Introduction :

Coronaviruses are common viruses that most people get some time in their life. Human coronaviruses usually cause mild to moderate upper-respiratory tract illnesses.

Coronaviruses are named for the crown-like spikes on their surface. There are four main sub-groupings of coronaviruses, known as alpha, beta, gamma, and delta.

Human coronaviruses were first identified in the mid-1960s. The six coronaviruses that can infect people are: alpha coronaviruses 229E and NL63, and beta coronaviruses OC43, HKU1, SARS-CoV (the coronavirus that causes severe acute respiratory syndrome, or SARS), and MERS-CoV (the coronavirus that causes Middle East Respiratory Syndrome, or MERS).

There are many coronaviruses that naturally infect animals. Most of these usually infect only one animal species or, at most, a small number of closely related species, but not people. However, SARS-CoV can infect people and animals, including monkeys, Himalayan palm civets, raccoon dogs, cats, dogs, and rodents. MERS-CoV has also been found to infect people and animals, including camels and bats.

In late 2012, a novel corona virus that had not previously been seen in humans was identified for the first time in a resident of the Middle East. The virus, now known as the Middle East Respiratory Syndrome Corona virus (MERS-CoV), has caused more than 50 laboratory-confirmed cases of human infection. Thus far, all patients infected with MERS-CoV have had a direct or indirect link to the Middle East, however, local non-sustained human-to-human transmission has occurred in other countries, in people who had recently travelled to the Middle East.

since 2012 it has resulted in cases in 23 countries in four continents. The majority of these cases

were reported from the Kingdom of Saudi Arabia. The disease caused a spectrum of illness, from asymptomatic to severe and possibly fatal

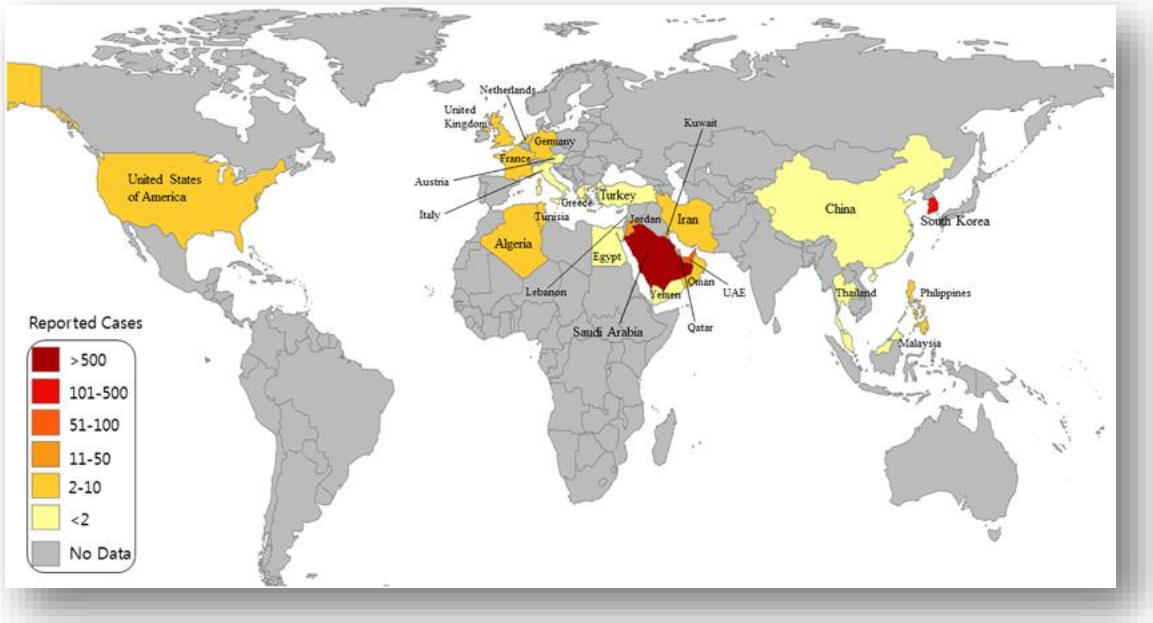
disease.

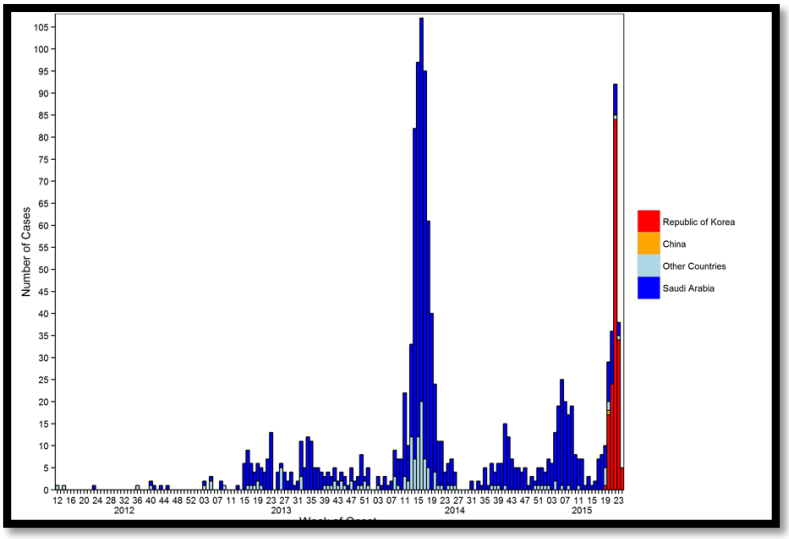
The first Middle East respiratory syndrome corona virus (MERS-CoV) case was a 60-year old Saudi businessman, previously healthy, non-smoker. He was admitted on 10 June 2012 to a local hospital in Bisha, Kingdom of Saudi Arabia (KSA) with 1-week history of cough, fever and shortness of breath.

Epidemiology and distribution :

Globally, as of November 2014, the virus has been reported in 23 countries in four continents. The number of countries reporting MERS-CoV in the Middle East is 10 (Saudi Arabia, United Arab Emirates, Qatar, Jordan ,Oman, Kuwait, Egypt, Yemen, Lebanon ,Iran), eight countries in Europe (Turkey, Austria ,UK, Germany, France, Italy, Greece, The Netherlands) and other countries including Tunisia, Algeria, Malaysia, the Philippines and the USA

In the KSA, from 1 June 2012 to 18 September 2014, there were a total of 748 MERS cases reported.





Introduction to the virus :

Corona viruses are a large family of viruses that can cause a range of illnesses in humans, from the common cold to severe acute respiratory syndrome (SARS). These viruses also cause disease in a wide variety of animal species

Corona viruses are medium-sized, enveloped, positive-stranded RNA viruses , crown-like appearance in electron micrographs

These viruses have the largest known viral RNA genomes, with a length of 27 to 32 kb

Replication of viral RNA occurs in the host cytoplasm by a unique mechanism

Classification of the virus

Some coronavirology facts	
Order	Nidovirales
Family	*Coronaviridae*
Subfamily	*Coronavirinae*
Genera	*Alphacoronavirus, Betacoronavirus, Deltacoronavirus, Gammacoronavirus*
Species	*Alphacoronavirus 1,* ***Human coronavirus 229E, Human coronavirus NL63****, Miniopterus bat coronavirus 1, Miniopterus bat coronavirus HKU8, Porcine epidemic diarrhea virus, Rhinolophus bat coronavirus HKU2, Scotophilus bat coronavirus 512,* Enveloped, roughly spherical, 120-160nm, large club like protrusion (spike protein)*;* ***Human coronavirus HKU1****, Murine coronavirus, Pipistrellus bat coronavirus HKU5, Rousettus bat coronavirus HKU9, Severe acute respiratory syndrome-related coronavirus, Tylonycteris bat coronavirus HKU4, Bulbul coronavirus HKU11, Munia coronavirus HKU13, Thrush coronavirus HKU12, Avian coronavirus, Beluga whale coronavirus SW1*
Genome	(+)ssRNA, ~30kb (20-33kb)
Genes & Proteins	Leader, ORF1a, ORF1b, S, 3a, 3b, E, M, 6, 7qq, 7b, 8a, 8b, 9b, N, Poly(A)
Virion	Enveloped, roughly spherical, 120-160nm, large club like protrusion (spike protein)

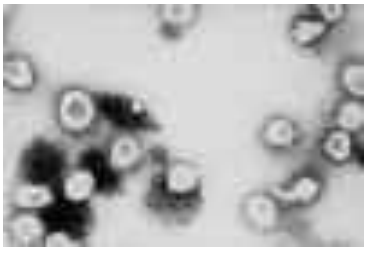
GENOME

Coronaviruses which are about 100nm in diameter, are the largest positive strand RNA viruses (indeed they have the largest genomes of any RNA virus). They infect humans and animals in which they cause respiratory and enteric disease. The coronaviruses, along with the toroviruses and arteriviruses, belong to a group, the nidovirales, that produce a nested set of mRNA with a common 3’ end .The coronaviruses and the toroviruses (which together make up the Coronaviridae) have helical nucleocapsids while the arteriviruses have icosahedral nucleocapsids. Coronaviruses have an envelope that is

derived from intracellular membranes and not the plasma membrane. In electron micrographs they have spikes sticking out of their surfaces (due to a large glycoprotein), leading to their name (corona = crown) .

in fact the largest of all of the RNA viruses. The genome is positive sense (that is, the same sense as the mRNA) and is non-segmented. The genomic RNA is capped and polyadenylated and ranges in size from 27 to 32kB. It is the large size of the genome coupled with the lack of proof reading in RNA polymerases that leads to the high mutation frequency in coronaviruses. Several coronaviruses have been sequenced, including the SARS virus. The order to the genes is always the same. At the 5’ end is the polymerase (pol) and this is followed by four structural proteins that are found in all coronaviruses.

Coronaviruses are a group of viruses that have a halo or crown-like (corona) appearance when viewed under amicroscope

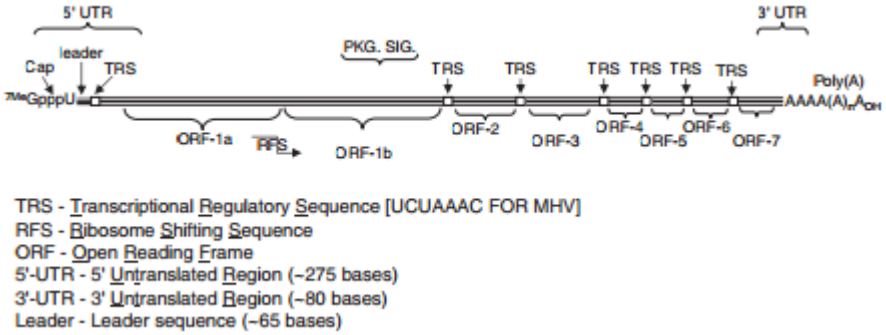


the Coronaviruses since they are particularly important in human respiratory disease, causing about one third of "common colds"

- The spike protein (S), so called because it sticks out of the surface of the virus
- The envelope protein (E)
- The membrane protein (M), that is incorporated into intracellular membranes of the host cells (particularly the Golgi Body)
    - The nucleocapsid protein (N)

Some coronaviruses also have a gene between the pol gene and the S gene that may have been picked up from a paramyxovirus, the hemagglutinin-esterase (HE) gene. There are also additional open reading frames (ORFs) which are not highly conserved among different coronaviruses. These genes likely code for proteins but their function is unknown. In addition to the protein-coding genes in the genomic RNA, all coronaviruses have 7 base sequences called intergenic sequences that

are at the 5’ end of each gene. If the intergenic sequence is altered (mutated), the sub-genomic mRNA that starts.



The 5` -end is capped although the exact structure of the capped 5` -end has not been determined. The 3 ` end is polyadenylated .

At the 5 -end there is an untranslated region (5 -UTR) of ~200–500 nucleotides (nts) before the initiation codon for the open reading frame (ORF) that is translated from the genome (ORF1).

The protein

S (spike) protein

This is a transmembrane glycoprotein with three domains . the large external domain (with two sub domains), the transmembrane sequence and the small internal domain. The external domain (N-terminal) folds to a globular shape and forms the spike structures in electron micrographs. This region gives the virus its antigenic properties and contains the binding site for the cell surface receptor. The inner part of the external domain is probably coiled-coil and contains heptad repeats. There is a fatty acyl molecule here which may stabilize the protein in the lipid bilayer. The inner part of the external domain forms a stalk-like structure that associates with other S proteins to form a trimer. In some coronaviruses, the external domain is cleaved but the two parts of the glycoprotein remain associated by ionic interactions (in a similar manner to the gp120 and gp41 of HIV). The inner part of the S protein, which may become exposed on binding to the host cell, is responsible for membrane fusion. Interestingly, the S protein has a region that is

similar to the Fc-gamma receptors for immunoglobulins allowing the virus to coat itself with these proteins and protect itself from immune attack (herpes viruses have a similar strategy). S protein can bind to sialic acid (9-O-acetyl neuraminic acid) on the host cell surface which gives the virus a hemagglutinating ability. Antibodies against S protein are neutralizing.

HE protein Only some coronaviruses have a hemagglutinin-esterase protein. This also forms spikes (shorter than S spikes) on the virus surface. It is a dimer and does not appear to be essential for replication in those types that possess it. This protein also binds sialic acid. . The esterase activity of HE protein can cleave the sialic acid from a sugar chain, which may aid the virus in escaping from the cell in which it was replicated. Antibodies against HE protein can also neutralize the virus.

M (membrane) protein

This is another membrane-spanning glycoprotein but most of the protein is internal with only a small external N-terminal domain. M protein spans the viral membrane three times. This protein helps in the attachment of the nucleocapsid to the membranes of internal structures

such as the Golgi Body and is not found on the plasma membrane of the cell (unlike the other glycoproteins).

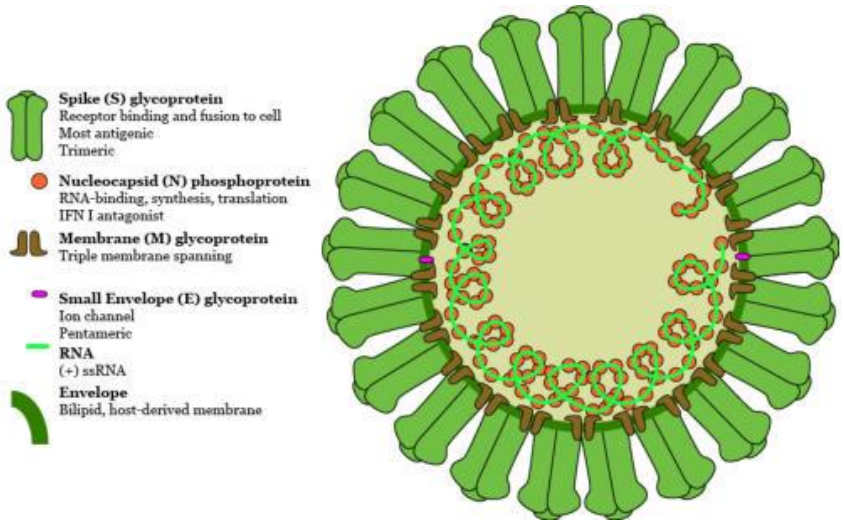
E (envelope) protein

This small protein is also on the viral membrane. In the infected cell it is found around the nucleus and at the cell surface.

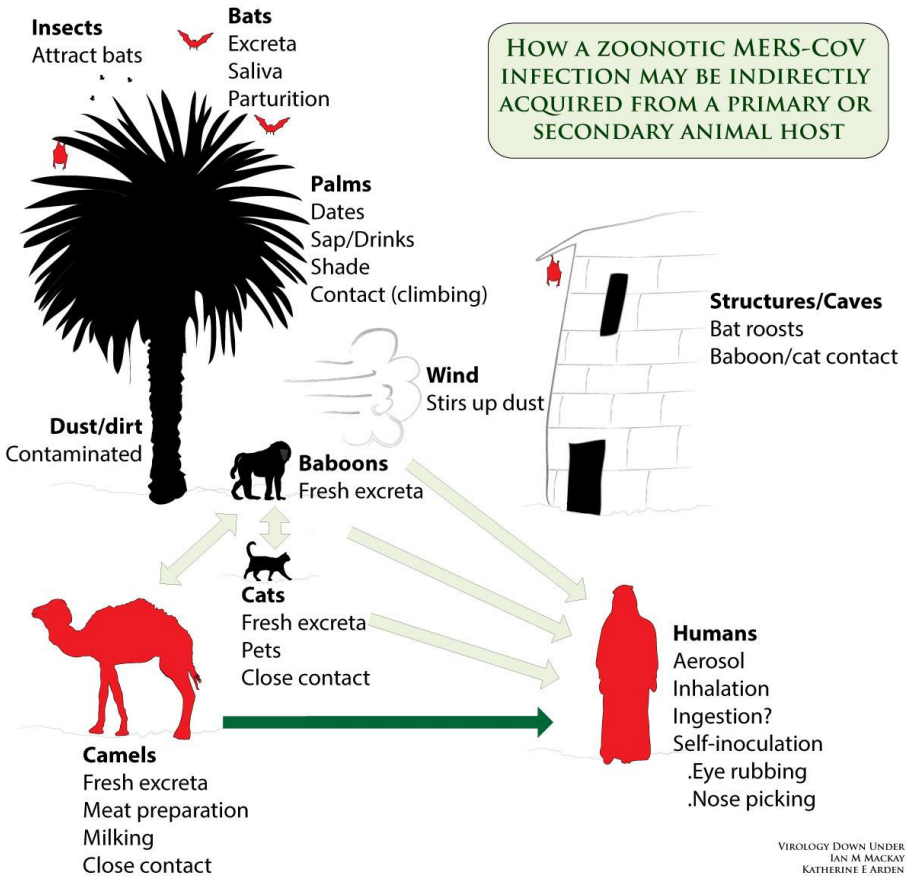
N (nucleocapsid) protein

The nucleocapsid protein binds to the genomic RNA via the leader sequence and to the M protein on the inner surface of the viral membrane. N protein is phosphorylated

Unlike many other RNA viruses, coronavirus do not incorporate the RNA polymerase into the virus particle; rather the polymerase is made after infection by using the positive sense genomic RNA as an mRNA. This is possible because the pol gene is at the 5’ end of the genome.



TRANSMISSIONOF MERS-COV:



MERS-CoV infection was initially thought to spread by zoonotic events via bats as phylogenetic studies revealed thatit is genetically connected to Tylonycterisbat coronavirus ,However, evidence indicates thatMERS-CoV originated from dromedary camels. A serologicalstudy suggests that almost 90% of all camels in Africa and theMiddle East were seropositive for MERS-CoV, whereas otheranimals such as sheep, goats and cows were found to benegative..A population-

based seroepidemiologic study suggeststhat the seroprevalence of the virus was several foldshigher in people who were exposed to camels Moreover, antibodies againstMERS-CoV were found in samples obtained from camels inSaudi Arabia in 1993, which reinforces the hypothesis thatdromedary camels are most likely the main reservoirs ofMERS-CoV.In contrast, no seroreactivities were reportedin the blood samples obtained from blood donors and abattoirworkers in Saudi Arabia during 2012. MERS-CoV wasdetected in camels in Egypt that were locally raised or importedfrom countries where no MERS casesThe mode of transmission is still unknown but is suspectedThe mode of transmission is still unknown but is suspectedto be through saliva during direct contact with infected camelsor through consumption of milk or uncooked meat. Howeverwe cannot rule out the existence of another intermediate hostfor MERS-CoV transmission to humans.Secondary infectionmay occur through droplets or contact, and the virus couldspread either via air or fomites .Human-to-human transmission is confirmed by the fact that secondarily infected individuals had come in close contact with a primarily infected individual; these

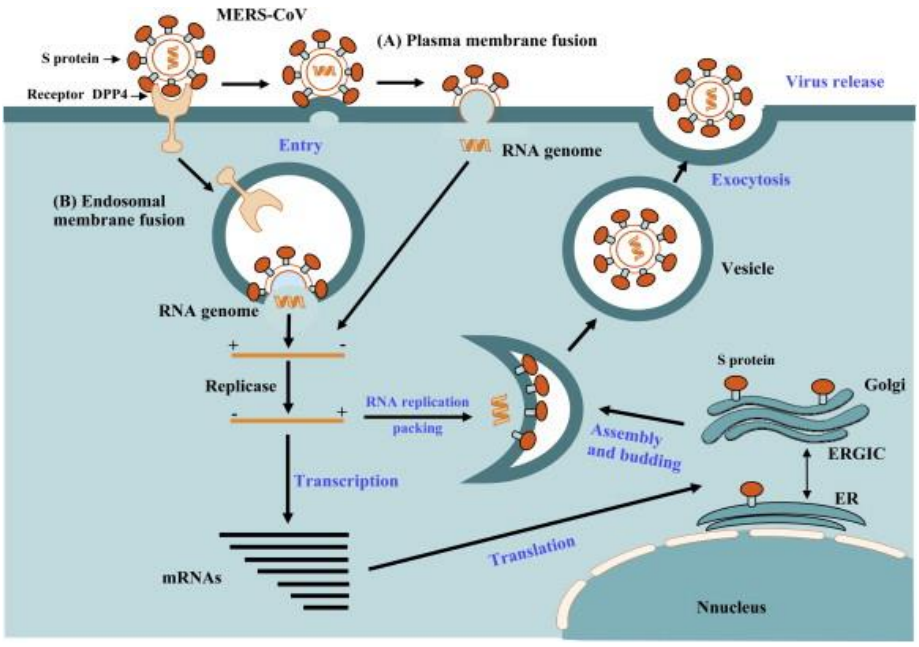
secondarily infected individuals included family members,health-care workers and people who shared the hospital room

Target Organ :

Respiratory system: human lungs and airway epithelial cell .

the replication cycle of Middle East respiratory syndrome coronavirus (MERS-CoV) :

Of all, the most important finding was the cellular receptor-dipeptidyl peptidase 4 (DPP4). The DPP4 binds to a 231-residue region in the spike (S) protein of MERS-CoV. The RNA genome is pumped in through a plasma or endosomal membrane fusion, into the target cell. The RNA immediately transcribes to proteins and RNA, which is packaged and released.



1) MERS-CoV binds to dipeptidyl peptidase 4 (DPP4) on the host cell through its receptor-binding domain (RBD) in the S1 subunit of the spike (S) glycoprotein, which leads to virus–cell fusion and the release of genomic RNA into the cytoplasm .[1]

2)Initially open reading frame 1a (ORF1a) and ORF1b are translated into polyproteins, polyprotein 1a (pp1a) and pp1ab, respectively, which are cleaved by the virus-encoded proteases papain- like protease (PLpro) and 3C-like protease (3CLpro) into 16 mature nonstructural proteins (nsps).[1]

3)The proteins involved in replication and transcription are gathered into replication-transcription complexes (RTCs) that associate with double-membrane vesicles (DMVs) derived from the endoplasmic reticulum (ER).[1]

4)The genomic RNA contains adenylate uridylate (AU)-rich sequences called transcription regulation sequences (TRSs).[1]

5)If the TRSs are recognized by RTCs, then RNA of subgenomic length for transcription will be generated, otherwise a full-length template RNA of genomic length for replication will be synthesized.[1]

6)The newly produced genomic RNAs are encapsidated in the nucleocapsid (N) proteins in the cytoplasm and then transported to the ER–Golgi intermediate compartment (ERGIC) for further assembly.[1]

7)The S, membrane (M) and envelope (E) proteins are inserted into the membrane of the rough ER (RER), from where they are transported to the ERGIC to interact with the RNA-encapsidated N proteins and assemble into viral particles.[1]

8)The budded vesicles containing mature viral particles are then transported to the cell surface for release after maturation in the Golgi bodies.[1]

9)Double-stranded RNAs (dsRNAs) are partially generated during viral replication.[1]

10)The 4a competes with Toll-like receptor 3 (TLR3) and retinoic acid- inducible gene I product)RIG-I)-like helicases (RIG-I and melanoma differentiation-associated protein 5 (MDA5)) to bind to dsRNAs and evades the host immune response.[1]

SYMPTOMS :

Corona viruses can cause a range of symptoms varying from mild symptoms such as the common cold to more serious respiratory illnesses. They primarily cause respiratory and enteric diseases.

symptoms include :

1-fever
2- headache
3- sneezing
4- cough
5- nasal obstruction
6- bronchitis
7- shortness of breath

8- breathing difficulties
9- cilia damage
10- muscle ache
11- diarrhea
12- bronchial epithelial cell peeling
13- the formation of multinucleated giant cells
14- pulmonary fibrosis
15- pneumonia
16- multi-organ failure
17- death

Diagnosis:

Laboratory Testing for Middle East Respiratory Syndrome Coronavirus (MERS-CoV)
these lab tests fall into two categories:

- Molecular tests, which look for evidence of active infection; and
- Serology tests, which look for previous infection by detecting antibodies to MERS-CoV.

Molecular Tests:

Molecular tests are used to diagnose active infection (presence of MERS- CoV) in people who are thought to be infected with MERS-CoV based on their clinical symptoms and having links to places where MERS has been reported.

Real-time reverse-transcription polymerase chain reaction (rRT-PCR) assays are molecular tests that can be used to detect viral RNA in clinical samples. The success of rRT-PCR testing depends on several factors, including the experience and expertise of laboratory personnel, laboratory environment (e.g., avoidance of contamination), and the type and condition of specimens being tested

The performance of this test is best with lower respiratory tract samples than upper respiratory specimens

Serology Tests

Serology testing is used to detect previous infection (antibodies to MERS-CoV) in people who may have been exposed to the virus. Antibodies are proteins produced by the body's immune system to attack and kill viruses, bacteria, and other microbes during infection. The presence of antibodies to MERS-CoV indicates that a person had been previously infected with the virus and developed an immune response

There is two-phase approach for serology testing, using one screening test and two confirmatory tests to detect antibodies to MERS-CoV.

Screening test: ELISA, or enzyme-linked immunosorbent assay, is a screening test used to detect the presence and concentration of specific antibodies that bind to a viral protein. ELISAs usually produce results within a few hours
if the result is positive then we use IFA assay and/or microneutralization assay to confirm the positive result.

Confirmatory test :IFA, or immunofluorescence assay, is a confirmatory test in which specific antibodies, if present in the person's blood, attach to virus-infected cells fixed on a glass slide. These attached antibodies are detected by adding a secondary antibody labeled with a compound that makes them glow an apple-green color when viewed under a special microscope. This secondary antibody will bind to any antibodies which are present in the blood and have attached to the virus-infected cells. Like the ELISA results, IFA results can also be obtained in a few hours.

- If a clinical sample is positive by both ELISA and IFA, the specimen is determined to be positive.

- If a clinical sample is positive by ELISA but indeterminate or negative by IFA, then we perform additional confirmatory testing

The microneutralization assay is a highly specific confirmatory test used to measure antibodies that can neutralize virus
compared with the ELISA and IFA, the microneutralization assay is labor-intensive and time-consuming, requiring at least 5 days before results are available.

- If a clinical sample is positive by ELISA, indeterminate by IFA, and positive by microneutralization, the specimen is determined to be positive.
- If a clinical sample is positive by ELISA, indeterminate or negative by IFA, and negative by microneutralization, the sample is determined to be negative.

Prevention

Currently, there is no vaccine to prevent MERS-CoV infection. The U.S. National Institutes of Health is exploring the possibility of developing one.

routinely advises that people help protect themselves from respiratory illnesses by taking everyday preventive actions:

•Wash your hands often with soap and water for 20 seconds, and help young children do the same. If soap and water are not available, use an alcohol-based hand sanitizer.

•Cover your nose and mouth with a tissue when you cough or sneeze, then throw the tissue in the trash.

•Avoid touching your eyes, nose and mouth with unwashed hands.

•Avoid personal contact, such as kissing, or sharing cups or eating utensils, with sick people.

•Clean and disinfect frequently touched surfaces and objects, such as doorknobs.

Prevention Steps for People Confirmed to Have, or Being Evaluated for, MERS-CoV Infection :

If you are confirmed to have, or being evaluated for, MERS-CoV infection you should follow the prevention steps below until a healthcare provider or local or state health department says you can return to your normal activities.

*Stay home

You should restrict activities outside your home, except for getting medical care. Do not go to work, school, or public areas, and do not use public transportation or taxis.

*Separate yourself from other people in your home

As much as possible, you should stay in a different room from other people in your home. Also, you should use a separate bathroom, if available.

*Call ahead before visiting your doctor

Before your medical appointment, call the healthcare provider and tell him or her that you have, or are being evaluated for, MERS-CoV infection. This will help the healthcare provider's office take steps to keep other people from getting infected.

*Wear a facemask

You should wear a facemask when you are in the same room with other people and when you visit a healthcare provider. If you cannot wear a facemask, the people who live with you should wear one while they are in the same room with you.

*Cover your coughs and sneezes

Cover your mouth and nose with a tissue when you cough or sneeze, or you can cough or sneeze into your sleeve. Throw used tissues in a lined trash can, and immediately wash your hands with soap and water.

*Wash your hands

Wash your hands often and thoroughly with soap and water. You can use an alcohol-based hand sanitizer if soap and water are not available and if your hands are not visibly dirty. Avoid touching your eyes, nose, and mouth with unwashed hands.

*Avoid sharing household items

You should not share dishes, drinking glasses, cups, eating utensils, towels, bedding, or other items with other people in your home. After using these items, you should wash them thoroughly with soap and water.

*Monitor your symptoms

Seek prompt medical attention if your illness is worsening (e.g., difficulty breathing). Before going to your medical appointment, call the healthcare provider and tell him or her that you have, or are being evaluated for, MERS-CoV infection. This will help the healthcare provider’s office take steps

to keep other people from getting infected. Ask your healthcare provider to call the local or state health department.

Prevention Steps for Close Contacts

If you have had close contact with someone who is confirmed to have, or being evaluated for, MERS-CoV infection, you should:

Monitor your health starting from the day you were first exposed to the person and continue for 14 days after you were last exposed to the person. Watch for these signs and symptoms:

*Fever. Take your temperature twice a day.

*Coughing.

*Shortness of breath.

*Other early symptoms to watch for are chills, body aches, sore throat, headache, diarrhea, nausea/vomiting, and runny nose.

Prevention Steps for Caregivers and Household Members

If you live with, or provide care at home for, a person confirmed to have, or being evaluated for, MERS-CoV infection, you should:

*Make sure that you understand and canhelp the person follow the healthcare provider's instructions for medication and care.

*Have only people in the home who are essential for providing care for the person .Other household members should stay in another home or place of residence. If this is not possible, they should stay in another room

*Keep elderly people and those who have compromised immune systems or certain health conditions away from the person. This includes people with chronic heart, lung or kidney conditions, and diabetes.

*Make sure that shared spaces in the home have good air flow

*Wash your hands often and thoroughly with soap and water. Avoid touching your eyes, nose, and mouth with unwashed hands.

*Wear a disposable facemask, gown, and gloves when you touch or have contact with the person’s blood, body fluids and/or secretions, such as sweat,

saliva, sputum, nasal mucus, vomit, urine, or diarrhea. Wash your hands immediately after removing your facemask, gown, and gloves.

*Avoid sharing household items.

*Clean all “high-touch” surfaces, such as counters, tabletops, doorknobs, bathroom, toilets, phones, tablets, and bedside, every day.

*Read label of cleaning products and follow recommendations provided on product labels .Use a diluted bleach solution or a household disinfectant To make a bleach solution at home

*Monitor the person’s symptoms.

***Currently available antiviral agents & vaccines**

Currently, there are no proven therapies for MERS-CoV infection. Useful antiviral agents for (MERS-CoV) infection include neutralizing antibody, convalescent plasma, polyclonal human immunoglobulin, Equine F(ab’)2 antibody fragments, anti-S monoclonal antibodies and interferons. Other medications could be repurposed for use against MERS-CoV, including ribavirin, protease inhibitors (lopinavir, nelfinavir),

cyclophilin inhibitors (cyclosporine, alisporivir), chloroquine, mycophenolic acid, nitazoxanide, recombinant human mannose-binding lectin and siRNA to key MERS-CoV genes. Approved antiviral agents can be repurposed for use against emerging viral infections to shorten the time from virus discovery to treatment availability. The use of interferon and ribavirin was tried in five patients with MERS-CoV infection. The median time from admission to therapy with these two agents was 19 days, and thus any benefit effect might have not been evident. A larger number of 20 patients received ribavirin and interferon treatment at a median of 3 days. The therapy resulted in improved 14-day survival of 70% (14 of 20 patients) in the treatment group, compared to 29% (7 of 24 of patients) in the comparison group with no survival advantage at 28 days.

In an experimental model of MERS-CoV infection in mice, a recombinant receptor-binding domain (rRBD) of MERSCoV spike (S) glycoprotein in association with Fc of human IgG (RBD-Fc) induced neutralizing antibodies. Intranasal and subcutaneous MERS-CoV RBD-Fc vaccination resulted in similar systemic humoral immune responses. A higher systemic cellular immune

response and local mucosal immune responses were achieved with intranasal vaccination. Other studies showed similar findings of antigenic property of a rRBD protein of MERS-CoV spike (S). Moreover, three adjuvants–alum, IFA, CpG and poly (I:C)–in rRBD subunit vaccines were effective in producing RBD-specific cellular and humoral immune responses . Since the N-terminus RBD of (S) glycoprotein is conserved in currently circulating MERS-CoV strains, this terminus is considered a possible vaccine candidate.

*Coronavirus vaccines can be inactivated coronavirus, live attenuated coronavirus, or S protein-based. Besides, there are still vectored vaccines, DNA vaccines, and combination vaccines against coronaviruses. Vaccines targeting several animal CoVs have been developed, and some have been demonstrated to be efficacious in preventing viral infection. However, a phenomenon of enhanced disease following vaccination has been observed in cats upon infection with feline infectious peritonitis virus following previous infection, vaccination, or passive transfer of antibody. The phenomenon is not fully understood but is believed to be a result of enhanced uptake and spread of the virus through binding of virus-

antibody immune complexes to Fc receptors on the surfaces of macrophages ; antibodies directed against the S protein are mainly responsible.

Inactivated Coronavirus Vaccine

The immunogenicity and efficacy of inactivated SARS-CoV vaccines have been established in experimental animals, and one such vaccine is being evaluated in a clinical trial. However, the development of inactivated vaccines requires the propagation of high titers of infectious virus, which in the case of SARS-CoV requires biosafety level 3-enhanced precautions and is a safety concern for production. Additionally, incomplete inactivation of the vaccine virus presents a potential public health threat. Production workers are at risk for infection during handling of concentrated live SARS-CoV, incomplete virus inactivation may cause SARS outbreaks among the vaccinated populations, and some viral proteins may induce harmful immune or inflammatory responses, even causing SARS-like diseases

Live Attenuated Coronavirus Vaccine

To date, live attenuated vaccines for SARS-CoV have not been evaluated. However, systems have been developed to generate cDNAs encoding the

genomes of CoVs, including SARS-CoV. The panel of cDNAs spanning the entire CoV genome can be systematically and directionally assembled by in vitro ligation into a genome-length cDNA from which recombinant virus can be rescued. This system has been used for genetic analysis of SARS-CoV protein functions and will enable researchers to engineer specific attenuating mutations or modifications into the genome of the virus to develop live attenuated vaccines. While live attenuated vaccines targeting respiratory viruses, including influenza viruses and adenoviruses, have been approved for use in humans, the observation that infectious virus is shed in the feces of SARS-CoV-infected individuals raises concerns that a live attenuated SARS-CoV vaccine strain may also be shed in feces, with potential to spread to unvaccinated individuals. Another concern is the risk of recombination of a live attenuated vaccine virus with wild-type CoV; however, there may be ways to engineer the genome of the vaccine virus to minimize this risk.

S Protein-based Coronavirus Vaccine

The roles of S protein in receptor binding and membrane fusion indicate that vaccines based on the S protein could induce antibodies to block virus binding and fusion or neutralize virus infection. Among all structural proteins of SARS-CoV, S protein is the main antigenic component that is responsible for inducing host immune responses, neutralizing antibodies and/or protective immunity against virus infection. S protein has therefore been selected as an important target for vaccine and anti-viral development.

Although full-length S protein-based SARS vaccines can induce neutralizing antibody responses against SARS-CoV infection, they may also induce harmful immune responses that cause liver damage of the vaccinated animals or enhanced infection after challenge with homologous SARS-CoV, raising concerns about the safety and ultimate protective efficacy of vaccines that contain the full-length SARS-CoV S protein.

Vectored Vaccines against Coronavirus

Several groups have reported preclinical evaluation of vaccines utilizing other viruses as vectors for CoV proteins, including a chimeric parainfluenza

virus, MVA, rabies virus, vesicular stomatitis virus (VSV), and adenovirus. Chimeric bovine/human parainfluenza virus 3 (BHPIV3), a live attenuated parainfluenza virus vaccine candidate, was utilized as a vector for the CoV structural proteins. Studies with vectored vaccines further demonstrate that induction of S protein-specific NAbs is sufficient to confer protection.

DNA Vaccines against Coronavirus

DNA vaccines have demonstrated strong induction of immune responses to viral pathogens in animal models, specifically in mice; however, clinical data on DNA vaccines in human subjects are limited. DNA vaccines encoding the S, N, M, and E proteins of CoV have been evaluated in mice. Vaccination with S-, M-, and N-encoding DNA vaccines induced both humoral and cellular immune responses, with some variation in the relative levels of induction.

Combination Vaccines against Coronavirus

Combination vaccines have also been evaluated for their ability to augment immune responses to CoV. Administration of two doses of a DNA vaccine encoding the S protein, followed by immunization with inactivated whole virus, was shown to be

more immunogenic in mice than either vaccine type alone. The combination vaccine induced both high humoral and cell-mediated immune responses. High NAb titers were also observed in mice vaccinated with a combination of S DNA vaccines and S peptide generated in Escherichia coli. Combination vaccines may enhance the efficacy of DNA vaccine candidates.

The CoV vaccine strategies reported to date demonstrate that S protein-specific NAbs alone are sufficient to provide protection against viral challenge. While CoV has not yet reemerged, its unknown reservoir leaves open the possibility that it, or a related virus, will again infect the human population. The development of vaccines targeting this virus will help, in the event of its reemergence, to potentially stop its spread before it wreaks the social and economic havoc caused by the previous outbreak.

Viral targets	**Currently available drugs for human use**	**Investigational agents**
Viral entry and fusion	Chloroquine	Convalescent plasma*, monoclonal antibodies, peptides representing different regions of ACE2, luteolin, other small molecules, peptides targeting S protein
Viral replication	Chloroquine	Calpain inhibitors

Viral protease	Protease inhibitors (lopinavir/ritonavir* and nelfinavir)	Quercetin
Viral RNA synthesis and gene expression	Ribavirin* and indomethacin	siRNA
Immunomodulation	Interferon alfacon-1*	Interferon-α and interferon-β
Unknown or other mechanisms	Nitric oxide*, niclosamide and reserpine	Glycyrrhizin, baicalin, valinomycin, nitric oxide donors (e.g. *S*-nitroso-*N*-acetylpenicillamine)

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