example, HCoV-OC43 leads to sore throats while HCoV-NL63 causes laryngotracheitis and nonfatal respiratory tract infections in children and the elderly. HCoV-HKU1 is known to cause mild respiratory disease, colds, pneumonia, fever, cough, febrile seizure and wheezing.

The mode of transmission is through inhalation primarily in the form of respiratory droplet aerosols but also can spread through the fecal-oral route or through fomites. The virus can be transmitted significantly by air and dust as well as wind leading to infection of respiratory system, coughing, eye redness and inflammation of the throat. It is possible that the rain may limit the spreading of the virus.

The first exposures to the dust waves in Arab countries were reported to be in Saudi Arabia and Jordan, followed by the Gulf States and other parts of the Arab world. According to the Meteorological Agency rating, the most dangerous dust waves followed one another in those areas until August 2012. There is also a relationship between dust and a lot of diseases that spread out over time, such as meningitis, which could be similar in the case of coronavirus.

In the majority of cases isolated from Saudi Arabia, the analyses indicate that the rate of molecular evolution of the viral gene is 1.48×10^{-3} , as published by Cotten et al. in 2014; through which it is shown that there is more than 60% of the viral genome sequence from Saudi Arabia back ground of the virus development the evolutionary theory [13]. Although the default rate in evolution may be slow, the genetic sequence of MERS from the samples derived from humans compared to the samples derived from camels within the infected cases and the suspected group show might explain the relation between human cases of to the reverse sequence and the virus from camels that isolated from Qatar, through such a relationship is yet to be confirmed.

Moreover, samples studied recently in March 2014, from reported cases of infection in people who had been in contact with camels, did not indicate definitively, nor add evidence to support the role of camels in the transmission of MERS-CoV. For example, if 7% percent of 94 confirmed human cases were exposed to or had direct contact with a camel, this is not significant when compared to the percent not exposed. However, if the camels were not the source of infection, and the correlation with camels was only random, the question arises, how likely to consider 7 infected patients out of 94 as an epidemic or not. The reports indicate the existence of more than one to two millions of camels in the Arabian Peninsula. If we assume that everyone in the population owns camels, we would expect that 2% of the population in the region have camels. It can then be concluded that 7 out of 94

having the infection transmitted from camel do not seem higher than what would be expected from the distribution. In fact, it is difficult to prove the link of the transmission unless we go for the Herical clustering.

Interaction with the cell

Interaction with the human body first occurs when the cells are exposed and the cytoplasm of the cell is affected where the virus penetrates the cell membrane (Figure 2). Due to the entry into the cell, the virus unpacks itself and deposits the RNA genome in the cytoplasm. The virus has a genome structure of a 3' polyadenylated tail and 5' methylated cap which attaches RNA to the ribosomes when translation takes place. The virus also contains a protein that identified as a replacement protein. This protein has the genome encoded on it, in order to allow the RNA viral genome to be written on the RNA copies of the host cell.

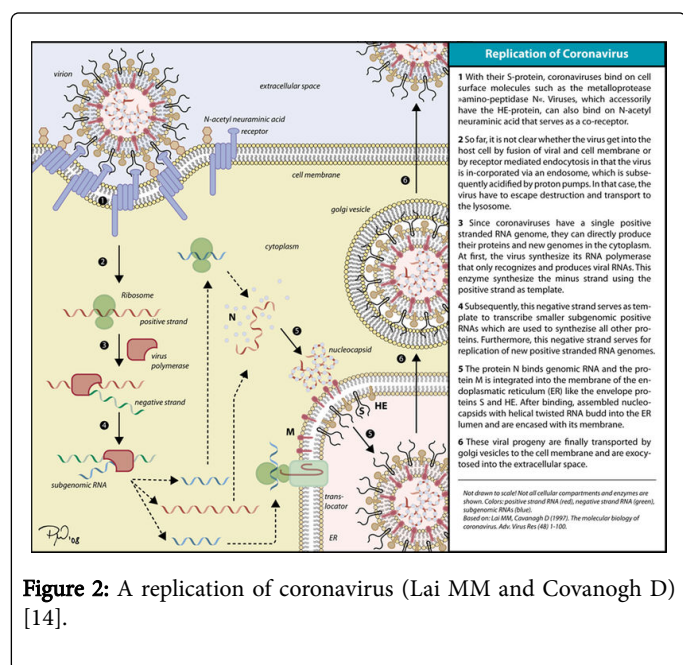


Figure 2: A replication of coronavirus (Lai MM and Covanogh D) [14].

The process starts when the virus produces replicase and once the translation inside the cell has taken place, the replicase is translated and any further translation is stopped by a stop codon. This process has the characteristics of a nested transcript and when this transcription is done on one gene, it is known as monocistronic translation.

After the RNA genome has been transcribed and is replicating the production of the new protein, all proteins are attached to it making it as a long chance of polyproteins. The virus has a non-structural protein called a protease which then starts to separate the proteins that exist in the chain, which enables the virus to encode and transcribe a large amount of genes while only using up of a small numbers of nucleotides.

Replication in the human body

As the coronavirus is first exposed to the human body the virus is able to attach itself through it S protein, the N-acetyl neuromeric acid of the skin, and receptors are activated to carry the virus through. The second step is that the virus is able to get inside the body and merge

itself with the cell membrane, assimilating with the endosome which is acidified by proton pumps. Before the cells can be destroyed by the virus, they have to be transported to the lysosome. Since the virus genome is made up of a single strand of RNA, they are then able to produce polyproteins and new genomes when they enter the cytoplasm.

The negative strands make up the template and are converted into more positive strands of the virus which are used to make up and produce more proteins. The negative strands also become the input for the production of new positive-stranded RNA genomes. The proteins that have been produced by the virus are then integrated into the membrane of the endoplasmic reticulum and the nucleocapsid is then merged with the helical twisted RNA and buds into the membrane. The final part of the process is the deposition of viral progeny into the new cell space.

Primary Types of Coronaviruses

SARS

The interaction between SARS and coronavirus was seen after there was an outbreak of SARS in Asia. The outbreak took place in 2003 and was mainly centered in Asia while having some secondary effects in the rest of the world. It was discovered that the active agent in the SARS virus was caused by the novel coronavirus which caused the name of the virus to become SARS-CoV due to the component of coronavirus that was attached to it. There were around 8,000 recorded cases of infection, from which about 700 - 800 resulted in death throughout the world over the past 10 years.

Tests performed since those outbreaks have demonstrated that there is a treatment for the disease and a vaccine can be designed against the virus. The host immune system can be made aware of the virus and the treatment can work by stopping any further progress inside the cell.

MERS

The recent outbreak of MERS (Middle Eastern Respiratory Syndrome) started off as a simple case. A patient experiencing respiratory complications was brought into Dr. Soliman Fakeeh Hospital in Jeddah and his condition was getting worse without any explanation. Dr. Ali Mohammed Zaki took a sample of the sputum and diagnosed the disease as one he had identified many times before. This case was different, however [15]. The normal tests performed were not positive for any of the known viruses as was expected.

The initial diagnosis was that the virus was a paramyxovirus, and in order to confirm this, the doctor contacted the Erasmus Medical College for assistance. The College had recent studies on paramyxovirus, but after analysis it was discovered that the virus was a strain of a novel coronavirus that had never been identified before.

The novel coronavirus, or as it has now been renamed to MERS-CoV, has been prevalent in much of the Middle East and Europe with the primary sites including the countries like Qatar, Jordan, the UAE and Saudi Arabia [16]. Secondary virus exposure has also been seen in the UK, France, Italy, Tunisia and Germany, believed to cause by some sort of human to human interaction. Middle East Respiratory Syndrome is closely linked to bat coronaviruses seen in China (BtCoV-HKU4 and BtCoV-HKU5) and is related to them phylogenetically.

The natural reservoir of the virus has not yet been identified; however, seeing as how it is so closely related to coronaviruses from bats, it is possible that it emerged from bats and their environment. SARS-CoV is thought to have the same reservoir. It is also thought that there was some form of transmutation to humans through domesticated pets and livestock; however that is yet to be proven by hard evidence [17].

Similarities between MERS and SARS

Based on the origin of SARS-CoV and MERS-CoV, there have been direct comparisons between the two. The molecular biology of both has been studied. The experiments have been performed via cell culture which has shown that the two viruses do not use the same receptor, ACE2, for entry and that MERS-CoV has a broader host range, making it more difficult to isolate. The structure of the two viruses is similar with the 5' two thirds of the genome used for replication while the 3' third of the genome has the spike, envelope, membrane and nucleocapsid proteins and four accessory genes [18].

The similarity between the two viruses are that they are both robust against type I interferon (IFN) even though MERS-CoV is seen as more sensitive to exogenous type IFN compared to SARS-CoV. The MERS virus affected human, primate, porcine and bat the infections occurring in the respiratory system epithelial cell [19]. There was also a case of endothelial cell infection which showed that there was a difference in the biology of the two viruses.

The MERS receptor is classified as dipeptidyl peptidase 4 (DDP4) based on mass spectrometry analysis of Huh7 cell proteins that are associated with the MERS spike protein *in vitro*. The receptor DPP4 is important in the infection of a non-permissive cell line where DPP4 has diverse functions in homeostasis, neurotransmitter function and modulation of cardiac signaling. For SARS, no enzymatic function is required for entry but the receptor is involved when SARS are attached [20]. *In vitro* virus entry was not seen for SARS and DPP4 was not a receptor part of the entry, however, no subsequent research was carried out in this issue.

Impact on the host

A transcriptional analysis shows that MERS affects several pathways during modulation of the infection. There is an immune response involving mitogen activated protein kinase (MAPK) but the virus reduces the inhibition of the MAPK. Studies show that SARS does not induce an early type-I IFN, which is seen in MERS where proteins are encoded that inhibit the sensing of the viral RNA during infection. The modulation and decrease in the inhibition explains the high mortality rate caused by MERS [21].

Some residents had direct contact with camels, and thus the isolated samples from them showed clear antibodies to MERS-CoV. However, the virus remained geographically confined within a specific area compared to other viruses. It is likely that humans initially transferred the virus to camels then bats, where it got mutated and then moved again between bats to camels and human. Based on viral evolution theory, the virus may have settled in the Arabian Peninsula for a period of time, due to Hajj and Umrah, or due to livestock trade (specifically of camels), and then somehow, as a result of repeated transfers between different breeds and families, it formed and mutated in a way that it produced MERS-CoV. Why was there no increase in human cases since early 2012, and then suddenly such cases began to

appear in this shocking way is a puzzling question. There are chances for new cases of animal origin to occur and the resulting variation may lead to a lack of control and diagnosis as well as the ability for the virus to infect humans. However, some of the cases of infection might be subjected to the wrong diagnosis and not reported correctly to the authorities.

So, how is it possible to explain these human cases with no direct exposure to animals? There are a number of cases registered with no exposure to animals like camels, which are definitely considered part of the strains that transmit the infection to humans.

Another question is raised: why is MERS-CoV found in camels with certain cases that are linked to humans? It seems reasonable that MERS-CoV infection in camels is not severe as the positive plasma test results offered to indicate a low rate. However, the rates may change accordingly among the population when the infection occurs at some point in life. Through the study of phylogeny, certain strains which originated in bats at some point in the past were found. It is also possible that there are some pets, or even a combination of animals, that may be the source of infection, but unfortunately nothing has been reported so far to confirm this notion.

The continuous viral evolution, and the transition between people, not only required transfer of the virus from an infected animal, but also a continuous transition of the virus from one human to another human, the time schedule of which can be estimated through evolution analysis of the virus. These human transmitted cases do not constitute an epidemic at this time, but the virus may be transmitted to and from the Arabian Peninsula through travels and the movement of people from one place to another. Results indicate that there is a wide range of coronavirus species in the Kingdom of Saudi Arabia; this is because of the fact that the MERS virus spread and mutated repeatedly in animals as an intermediate hosts.

Studies and estimates indicate a common ancestor of the MERS-CoV. A virus from South Africa has been existence for more than fifty years and probably longer, has been replaced. There are several hypotheses used in this context of simple analysis, but most probably they significantly concern certain strains, in addition to MERS; for example, the virus genome represents the maximum limit of coronavirus strains compared with SARS in which it is at the very least the same. Moreover, the genetic distance is considered a simple scale of nucleotide differences between them if compared with the length of the genetic sequence.

Are there successful cures?

Unfortunately, there are no adopted and effective anti-virus medicines; however, the Ministry of Health does provide treatment with Interferon which is used as an anti-virus medicine for most infectious cases of RNA viruses. Moreover, there are several pharmaceutical companies which now aim to develop some anti-disease drugs. It is important for us to know, from a scientific view point, that the coronavirus infection starts with Protein (S) that exists in the viral envelope, where it communicates changes with receptors on the cellular membrane that are supposed to have induced different mutations, and that this (S) protein leads to fusion. At this point, inhibition of infection must target this process. Accordingly, a cure developed to inhibit this step would be useful, as it would prevent fusion and entry into the cell. The focus should be on treatment instead of prevention because the virus can hardly be implanted in the lab, and accordingly it is rather difficult to form or produce a vaccine

that can weaken the infection and spread of the virus. But this is not impossible, as with developing modern molecular science, it is possible to manipulate formation of the virus in the lab, and modify the basic virus so that its ability to cause infection is disabled. Consequently there is the possibility of producing a vaccine. However, this research will be time consuming. Therefore, the first steps depend on development of a strategy to combat infection, along with minimizing risk of spread. Some drugs and suppressive agents are currently being produced, and are still being tested for anti-virus properties. Recently, however, the Ministry of Health has recommended the use of Interferon as a method to suppress spread of the virus inside the body. Fortunately, the drugs developed for treatment of the disease will also be effective in curing the common cold diseases such as influenza and other infectious pulmonary diseases.

With the virus currently now out of control, it is so difficult to limit its spread, because of the lack of clear strategies to do so. The Ministry of Health's decisions and precautions are very weak regarding limitation of the infection spread. Therefore, it is necessary to have the matter studied effectively, and put controls in place to protect the community from the spreading of this epidemic. It will be a paradox that the world will impatiently watch this race between the epidemic spreading and the development of active drugs and effective vaccines against it.

These coronaviruses that appeared in the Middle East and threatened public health on the global level will eventually inspire researchers and officials in the field of health to find solutions to combat this epidemic and prevent spread within communities. Moreover, thorough knowledge and the study of geographic distribution of species and strains is very important, because the virus may spread in limited extent, at least from one person to another, on a geographic range.

Most recently, the World Health Organization (WHO) has urged that the method of the diagnoses of virus extended to far-reaching countries all over the world, particularly focusing on human communities that suffer pneumonia, whether acute or chronic, especially among those personnel of the health sector [1]. Epidemiologists suppose that the threat is indistinct, and needs health surveillance and close epidemic protection through investigation and strict control of any new cases within human communities; new cases may be an indication that the virus has accommodated itself and spread more easily.

Treatment for MERS

Currently, there is no treatment or vaccination available for MERS, but as an outbreak has already taken place, developing a treatment or vaccine is of high priority. There are many therapies that have reduced or inhibited the protein production in cells and cell cultures but none have been tested *in vivo* due to a lack of appropriate models. One fact that has been considered is the similarity between SARS and MERS and the use of effective treatment against SARS. The MERS virus is protected from IFN alpha treatments but has shown signs of withdrawal when IFN beta was used *in vitro* [18]. Ribavirin, which is used for SARS, has also shown efficacy against MERS and has decreased the replication of MERS in humans

Drugs: Currently, there are no drugs or treatments that are able to treat any form of coronavirus. Some research has shown that disinfectants are successful to an extent with sodium hypochlorite and organochlorine the susceptibility shows 0.1%, for Iodophor has shown

a susceptibility of 10%, for glutaraldehyde 2% and for ethanol shows 70%. Resistance to a degree of 0.04% has been observed for quaternary ammonium compounds and phenolics. Ultraviolet light inactivation from exposure to about 1200 μ J/cm² for 30 minutes has also been effective. The virus can survive up to six days in water and up to three hours on dry surfaces after it has been exposed to an environment.

Diagnoses: The major complexity involved in the diagnosis of this virus is that it is prevalent as a mild virus that exists in the body, and therefore powerful testing is needed with isolation methods, electron microscopy and PCR-based assays. In diagnosis and prevention the best way is to carry out surveillance of the patients and monitor their condition for changes.

The World Health Organization disclosed that there were some cases in Saudi Arabia in which a number of people died, and coronavirus was uncovered in the samples, and reported that the disease involved respiratory symptoms [1]. This off course leads us to the first known emergence of the virus outside of Saudi Arabia and Qatar, when it was reported in Jordan.

Future research questions

This is a newly discovered virus about which further research is needed. Until recently the environmental reservoir of MERS had not been determined, and even though it seems to have been transmitted from bats, camels and goats, we still need to figure out how it originated and what the environmental factors are that are favorable for its sustained growth. So far, most of the patients who have been diagnosed with MERS have been older males.

This begs the question about a genetic susceptibility to the infection which is primarily triggered by age; however a link has yet to be established between age and prevalence of the disease. It also has to be determined whether this species of virus is new in both humans and animals or if it has been present in animals for a long time and has recently mutated and been able to infect human. This information will allow researchers to know how fast the transformation took place and how to address the issue for developing therapeutic strategies.

Studies have demonstrated that mouse cells are immune to this virus. However, this needs to be studied further to know whether it is the spike protein that doesn't bind to the DPP4 of the mice or if there are certain host factors that mitigate entry and replication in mice. Additional studies include evaluating whether future and further mutations of MERS can lead to further impact on the host body. The proteins that cause the disease can also be studied and their functions can be determined. Lastly, what is it about these few bat coronaviruses that have mutated into a form able to infect humans, and why has this not taken place before? Why is the virus growing in the Middle East and why does it have a mortality rate so much higher than any other coronavirus species? These questions must be quickly addressed.

Recent Studies on the Virus

The outbreak and prevalence of coronavirus in SARS led to more virologists becoming interested in a virus that was once ignored. Until 2003, it was thought that the coronavirus had two human strains manifested as HCoV-229E and HCoV-OC43. This new discovery added another strain into the equation. Following the discovery of MERS-CoV, subsequent research determined that there is also a fourth

human related coronavirus called NL63. The name have been given by different research groups, however, the characteristics of the strain are fairly identical.

In 2005, a fifth species of coronavirus was discovered in Hong Kong and named human coronavirus HKU1, and in September 2012, a sixth type was discovered in the Middle East and called MERS-CoV (although initially it was known as Novel Coronavirus 2012). There was little research supporting the transmission of the virus until 2013, when a case in France was seen was due to human to human transferring virus.

Further cases reported in Tunisia, and the recent outbreak of cases in Saudi Arabia do point towards human-to-human transferability of this virus, following the appearing of 124 cases of the new virus that emerged in Saudi Arabia leading to 52 deaths it renamed Human Corona Virus Erasmus Medical Centre (HCov-EMC) after the center that discovered the sequence of the virus. It was later changed to Middle East respiratory syndrome coronavirus (MERS-CoV).

Meanwhile, there were no increase in human cases until early 2012, then suddenly such cases began to appear again and chances for new cases of animal also occurred as a result of the variation subjecting humans to infection. Accordingly, some of the MERS-CoV cases may be subjected to the wrong diagnosis, as it might be assumed that it is another disease and therefore, not reported correctly to the authorities.

So, how it is possible to explain these human cases that did not have any exposure to infected animals? There are a number of cases registered with no exposure to animals like camels, which are definitely considered part of the strains that can transmit the infection between people.

MERS-CoV was found also in camels with certain cases that are linked to humans. It seems reasonable that MERS-CoV infection in camels is a severe and moderate infection at the same time, but at a low rate, as stated earlier. It is important to know that the virus spread is very low through direct contact with an infected person (via air and droplet transmission). In order to determine this, samples have to be collected and suspected animals have to be quarantined away from healthy ones. If the strains are isolated from camels through arbitrary surveillance all over the Arabian Peninsula without uncovering any antibodies, then we will show that camels can be a virus host and might constitute the source of infection. Until this matter is proven, another hypothesis arises which is the possibility of another animal as the source of infection. Through the study of phylogenetic trees, similar strains were present in bats at some point in the past, but it is also possible that some pets or a mixture of animals may constitute the source. Unfortunately, however, nothing has been reported so far on this issue.

Transmissions and MERS-CoV

MERS-CoV has three known ways of spreading or transmission which are by; direct contact, air and healthcare workers (Table 1 and Figure 3). Forty seven percent (47%) of cases were infected by one of the known methods, whereas other cases have unknown source of transmission.

Table 1 and Figure 3 illustrated that the 15% is the transmission through healthcare worker cannot be ignored, as the results they must follow the CDC guiding to prevent the infection. The highest rate of infection is from the air that is in hospital and public places without contacting with infected cases.

Infection	n (%)	Asymptomatic *n/all asymptomatic cases (%)	Median age	Sex ratio (M/F)
Direct Contact	258 (16%)	52/140 (37%)	39 Years *3 Missing data	135/110
Air	286 (17%)	5/140 (4%)	60 Years	181/83
Healthcare Worker	240 (15%)	52/140 (37%)	37 Years *4 missing data	95/98
Total	784 (47%)	109/140 (78%)	45 Years	411/291 *4 Missing data

Table 1: Details of MERS-CoV infected cases by method of transmission.

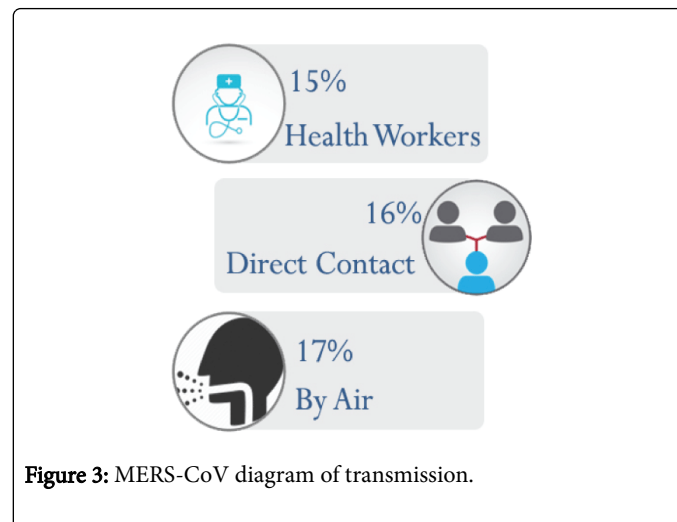


Figure 3: MERS-CoV diagram of transmission.

Animals and MERS-CoV

There was a claim that the camels are the sources of MERS-CoV, where the statistics rejects this claim even though some studies on the virus isolation or PCR confirmation recommended investigation of other animals' sources. The percentage of cases reported to be due to contact with camels or the consumption of raw camel milk is only 5%. Whereas 2.5% of the cases were reported to be due to contact with different types of other animals (sheep, pigeons, ect) (Figure 4).

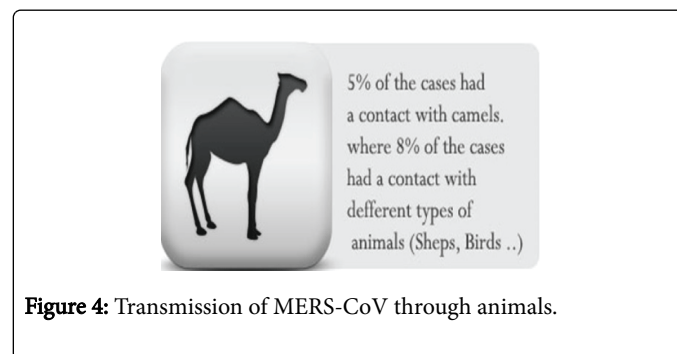


Figure 4: Transmission of MERS-CoV through animals.

Studies indicate that there is a wide range of coronavirus species in Saudi Arabia, in spite of the fact that MERS spread and are repeatedly

mutated among animals (intermediate hosts), through its origin has yet to be confirmed. The bats and rats may also have played an important role in the dramatic transition to this type of virus. However the role of rats was only hypothesized by a specialist who searched the ventilation operations for rodents. The hypothesis was that the virus spread through ventilation holes from rats breeding inside the vents in hot rooms or in camel farms, which would be the optimal source of transmission if rats can be proven as a primary host. However, this hypothesis has not been researched enough to prove it, making it under wraps and under a lot of question as that did not attract enough attention minimizing the search for knowledge to answer them on finding solutions.

Studies and estimates pointed to common ancestor of the MERS-CoV and South Africa which have been in existence for more than fifty years, and probably longer. There are several hypotheses used in this context of simple analysis, but most probably they significantly affect certain strains.

Evolution of the Virus

Another task carried out by virologists was to find how the virus came about and when the virus occurred previously. Research has determined that there is an ancestor of the virus that can be dated back to around 10,000 years from today, and it is likely that the virus could have originated even before that. The most recent common ancestor of the alpha, beta, gamma and delta coronaviruses can be dated to between 2400 BC and 3300 BC.

The virus is highly prevalent in warm-blooded flying vertebrates which could have made bats and birds the perfect hosts for this virus in earlier times. The evolution of the virus could have started from there, with the alpha and beta coronaviruses prevalent in bats while the gamma and delta coronaviruses were seen in birds. Through these two animals, the virus could have evolved a recombination in the state that it is in today and the distribution of the virus could have taken place through this channel as well.

It is useful to know that weakening viruses in which the nucleic acid or a genetic RNA increases the paths changes and then mutate, with the ability to jump to the human races over and over again. However, analysis of the emergence and evolution of the genome, and the representation of the phylogenetic tree arbor between different species Figure 5, where gene sequencing and protein in isolation, can indeed explain aggregates discrete the associated relation of coronaviruses, and the exact locations that represent the similarities and differences, and thus clarifies the relationship between correlated and non-correlated species. The evolution and the transition between populations not only require the transfer of the virus from an infected animal to another animal or human but it should occur throughout the timetable estimated by the evolution of the virus. It is useful to know that studies of the evolutionary relationship between viral species via

molecular phylogenetic analysis and molecular epidemiology indicates that the virus had continued over a period of time and was associated geographically with a certain area.

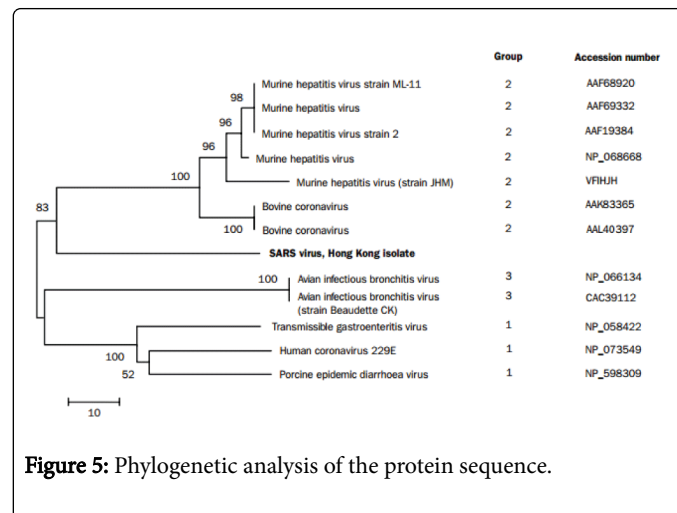


Figure 5: Phylogenetic analysis of the protein sequence.

Precaution and Avoidance

The virus is seen as one that is not very risky; however, its mild nature can make it dangerous as time goes on. In order to contain it, level 2 facilities, equipment and operational practices are required. These protect against any infectious or potentially infectious materials from coming into contact in the laboratories. These precautions are applied to all species of the virus as they are all categorised under the same heading and protection. Protective guidelines have already been approved by CDC and then distributed to people who come in contact with the virus; these people are required to wear lab coats, as well as gloves to protect from direct contact with the skin, and eye protection for any splashes that might take place.

In cases where aerosols are produced or there is a high concentration of the virus, a biological safety cabinet should be used for any sample handling, and the use of needles, syringes and other sharp objects should be minimized. In order to protect people from exposure to the virus, visits to areas that have reported to have a high prevalence of the virus should be minimized, and people should be evaluated by health care institutions when exiting those countries.

Statistical Analysis

First cases infected by virus

Table 2 shows the first infected cases by Coronavirus.

Country	Date	Details
Jordan	21-Mar-2012	40 years female nurse working in a hospital in Azzarqa City, she nursed a male patient (25 years) who was the first case in the world in 21-Mar-2012. In 30-Nov. 2012 after Saudi Arabia Announced that they discover a new family of coronavirus. Jordan's Ministry of health announced their two cases. The cases cause of death was not defied yet
Saudi Arabia	5-Oct-2012	The first infection in Saudi Arabia was in Al Hassa for 2 Family member of an infected case how developing symptoms and died.

Tunisia	22-May-2013	Two cases male (34) and female (35) had a contact with their father who got sick after visiting Qatar and Saudi Arabia though the father's test was negative for Mers-Cov
Italy	25-May-2013	45 male travelled to Jordan
France	23-Apr-2013	64 years old Male was infected; he was in Dubai in United Arab Emirates
United Kingdom	26-Jan-2013	A 60 years old male UK resident, the patient had a history of travel to Pakistan and Saudi Arabia
United Arab Emirates	18-July-2013	In 18-Jun.2013 a 28 years health worker male was infected and there is no data about the transfer of the first case in Emitters
Oman	7-Nov-2013	The first infected case in Oman was a 75 years old male who travelled to United Arab Emirates
Netherlands	1-May-2014	70 years male his symptoms appears while he was in Saudi Arabia, then he travelled to Netherlands
Iran	11-May-2014	52 years old female, she contact with a case that had Omrah and was sick with Influenza
Korea	11-May-2015	68 years male who travel history: 18-29 April, Bahrain; 29-30 April, United Arab Emirates; 30 April to 1 May, Bahrain; 1-2 May, the Kingdom of Saudi Arabia; 2 May, Bahrain; and 2-3 May, Qatar. He flew to Korea from Qatar on 4-May.
United States	14-Apr-2014	A 60 years resident male work in Riyadh was infected and traveled to Chicago
Lebanon	22-Apr-2014	A 60 years male Health worker who had travelled to the Gulf region (United Arab Emirates – Kuwait – Saudi Arabia)
Egypt	22-Apr-2014	27 years old male who lived in Saudi Arabia for 4 years
China	21-May-2015	44 years male from Korea he was a son and a younger brother for two cases in Korea. He traveled to China

Table 2: Shows first cases of MERS-CoV among the countries and the date of each case that had been reported.

Coronavirus affected 11 countries (Saudi Arabia, UAE, Qatar, Kuwait, Oman, Jordan, Tunisia, Italy, France, Britain, and Germany). A recent study indicated that there were more cases that likely went unreported. Researchers and healthcare specialists believe that for every confirmed case of coronavirus, 5 to 10 cases may go unreported. This is especially true for cases with mild symptoms that do not require intensive care.

Since March 2012 to the end of November 2015, a total of 1655 were reported and the virus has been detected in Arabian Peninsula; European countries such as Britain, Germany, France, Italy and Middle East (Table 3).

Country	Infected Cases	Deaths	Mortality rate %	Recovered*	
Middle East	Saudi Arabia	1308	501	38.3	470
	United Arab Emirates	78	12	15.38	5
	Jordan	22	8	36.36	
	Qatar	13	5	38.46	4
	Oman	8	3	37.5	1
	Kuwait	6	1	16.67	
	Iran	6	1	16.67	1
	Lebanon	1	0	0	1
	Yemen	1	1	100	0
	Egypt	1	1	100	0
	Turkey	1	1	100	0

East Asia	Korea	186	36	19.35	145
	China	1		0	
Southeast Asia	Malaysia	1	1	100	0
	Thailand	1		0	
	Philippines	1		0	
Maghreb	Tunisia	3	2	66.67	
	Algeria	2	1	50	
European	United Kingdom	3	2	66.67	1
	France	2	1	50	
	Netherlands	2		0	
	Germany	1	1	100	0
	Austria	1	0	0	1
	Spain	1	0	0	1
	Italy	1		0	
	Greece	1		0	
Americas	United States	3		0	
Total		1655	578	34.98	630
*not all data is available					

Table 3: Show number of cases, deaths and recovered, the mortality rates were shown during March 2012 to Nov 2015.

There have been 75 reported deaths from the virus in Middle East, Korea, Malaysia, Maghreb, United Kingdom, France and Germany which constitute a mortality rate of 42.134% compared to the Middle East, mainly in Saudi Arabia which had 81% of deaths (Figures 6 and 7).

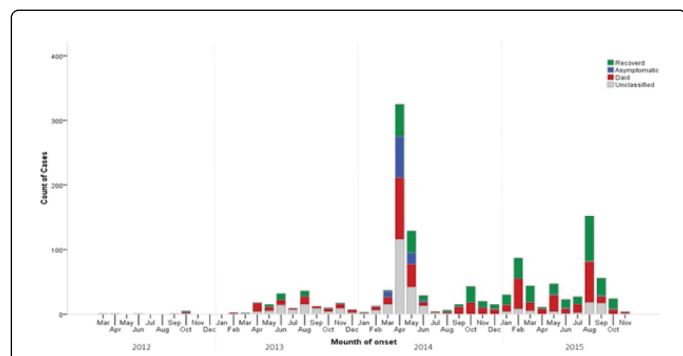


Figure 6: Distribution in the Middle East by month between March 2012 to Nov 2014 (n=1314). * Month of the onset is unknown, month reporting has been used.

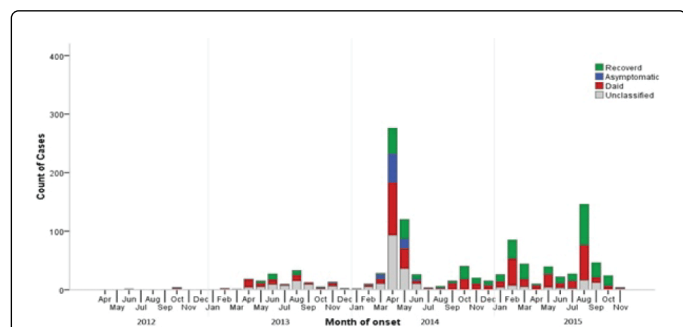


Figure 7: Distribution of confirmed cases in Saudi Arabia by month of onset* and patient status, from March 2012 to Nov 2014 (n=1176). * Month of the onset is unknown, month reporting has been used.

Saudi Cases distribution by geographical location

The geographical distribution in Saudi Arabia has been studied in detail to find out if MERS-CoV affected by geographical location or not, it can be also affected by wells and agricultural areas.

Geographical location in Saudi Arabia: Dammam, Al-Ahsa, Riyadh, Dubai, Doha and Asir are located between longitudes 36.55 and 17.25 latitude and 26.5, these areas were often characterized by severe drought and desertification, according to the Gulf States, which are known to be the desert climate.

Wells and agricultural areas in Saudi Arabia: From other studies the relationship in agricultural activities shows that kingdom turned out to have been more areas with wells used by humans and those are Asir, Mecca, Medina, Riyadh, Eastern Province, Tabuk. It is possible that these wells can be a factor or broker assistant for the transfer of the virus from the air with the help of the bat or rate or any other factors such as farmers irrigating their farms and using them for cattle drink (Table 4).

Region	Cases
Riyadh Region	617
Mecca Region	361
Eastern Region	164
Madinah Region	61
Najran Region	26
Qassim Region	19
Jouf Region	18
Tabuk Region	16
Aseir Region	16
Northern borders Region	3
Hail Region	2
Al-baha Region	1
Total	1304

Table 4: Distribution of the reported cases in Saudi regions.

The geographical location of viral infections has occurred between longitudes 36 and 55 and latitudes 17.25 and 25.6 (Dammam, Al-Ahsa, Riyadh, Dubai, Doha and Asir), and these areas are often characterised by severe drought and desertification.

The Figure 8 shows the number of cases by each region. First case reported in Saudi Arabia was in Bisha in Asier Region was on Jun 2012. The next cases were reported on Oct 2012 in Alahsaa in Eastern Region, whereas on Apr 2013 the virus spread in the eastern region and on Feb 2013 the first case was reported in Riyadh region. In Jun 2013 the viruses spread in the Riyadh region and in the same month a new infected case was reported also in Mecca Region, but the spreading appeared to be during Apr 2014. For Medina Region the first case was report on Aug 2013.

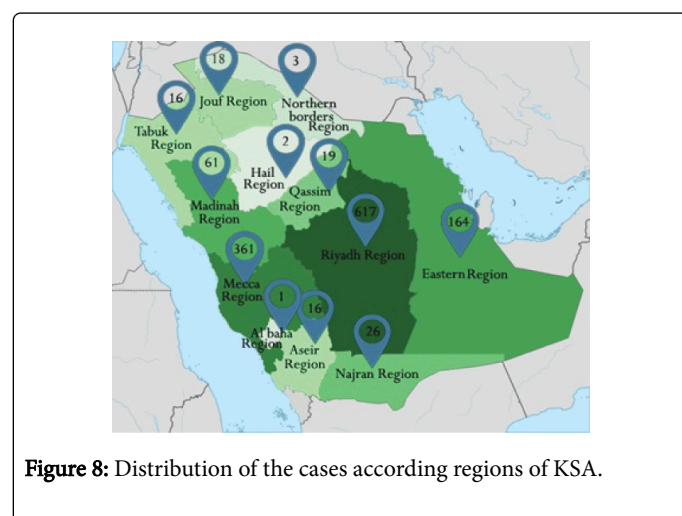


Figure 8: Distribution of the cases according regions of KSA.

The role of wind in the spread of this disease cannot be neglected, as most cases involving the 45 Saudis infected were in the summer, where blowing in the summer wind North West, North and North East wind direction of the Kingdom. It is known that influenza virus spreads in one season more than the other. The majority of coronavirus spread occurs in the winter and autumn, but in general the virus has spread further in the year that has passed since its discovery. The seasonal variation in the occurrence of MERS cases in Saudi Arabia is shown in Figure 9.

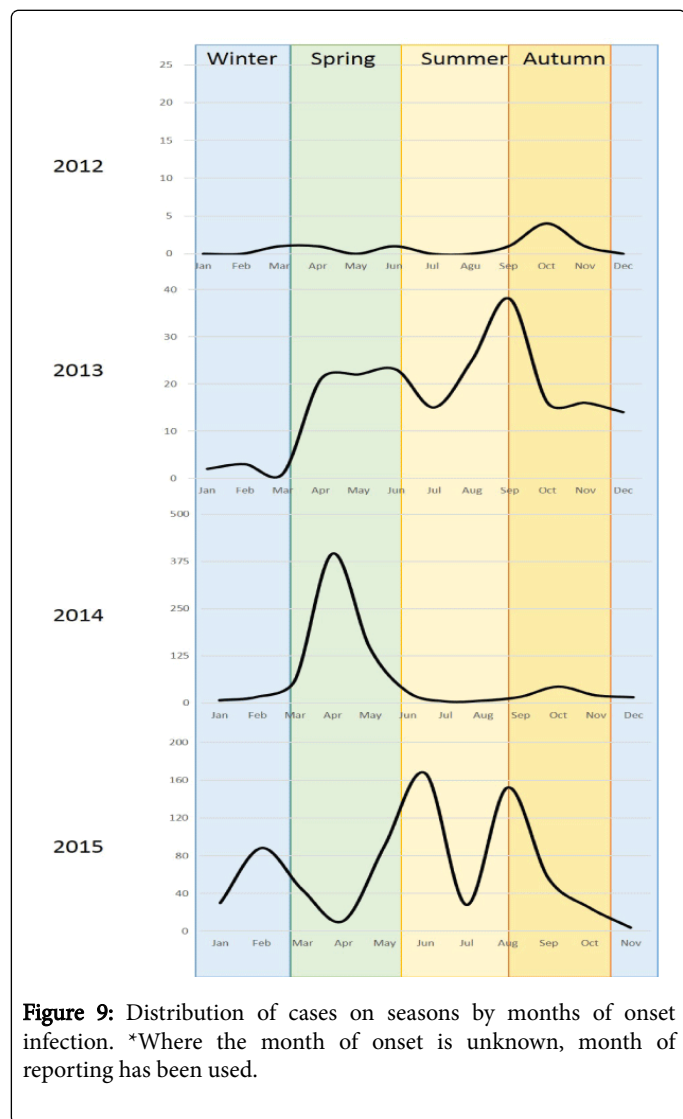


Figure 9: Distribution of cases on seasons by months of onset infection. *Where the month of onset is unknown, month of reporting has been used.

The Figure 9 shows that more cases occur in the spring, which accounts for 36% of the cases, followed by the summer (31%), while the spring represents 28% and the winter 5%. Through studies, the causes of the new coronavirus can direct infected cases and might be mixing with some of the animals, as well as the traveler to one of the countries affected.

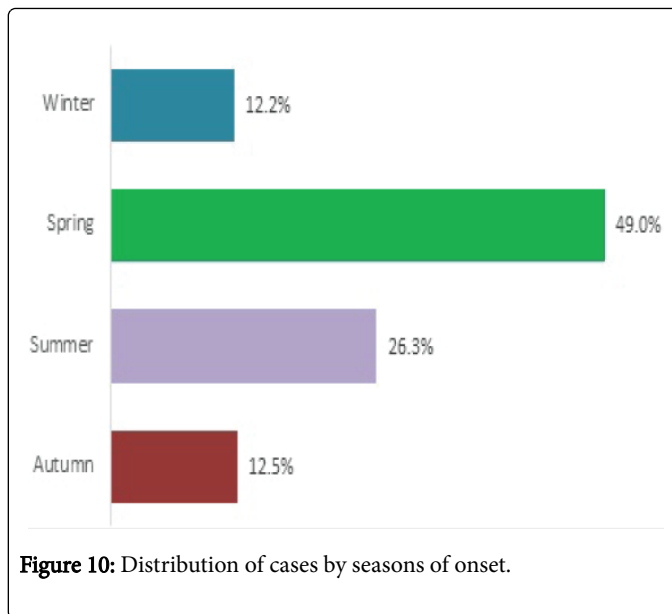


Figure 10: Distribution of cases by seasons of onset.

As shown in Figure10 most of the cases were get infected in spring (810 cases of 1655), while (437) were infected in summer, which indicate that spreading of MERS-CoV differs and associated to season. Although, the prevalence of spreading of the virus, shows 49% of cases occur in the spring, followed by 26.3 % in summer.

Figure 11 shows comparisons of MERS-CoV infection between age and sex and that the incidence in males and females by 25%. More casualties for both sexes occurred between the ages of 30 and 80 years, which comprised 77% of the total cases.

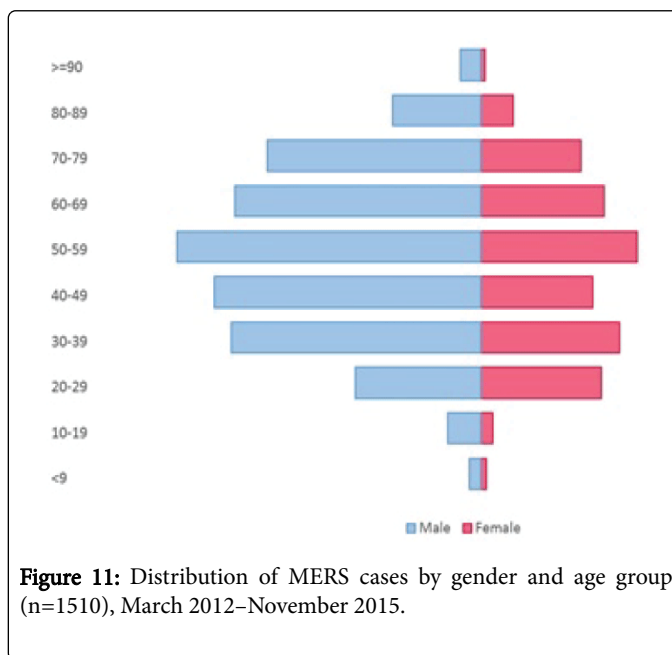


Figure 11: Distribution of MERS cases by gender and age group (n=1510), March 2012–November 2015.

Figure 12 shows MERS-CoV cases were more among males with a percentage of 66% (993 cases of 1510 cases) whereas the middle age was distributed between 50 to 69 years old in both male and female.

It makes sense that people would be increasingly predisposed with advancing age, as a person's immunity naturally decreases with the age increasing and also, because of the burden of chronic diseases such as diabetes, heart or kidney and respiratory disease.

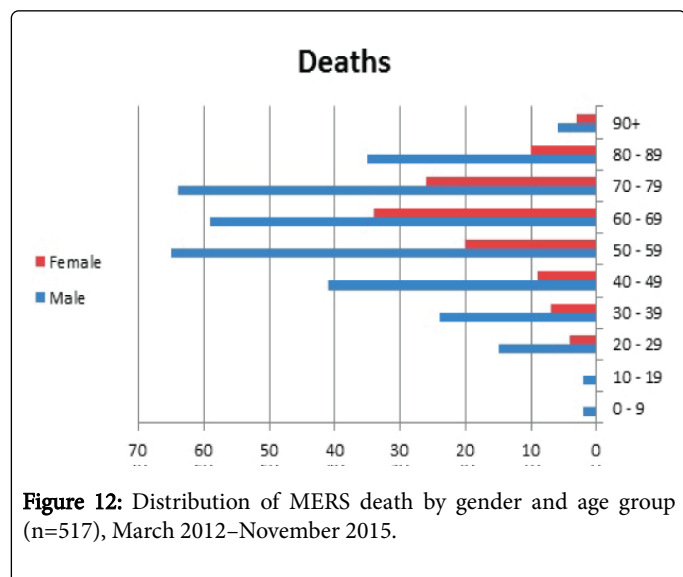


Figure 12: Distribution of MERS death by gender and age group (n=517), March 2012–November 2015.

Most of the MERS-CoV deaths were in males with percentage of 73 (379 deaths of 517 deaths). The mean of age for the cases were 63 years old, the deaths were mostly in the age between 50 to 69 years old for each male and female, as shown in Figure 12.

As for the differences in gender in Saudi Arabia, it may be that females in the Kingdom wearing veils which might have prevented against infection, as the covering protects the nose and mouth from exposure to air pollution or to carriers of the virus as they were only comprised of 35% from the total cases in Saudi Arabia.

The higher proportion of infected males occurred for many reasons: they travel to work and spend most of their time outside the home in order to earn a living for their families, and are therefore, in contact with a large number of people.

The month of April of 2013 (the spring) marked the beginning of the high number of casualties. The reason for the weakness of its spread or how it is transmitted is limited. It was expected to increase these cases during the months of November and December of 2013, where a delegation of 3 million pilgrims to Saudi Arabia in October come to perform the Hajj, but the injuries in these two months were not expected (without any reported cases).

The previous Figures demonstrate that the trend in mortality rate was high at the beginning of the infection, and then it gradually declined and the rate of males is 46% higher than females. Meanwhile the overall mortality rate was 73% in both males and females and a deaths mostly occurring in those who are above 50 years old (Table 5).

German researchers published a study the Virology Journal which showed a relationship between this virus and kidney disease, where about a thousand weak versions of what is produced in the bronchial cells. Through this study, scientists found that infection occurs when the virus reaches only kidney cells, in cases where the disease doubles, and leads to kidney failure.

Region	Deaths	Recovered
Riyadh Region	216	236
Mecca Region	108	66
Eastern Region	78	62
Madinah Region	19	16
Najran Region	9	13
Qassim Region	14	4
Jouf Region	4	10
Tabuk Region	4	5
Aseir Region	4	2
Northern borders Region	1	2
Hail Region	2	0
Al-baha Region	1	0

Table 5: Shows numbers of reported death and recovered cases from different areas in Saudi Arabia during March 2012 to November 2015. From regions of Eastern Province, Riyadh Province, Asir, Al Madinah, Makkah region and Al-Jouf, Qassim region. Some of the cases were reported missing.

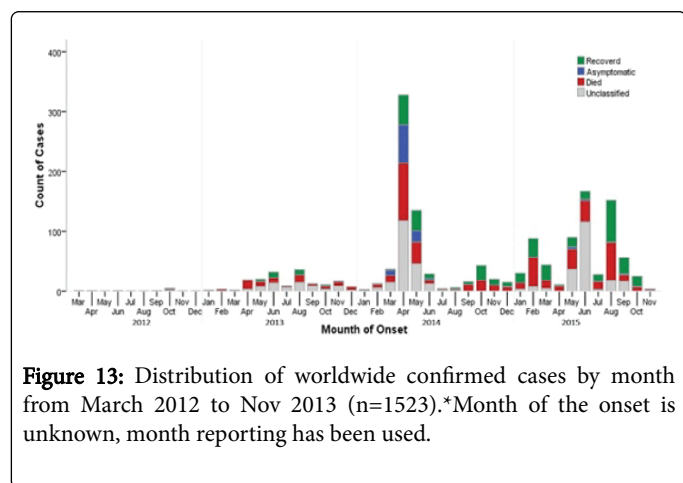
Discussion and Recommendations

Initially coronavirus was not known among the general public as it because known only during the period when researcher had to understand the complexity of this virus and could not determine the period of appearance or accurate source or method of transmission. There has been a lack of community awareness about the disease and the spread of rumors without a reliable source, with only social networking and personal correspondence that have allowed people to understand how this virus can be transitly. However, data collected from all reliable and available on-line sources provide only limited statistical information which can't explain how the virus is transmitted. Prevention by following precautions according to the CDC and infection control was the only way to control viral spread. The limited knowledge was the reason for further studies. A study was performed by Dudas and Rambaut (2015), with the hope of finding a correlation between immunity and MERS evolutionary process [22]. Those authors studied recombinant MERS to investigate excessive homoplasies, decay of linkage disequilibrium and the presence of alternative topologies, and their study showed that the MERS genome has well-supported alternative tree topologies and some degree of rate heterogeneity. Their ancestral sequence of the reconstruction indicates excessive numbers of homoplasies in the MERS genome and the host-polymorphism association analysis data did not show the presence of "human" or "camel" alleles, but the samples size was also too small to address the question in great detail. Their heterogeneity and tree topologies appeared to support a model with rate heterogeneity introduced by another phylogenetic tree.

However, a study by Cotton in 2013 (who described and sequenced a number of MERS-CoV full genomes) tracked viral transmission in greater detail. Multiple introductions of MERS-CoV were identified and the study suggested lower R0 values. The estimation of the

evolutionary rate for the expanded number sequences showed MERS-CoV evolving at 6.3×10^{-4} substitutions/site per year (95% highest posterior density, HPD, 1.4×10^{-4} to 1.1×10^{-3}), establishing the time of the most recent common ancestor for clade B (excluding EMC/2102 and Jordan-N3) as July, 2011 (95% HPD July, 2007, to June, 2012). Transmission within Saudi Arabia is consistent with either movement of an animal reservoir, animal products or infected people. Other studies illustrated that the virus spread to other countries by infected travelers moving among countries, however, the exposures responsible for the sporadic introductions of MERS-CoV into the human population must be further investigated. Hence, countries are advised to take precautionary measures and examine visitors from infected or endemic countries before allowing their entrance.

Statistical studies have shown that cases of infections and death within the geographic region were associated with the mode of transmission, and these studies were able to count the number of confirmed cases and deaths worldwide since the onset of the disease in September 2012 until November September 2015. The impact of geographic areas on the infection in a particular source could be found by using a map of Saudi Arabia. The impact of the seasons indicated by fall coronary syndrome which suggest a spread during the fall and winter period while, the inventory of cases showed that more cases were spread in spring and summer. The analysis of the effect of age and gender on infection indicated that males are more susceptible to infection with the virus. This may be due to several reasons such as the nature of Arab communities, the male rate increases compared to female; in addition to that most of the Saudi females wear a veil, which can protect the body from infection through the nose or mouth. Also they may have found that infection increases among the elderly and those who are greater than 40 years of age; the elderly are more prone due to weaker immune systems and the fact that they tend to have more chronic diseases. It is recommended that the an environment be created to analyze the viral impact on the health work fares and to allocate research specialized medical crew who do the work in an environment increase their susceptibility to infection because of mixing with cases where suspected and confirmed cases in the laboratory could be considered as factor Assistant to the spread of the virus by being carriers of the disease to the patients. The extent of the spread of this virus is shown in Figure 13 the number of cases from March 2012 until November 2013 demonstrates the extent of viral spread during those twenty months.



As shown in Figure 13, the highest peak in the cases in April 2015 which include 395 cases, most of them were from Saudi Arabia (342 cases). The next peak was in Jun 2015, which includes 167 cases; most were from Korean of (134 Cases).

Since March 2012 until November 2015 the total numbers of recovered cases were 630, death were 579 cases, whereas the total numbers of asymptomatic cases were 140 worldwide.

Throughout the cumulative curve for the number of cases and deaths that the virus is relatively risky in terms of proportion and that the highest morbidity and mortality is among the elderly. The extent and seriousness of the virus is shown in Figure 14 which demonstrates the cumulative curve of infections and deaths in Saudi Arabia compared to the world over those months.

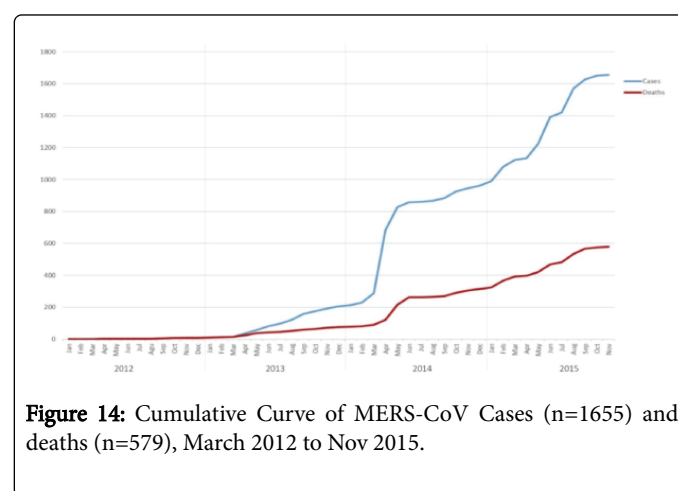
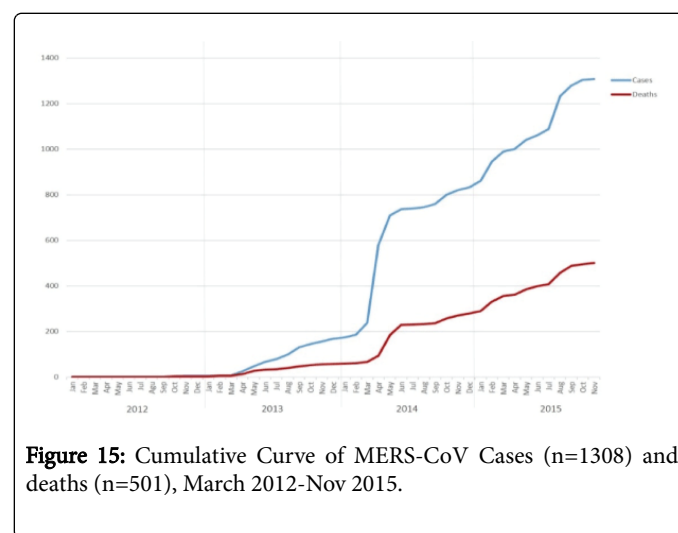


Figure 15 shows the cumulative curve of cases describing the way of MERS-CoV spread and how fast it does, MERS-CoV is increasing by each month and more shown in 2014, but it became slower in 2015. On the other hand, the curves of deaths represent the risks of the virus, at the beginning of the virus mortality rate was very high, then it became less according the years.



A sensitivity and specificity account at the negative error rate "False Negative Error Rate", and the positive error rate "False Positive Rate", for the diagnosis of cases is needed to found if the samples available to find out if the proteome analysis of immunologic polymorphism in symptomatic and asymptomatic MERS-CoV infections among the Saudi population can guide a comparison of the immunological markers with different ORF polymorphisms that correlates with symptoms and syndromes. Due to insufficient information about the molecular evolution of MERS-CoV and how this relates to virus transmission, a hierarchical cluster analysis (HCA) with a further definition for phenotypic consequence of the virus variants could also be useful for tracking transmission between animals and humans. Climate change causing waves of dust, which occur frequently within the Arabic Peninsula, can also encourage spreading of the virus. The impact of climate change in the production of new viral strains, as happened in 1990 in the southeastern United States where this led the phenomenon known as El Nino and increased rainfall, in addition to the increasing amounts of waste which rodents feed on to increasing their numbers, thereby proportionately increases human exposure.

Controlling and creating guidelines is the only way at the moment to prevent the community from spreading of the virus. It should be clear by now that gene expression of MERS-CoV repetition entails on frame shifting at the ribosomes through translation and that these types of viruses are unique among RNA viruses. Through genetic development studies, it was obvious that coronaviruses have the characteristic of reverse genetic systems, have hosts such as mammals and birds, and cause respiratory and intestinal tract diseases. Coronavirus normally infects species in a specific manner, and it can be an acute or persistent infection. The infection is mainly transmitted through respiratory tract secretions, or through the fecal-oral route in some cases. Perhaps what distinguishes this family of viruses is that it is the largest among all of the genomes of viral RNA, and additionally the different types of coronaviruses cause colds in 15-30% of cases, which are common in the winter. Some studies have shown that older patients can have the infection in the lower respiratory tract. However, the coronavirus mutated and merged with others within its family is considered the most lethal strain.

Summary of Results of MERS-CoV

The summary of results is shown in Tables 6 and 7.

	World	Middle east	Saudi Arabia	Middle without Arabia	east Saudi
Cases	1655	1445	1308	137	
Deaths	579	534	501	33	
Mortality %	34.98	36.96	38.3	24.09	
Recovered	630	482	470	12	
Percentage of Recovering	38.07	33.36	35.93	8.76	

Table 6: Comparison of results between World, Middle east, Saudi Arabia, Middle east without Saudi Arabia.

	Saudi Arabia		Worldwide	
	Deaths	Cases	Deaths	Cases
General percentage %	86.35	79.03	-	-
Median age	63 *60 Missing	52 *140 Missing	63 *63 Missing	52 *143 Missing
Male Rate %	64.47 *56 Missing	58.49 *137 Missing	65.8 *60 Missing	65.46 *138 Missing
> 50 years %	67.66	47.17	67.88	47.85

Table 7: Comparison of results between world and Saudi Arabia.

References

1. <http://www.who.int/en>
2. Ministry of Health (KSA) Command and Control Center (2014) Command & Control Center (CCC).
3. <http://www.cdc.gov>
4. <http://www.ecdc.europa.eu/en/Pages/home.aspx>
5. Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, et al. (2003) Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 361: 1767-1772.
6. Peiris JS, Lai ST, Poon LL, Guan Y, Yam LY, et al. (2003) Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 361: 1319-1325.
7. Rota PA, Oberste MS, Monroe SS, Nix WA, Campagnoli R, et al. (2003) Characterization of a novel coronavirus associated with severe acute respiratory syndrome. *Science* 300: 1394-1399.
8. Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, et al. (2003) A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 348: 1953-1966.
9. Marra MA, Jones SJ, Astell CR, Holt RA, Brooks-Wilson A, et al. (2003) The Genome sequence of the SARS-associated coronavirus. *Science* 300: 1399-1404.
10. Drosten C, Gunther S, Preiser W, van der Werf S, Brodt HR, et al. (2003) Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 348: 1967-1976.
11. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, et al. (2003) Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 426: 450-454.
12. Guan Y, Zheng BJ, He YQ, Liu XL, Zhuang ZX, et al. (2003) Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science* 302: 276-278.
13. Cotton M, Watson SJ, Zumlab AI, Makhdoom HQ, Palser AL, et al. (2014) Spread, Circulation, and Evolution of the Middle East Respiratory Syndrome Coronavirus. *mBio* 5: e01062-13.
14. Lai MM, Cavanagh D (1997) The molecular biology of coronaviruses. *Adv Virus Res* 48: 1-100.
15. Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, et al. (2013) Hospital outbreak of Middle East respiratory syndrome coronavirus. *N Engl J Med* 369: 407-416.
16. Agnihothram S, Gopal R, Yount BL, Donaldson EF, Menachery VD, et al. (2014) Evaluation of serologic and antigenic relationships between Middle Eastern respiratory syndrome coronavirus and other coronaviruses to develop vaccine platforms for the rapid response to emerging coronaviruses. *Journal of Infectious Diseases* 209: 995-1006.
17. Reusken CB, Haagmans BL, Muller MA, Gutierrez C, Godeke GJ, et al. (2013) Middle East respiratory syndrome coronavirus neutralizing serum

-
- antibodies in dromedary camels: A comparative serological study. *The Lancet Infectious Diseases* 13: 859-866.
18. de Groot RJ, Baker SC, Baric RS, Brown CS, Drosten C (2013) Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. *J Virol* 87: 7790-2.
19. Memish ZA, Zumla AI, Al-Hakeem RF, Al-Rabeeh AA, Stephens GM (2013) Family cluster of Middle East respiratory syndrome coronavirus infections. *N Engl J Med* 368: 2487-2494.
20. de Wit E, Rasmussen AL, Falzarano D, Bushmaker T, Feldmann F, et al. (2013) Middle East respiratory syndrome coronavirus (MERS-CoV) causes transient lower respiratory tract infection in rhesus macaques. *Proceedings of the National Academy of Sciences* 110: 16598-16603.
21. Hayden FG, Farrar J, Peiris JS (2014) Towards improving clinical management of Middle East respiratory syndrome coronavirus infection. *Lancet Infect Dis* 14: 544-546.
22. Dudas G, Rambaut A (2015) MERS-CoV recombination: implications about the reservoir and potential for adaptation. *Biorxiv*.