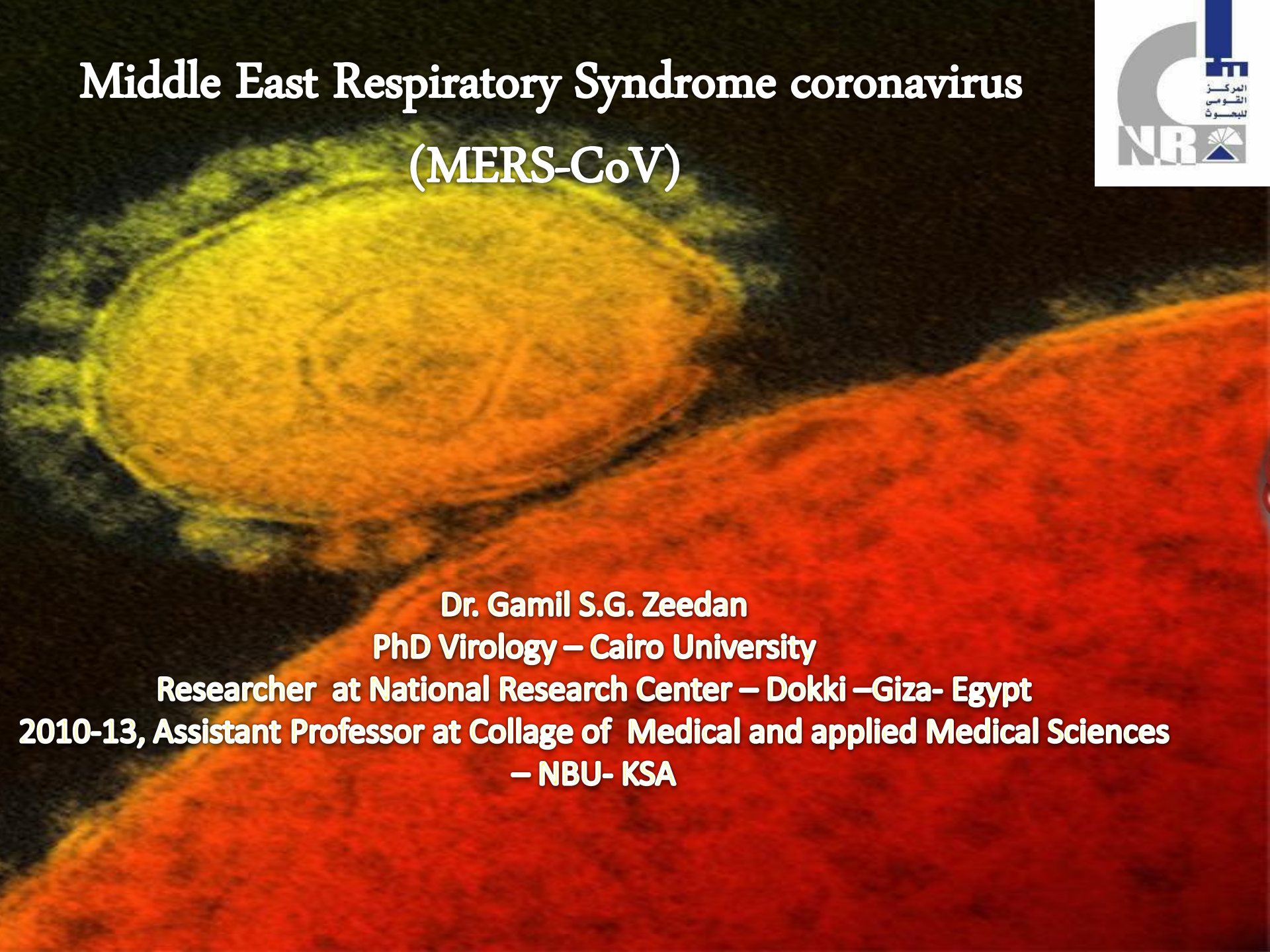
Middle East Respiratory Syndrome coronavirus (MERS-CoV)



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Researcher at National Research Center – Dokki –Giza- Egypt

2010-13, Assistant Professor at Collage of Medical and applied Medical Sciences – NBU- KSA

Overview

- Twelve years after the outbreak of Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) 2002-2003

Another threat to global public health.

- In September 2012 , the virus discovered in Saudi Arabia,, causes infections with a clinical manifestation similar to SARS-CoV.

This virus was identified as a novel human coronavirus

, Middle East respiratory syndrome coronavirus (MERS-CoV) or EMC/2012 (HCoV-EMC/2012), **is novel species of the genus Betacoronavirus.**

Although certain aspects related to this novel virus have already been unraveled

Source

But still knowledge of its source, pathogenesis and ways of transmission remains limited.

Pathogenesis

Transmission

What are Corona viruses?

RNA VIRUSES

SINGLE STRANDED positive sense

ENVELOPED

ICOSAHEDRAL

FLAVIVIRIDAE

TOGAVIRIDAE

RETROVIRIDAE

HELICAL

CORONAVIRIDAE

NONENVELOPED

ICOSAHEDRAL

PICORNAVIRIDAE

CALICIVIRIDAE

SINGLE STRANDED negative sense

ENVELOPED

HELICAL

ORTHOMYXOVIRIDAE

PARAMYXOVIRIDAE

RHABDOVIRIDAE

FILOVIRIDAE

BUNYAVIRIDAE

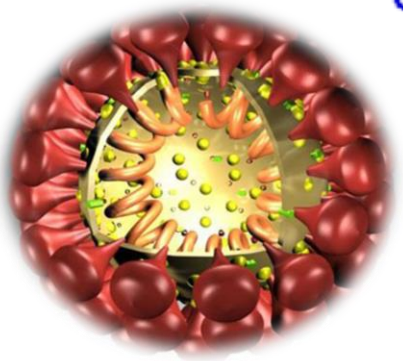
ARENAVIRIDAE

DOUBLE STRANDED

NONENVELOPED

ICOSAHEDRAL

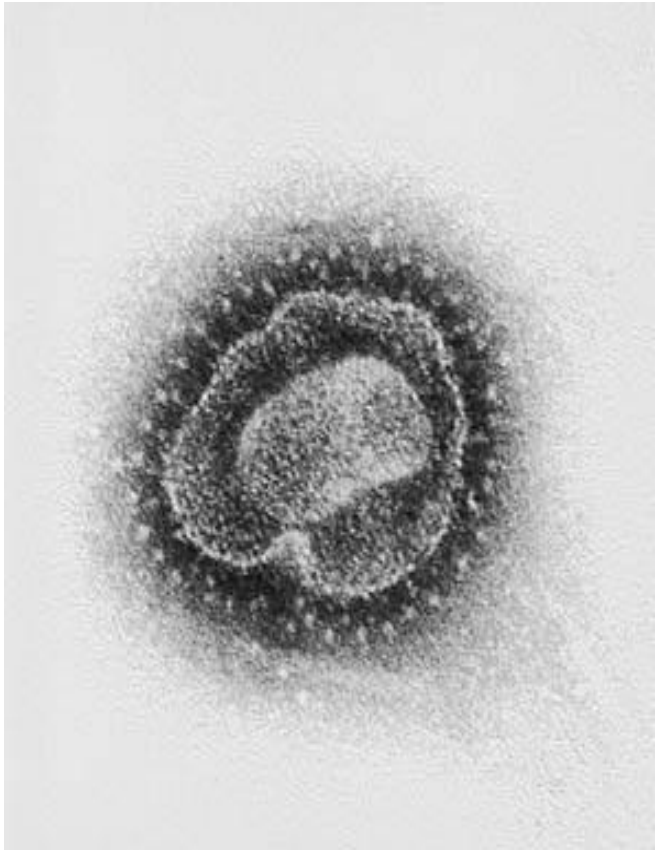
REOVIRIDAE

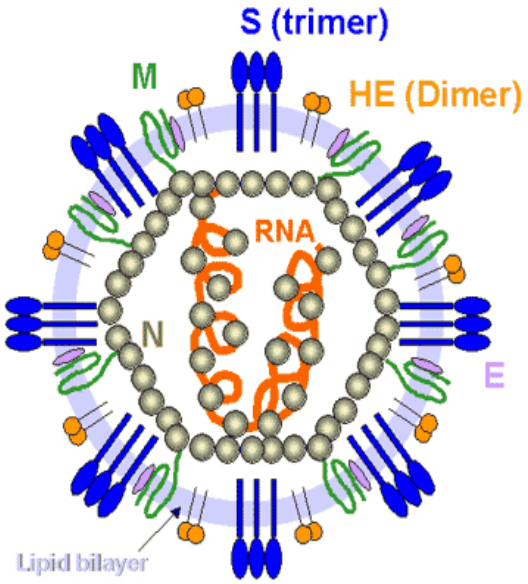


Modified from Volk et al., Essentials of Medical Microbiology, 4th Ed. 1991

Coronavirus structure

A Crown-like Appearance by E/M



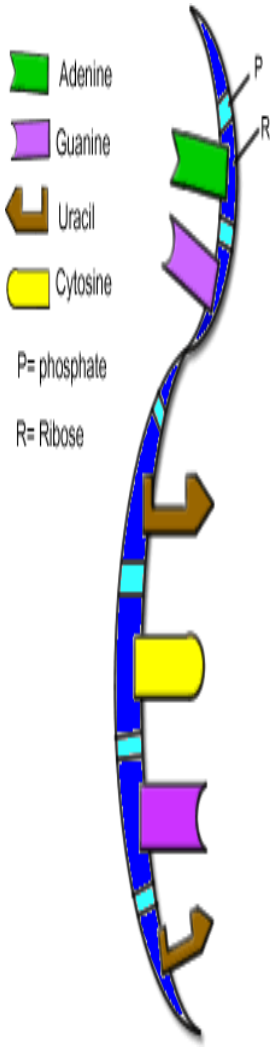


- Coronaviruses are large enveloped virions 80 to 160 nm,
- Helical nucleocapsids.
- ssRNA Virus
- 2 serogroups: OC43 and 229E
- Severe Acute Respiratory Syndrome (SARS)
- Middle East Resipatory syndrome MERS-CoV

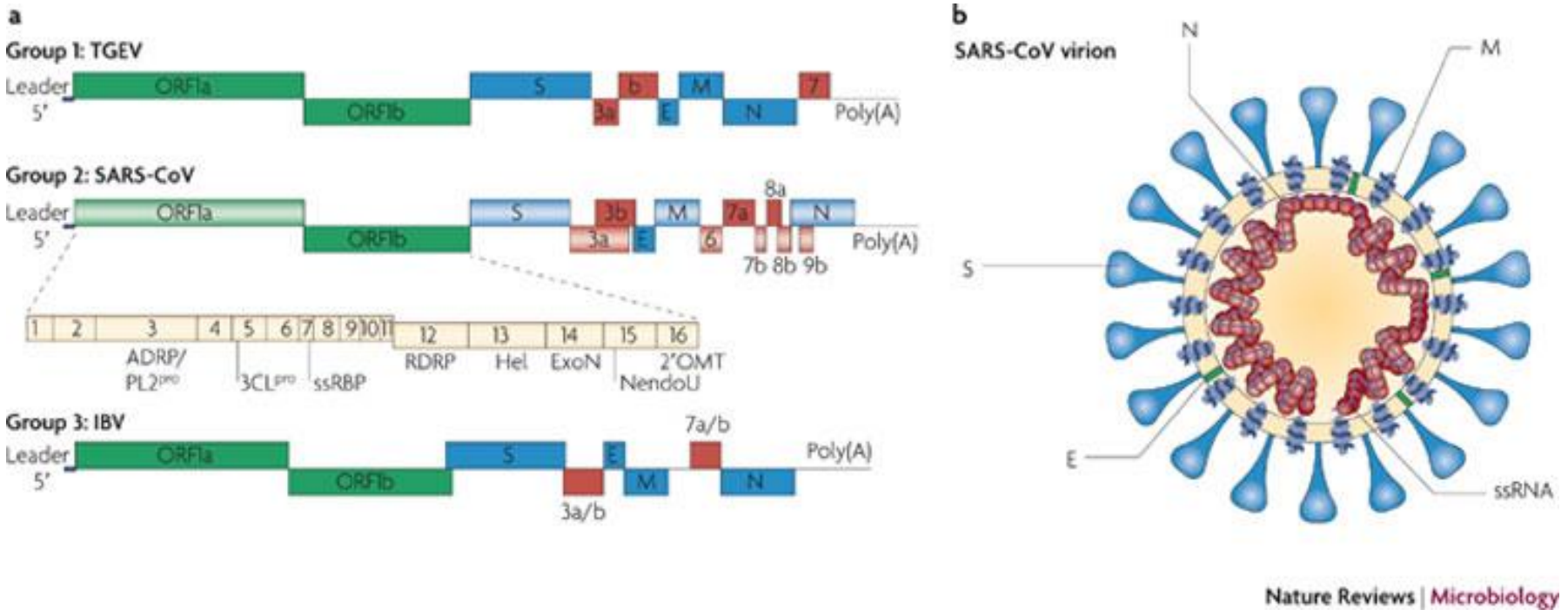
Properties of cornavruses

- Morphology: “Crown-like” appearance under EM
- Genome: 80~160nm, ssRNA (+), 27-31 kb (longest RNA)
- Sensitive to acid, ether, chloroform, lipid solvents, drying, heating to 56^{o}C/15-20 minutes, but some can through GIT (optimum temperature for virus:33~35^{o}C).
- Inactivation within few minutes at room temperature in 1% formalin,1% cresol and 70% alcohol

They are difficult to isolate in cell culture so rarely diagnosed in clinical practice

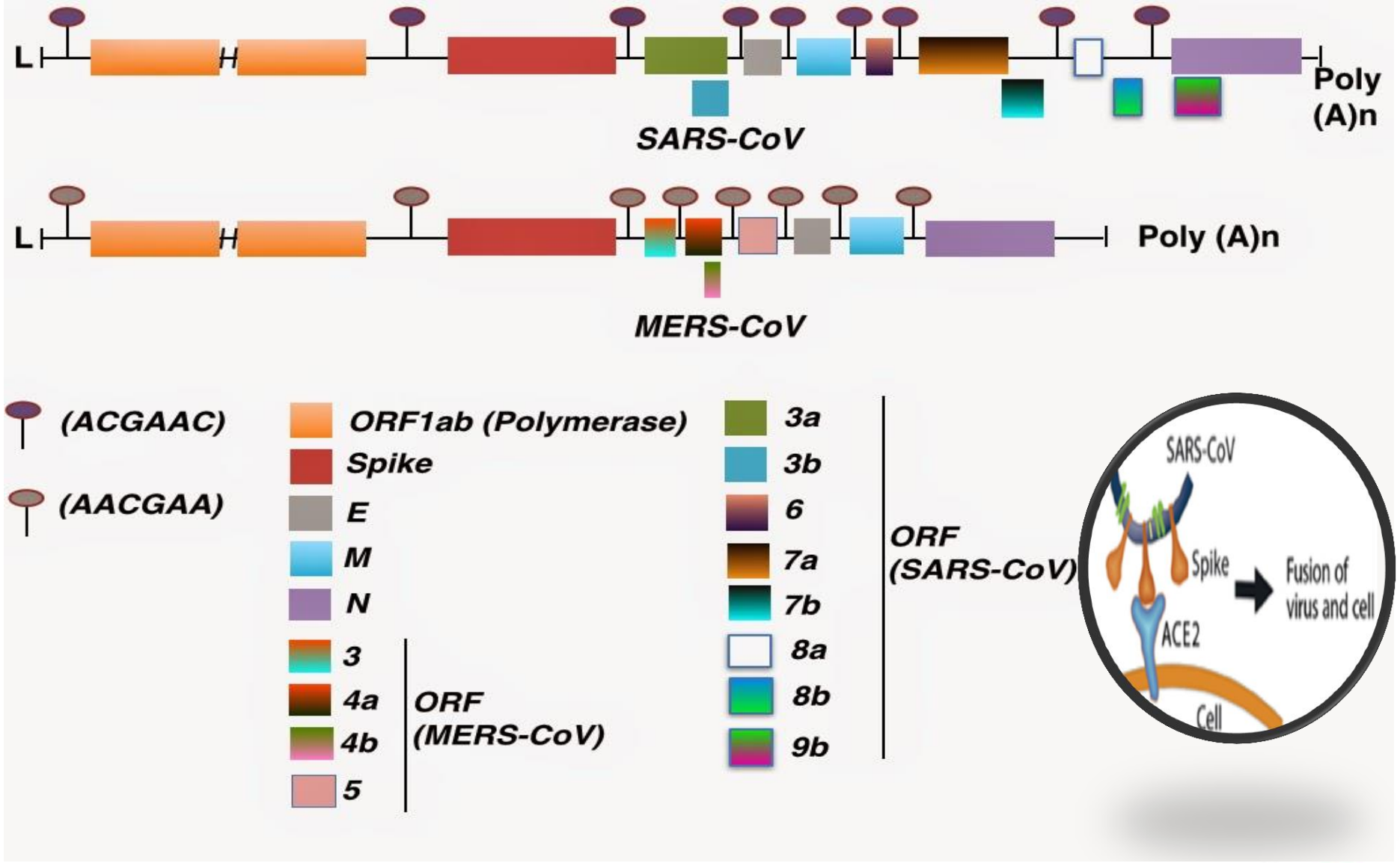


Genome organizations



- The gene order for the proteins encoded by all coronaviruses is **Pol-S-E-M-N-3'.** Several open reading frames encoding nonstructural proteins and the HE protein differ in number and gene order among coronaviruses. The SARS virus contains a comparatively large number of interspersed genes for nonstructural proteins at the 3' end of the genome.

Genome Organization



Genetic variation & evolution of new strains

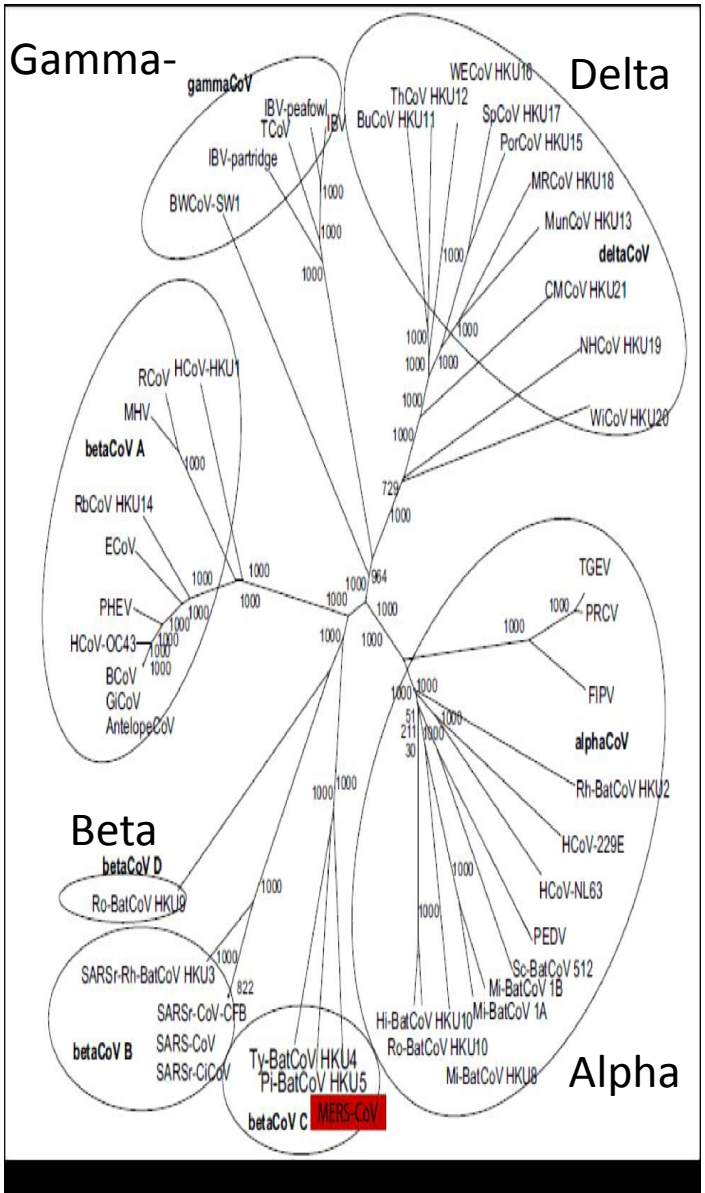
a high frequency of:

- **deletion mutations**
- high frequency of recombination during replication which is unusual for an RNA virus with unsegmented genome

Classification Coronaviruses

The International Committee on Taxonomy of Viruses (ICTV) has divided the family Coronaviruses based on genome sequence analysis, into four genera Alpha-, Beta-, Gamma- and Delta coronavirusidae

- Sixth different currently known strains of Coronaviruses infect humans .
- SARS–Co V represents a new fourth antigenic group intermediate between groups I & III
- A sixth was discovered at 2012, known as Novel Coronavirus or MERS-CoV .



Host Ranges and Disease of Cornviruses

Genetic Group	Virus	Host	Diseases (infection sites) Respiratory	Enteric	Other Site	Receptor
1	HCoV- 229E	human	X			* APN CD 13
	TGEV	pig	(X)	X		
	PRCoV	pig	X			
	PEDV	pig		X		
	FIPV	cat	X	X	Systemic	
	FCoV	cat		X		
	CCoV	dog		X		
2	HCoV- OC43	human	X	??		CEACAM1 CD66a
(HE)	MHV	mouse	X	X	CNS, systemic +	
	RCoV	rat	X		Eye, GU	
	HEV	pig		X	CNS	
	BCoV**	cattle	X	X		
3	IBV	chicken	X	X	Kidney	
	TCoV	turkey		X		
4	SARS- CoV	human	X	(X)	(Kidney)	??

* APN (Aminopeptidase N; CD13): Antigen processing & presentation

The three major antigenic groups of CoV

- **Group I** contains canine, feline, swine coronaviruses and a human corona virus **HCoV 229E** the prototype of the group
- **Group II** contains bovine, swine, rat and mouse CoV and the other **human strain which is OC43**
- **Group III no human strains** only Turkey and Avian CoV

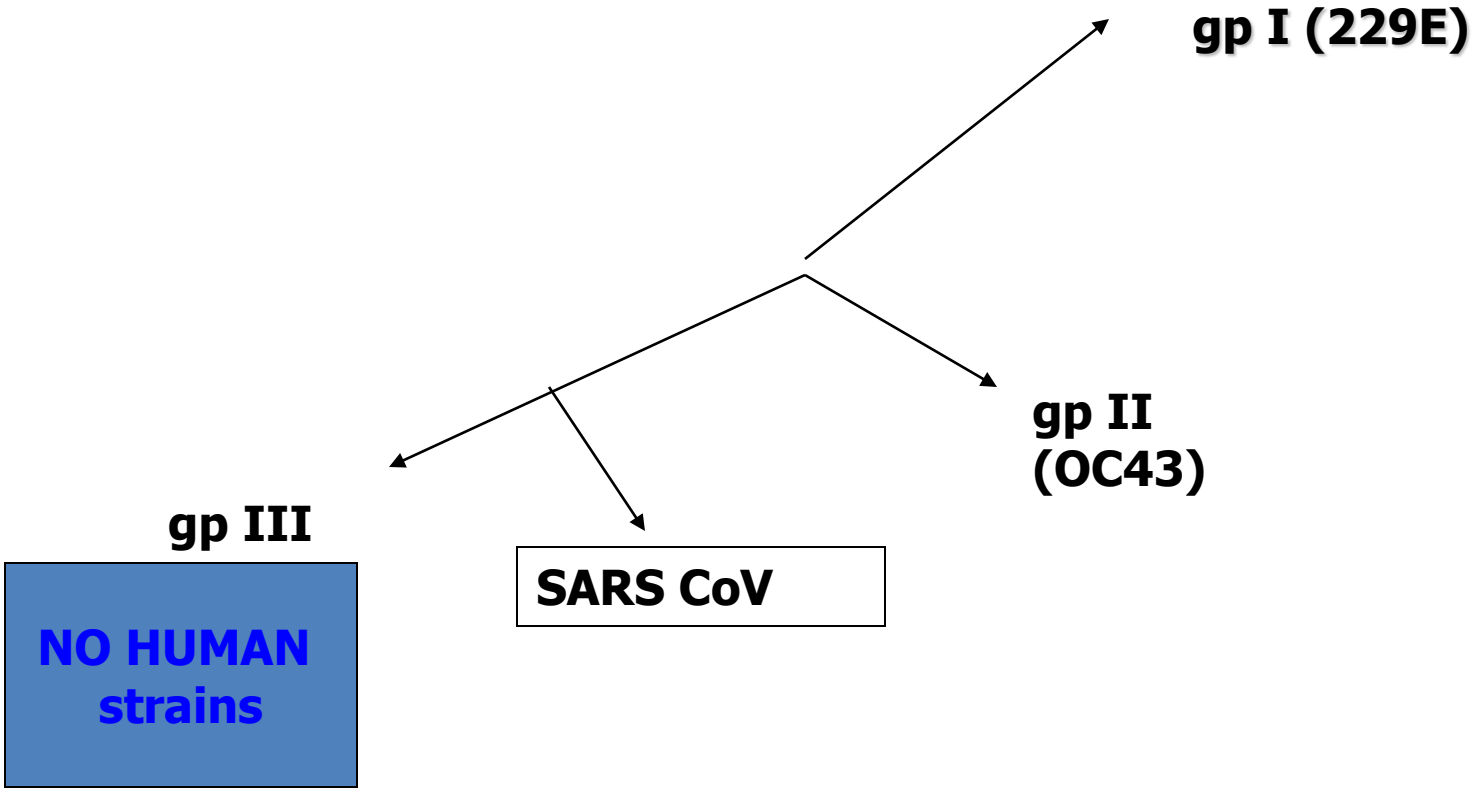
Evolution of SARS 2002

- **A novel human corona virus named SARS associated corona virus represents a new fourth antigenic group intermediate between groups I & III**

A NOVEL FOURTH ANTIGENIC GROUP

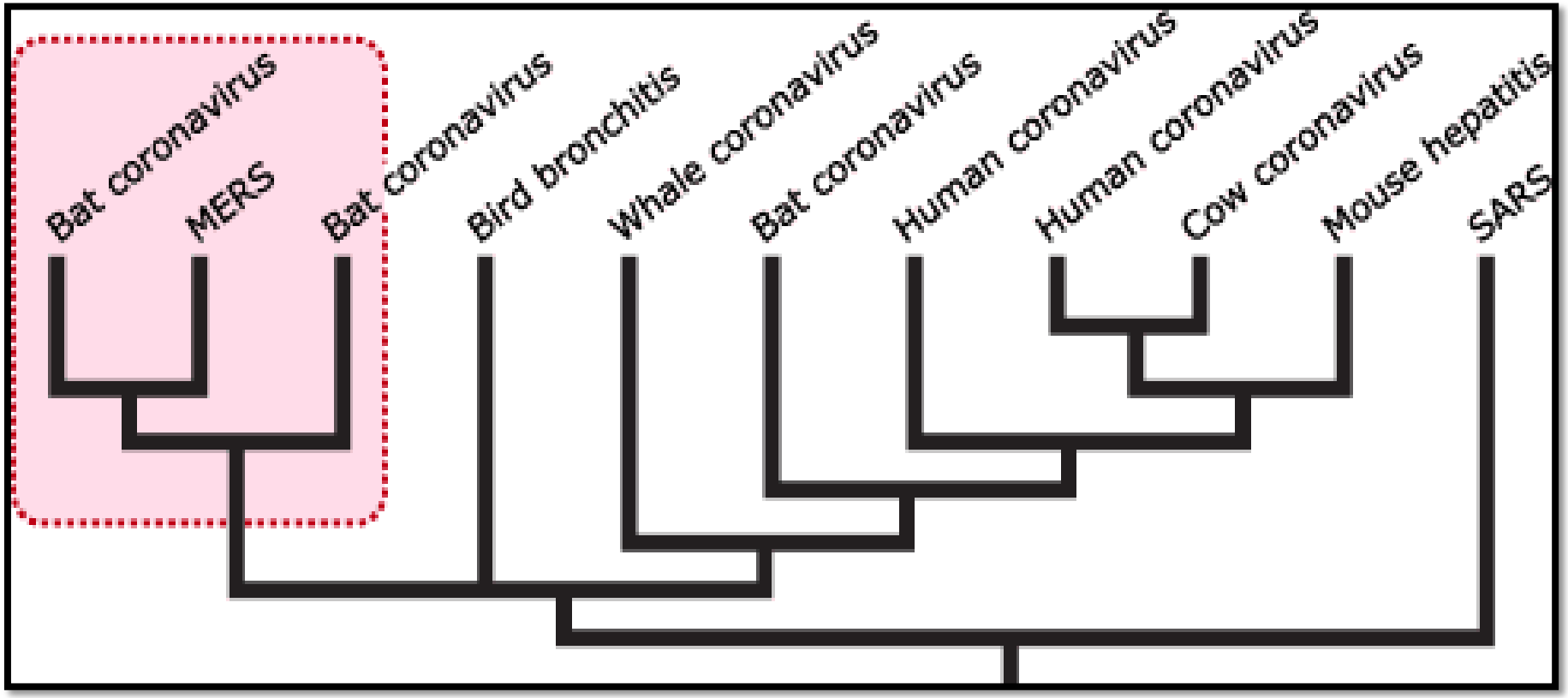
SARS

Evolution of SARS

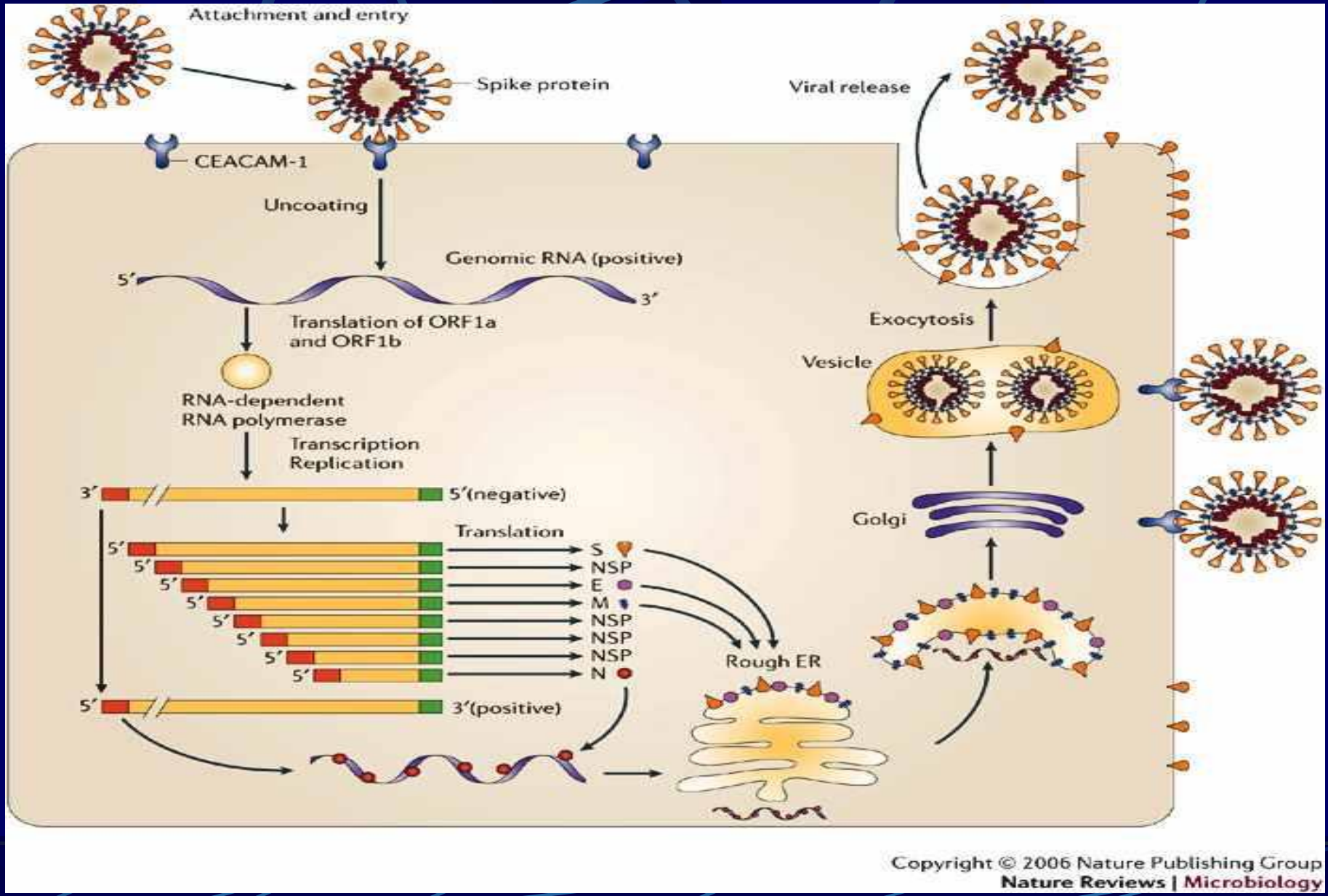


Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

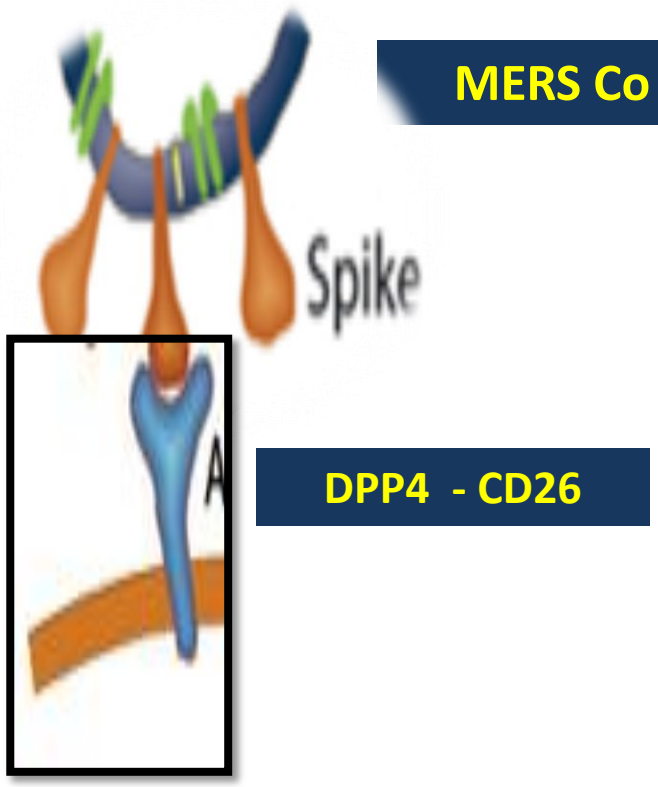
Novel coronavirus that emerged in 2012 ,Causes severe acute respiratory illness

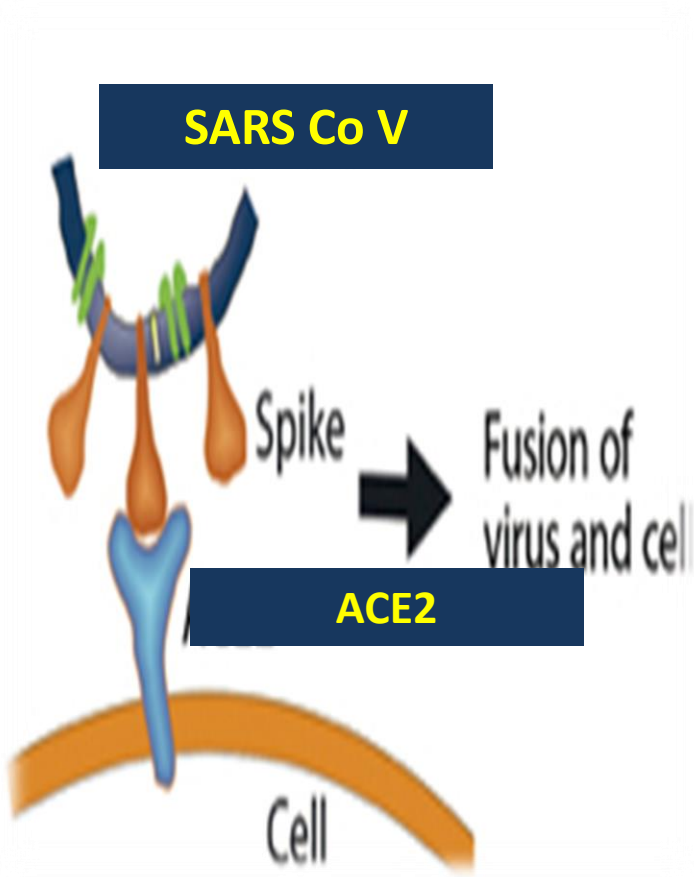


Coronaviruses Replication



Different between SARS-CoV and MERS-CoV receptors





Due to the clinical similarity between MERS-CoV and SARS-CoV . Exopeptidase, Angiotensin converting enzyme 2 (ACE2) Neutralization of ACE2 by recombinant antibodies does not prevent MERS-CoV infection Dipeptyl peptidase 4 (DPP4; also known as CD26) as a functional cellular receptor for MERS-CoV.

Coronaviruses Infections in Humans

Pathogenesis

- Limited knowledge
- Highly species-specific
- Typically mild upper respiratory infections ("colds") that remain localized
  - Exception: SARS
- Immunity is not durable
  - Many people become resusceptible after a few years

Tissue tropism

Susceptibility studies testing the ability of MERS-CoV to infect cell lines derived from different organs provided indications about the tissue tropism of the virus. MERS-CoV was found to infect cells of the human respiratory tract, kidney, intestine and liver

Tropism of MERS-CoV for cells of the respiratory tract, kidney and intestine is correlated with the detection of the virus in respiratory swabs, tracheal aspirates, sputum, urine and stool of MERS

How are Novel Coronaviruses transmitted?

How are Novel Coronaviruses transmitted?

Airborne

Incubation period is 10-14 days

- Transmitted between family members or in a health care setting, the WHO said in an update .

- Human-to-human transmission, the exact mode of transmission is unknown.

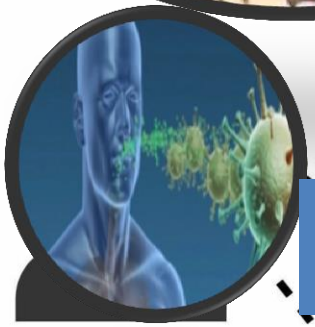
- Transmission between close contacts

Contamination of foodstuffs?

Transfer within shelf-life

Inactivation

Source - presumed to be bats



Transmission close cont

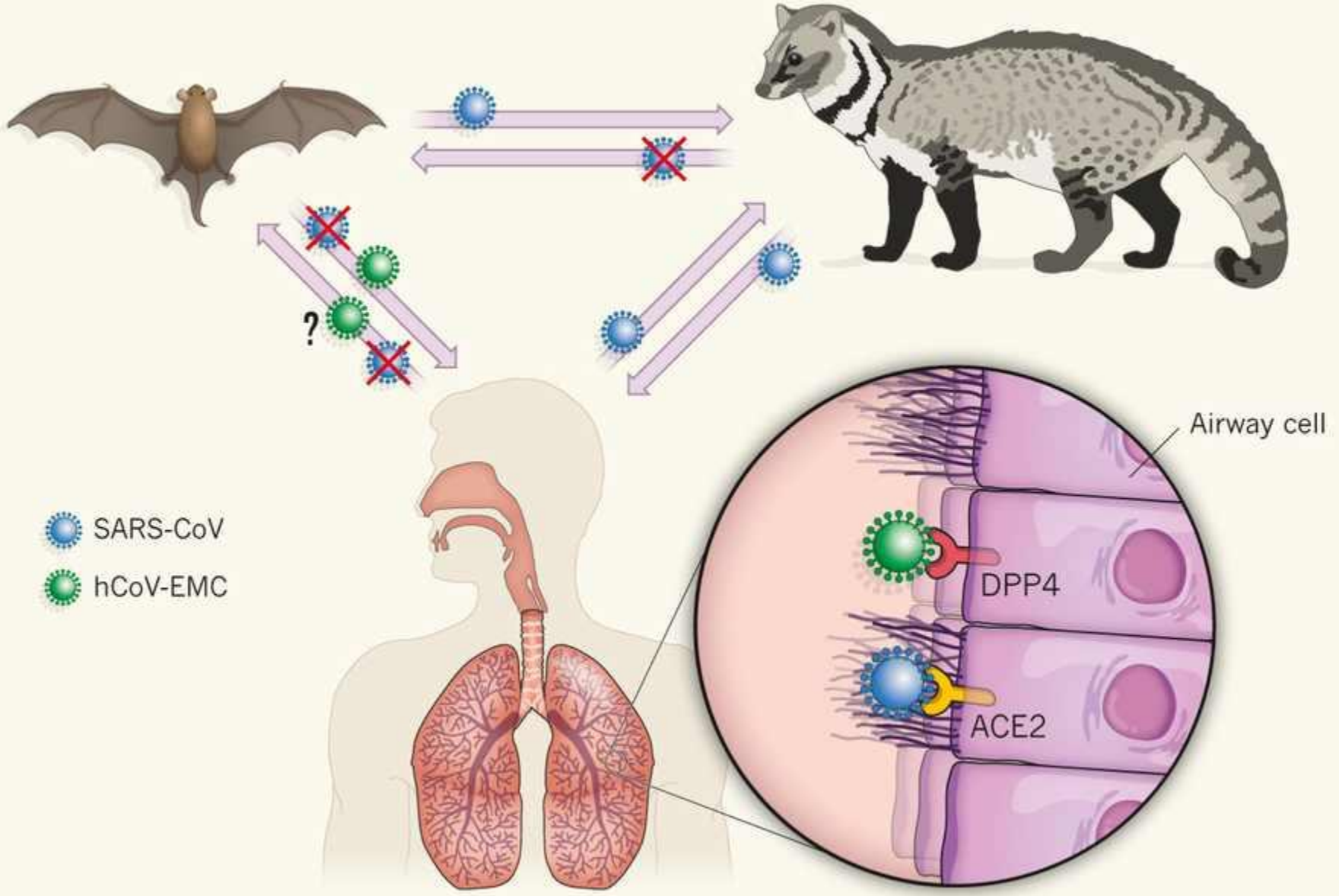
Direct transmission (unlikely)

Infection

Intermediate host Dromedary camel?

Human contact

Limited replication/adaptation?


?
SARS-CoV
hCoV-EMC
Airway cell
DPP4
ACE2

How a zoonotic MERS-CoV infection may be indirectly acquired from a primary or secondary animal host

Insects
Attract bats

Bats
Excreta
Saliva
Parturition

Palms
Dates
Sap/Drinks
Shade
Contact (climbing)

Structures/Caves
Bat roosts
Baboon/cat conta

Wind
Stirs up dust

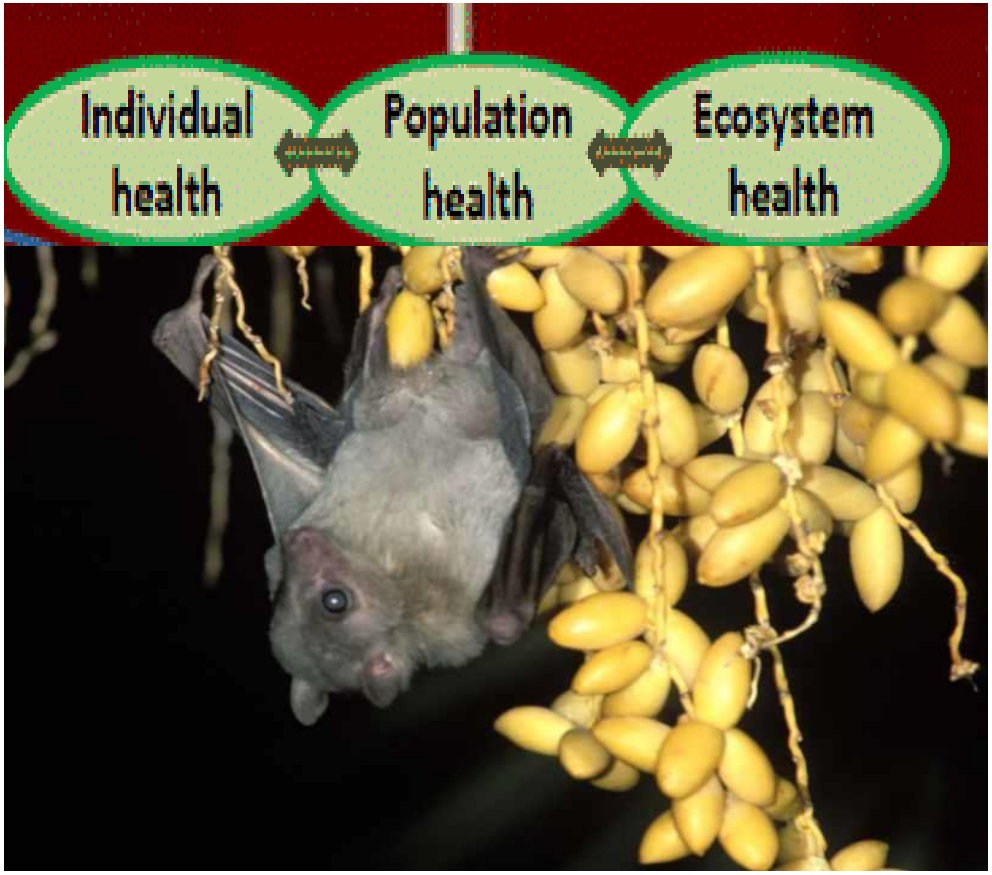
Dust/dirt
Contaminated

Baboons
Fresh excreta

Cats
Fresh ex
Pets
Close co

Humans
Aerosol
Inhalation
Ingestion?


SPL


Individual health
Population health
Ecosystem health


alegt.com

Clinical picture & epidemiology

- **Upper respiratory infections, similar to "colds" caused by rhinoviruses, but with a longer incubation period (average three days).**
  - **15-30% of respiratory illness in adults during winter months but lower respiratory infections were rare.**
  - **Antibodies appear early in childhood and are found in 90% in adults**

SARS Corona Virus

This has a unique pathogenesis because it causes both upper and lower respiratory tract infections and can also cause Gastroenteristis.

Recent History

- **In 2003 The SARS epidemic resulted in over 8,000 infections, about 10% of which resulted in death.**

MERS- CoV Symptoms

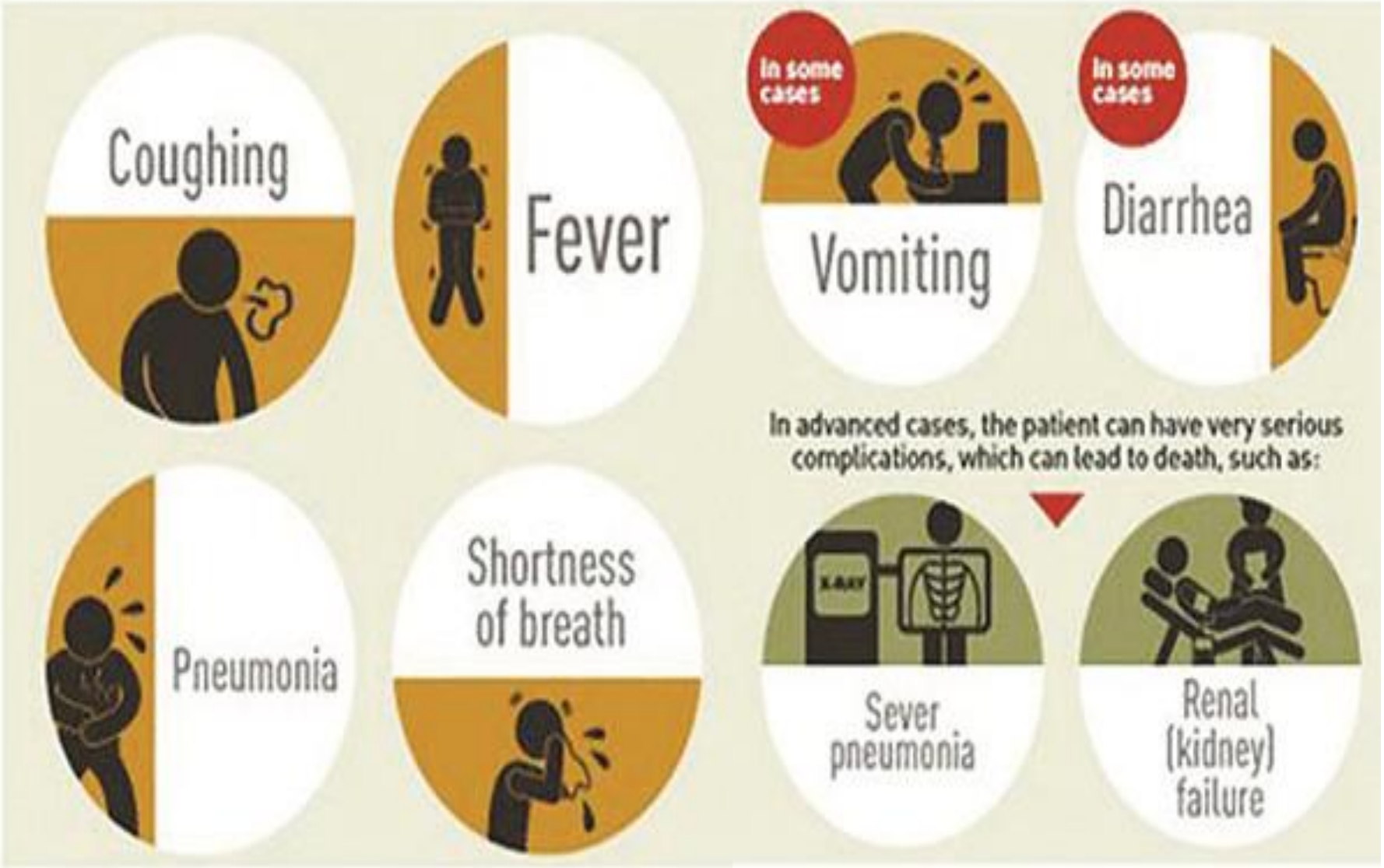
- **A person will show the symptoms after a week**

- **Flu-like symptoms,**

a heavy cough.

Some cases have had atypical presentations : Initially presented with abdominal pain and diarrhea and later developed respiratory complications

Signs and symptoms of MERS coronavirus infection

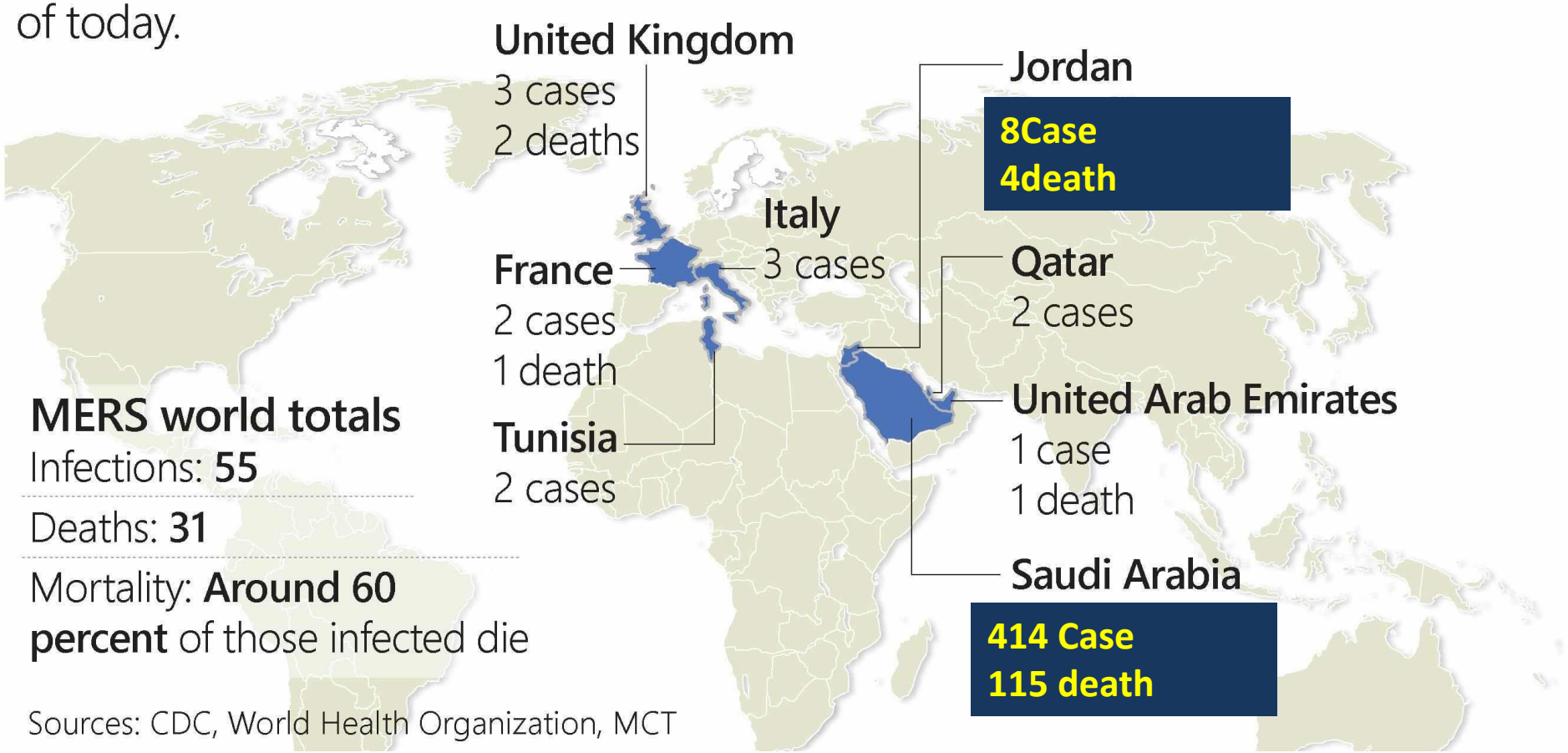


Epidemiological summary MERS-CoV Cases

- As of 16 April 2014, MERS-CoV cases have been reported in several countries, including
  Saudi Arabia,
  Malaysia,
  Jordan
  Qatar,
  the United Arab Emirates,
  France
  Germany
  Italy
  UK
  USA
  Tunisia,
  Philippines.
- The official WHO MERS count
- In 6 May 2014 there are 339 confirmed cases in Saudi Arabia, with 115 deaths.

MERS cases and deaths

Cases of Middle East respiratory syndrome coronavirus (MERS) worldwide as of today.



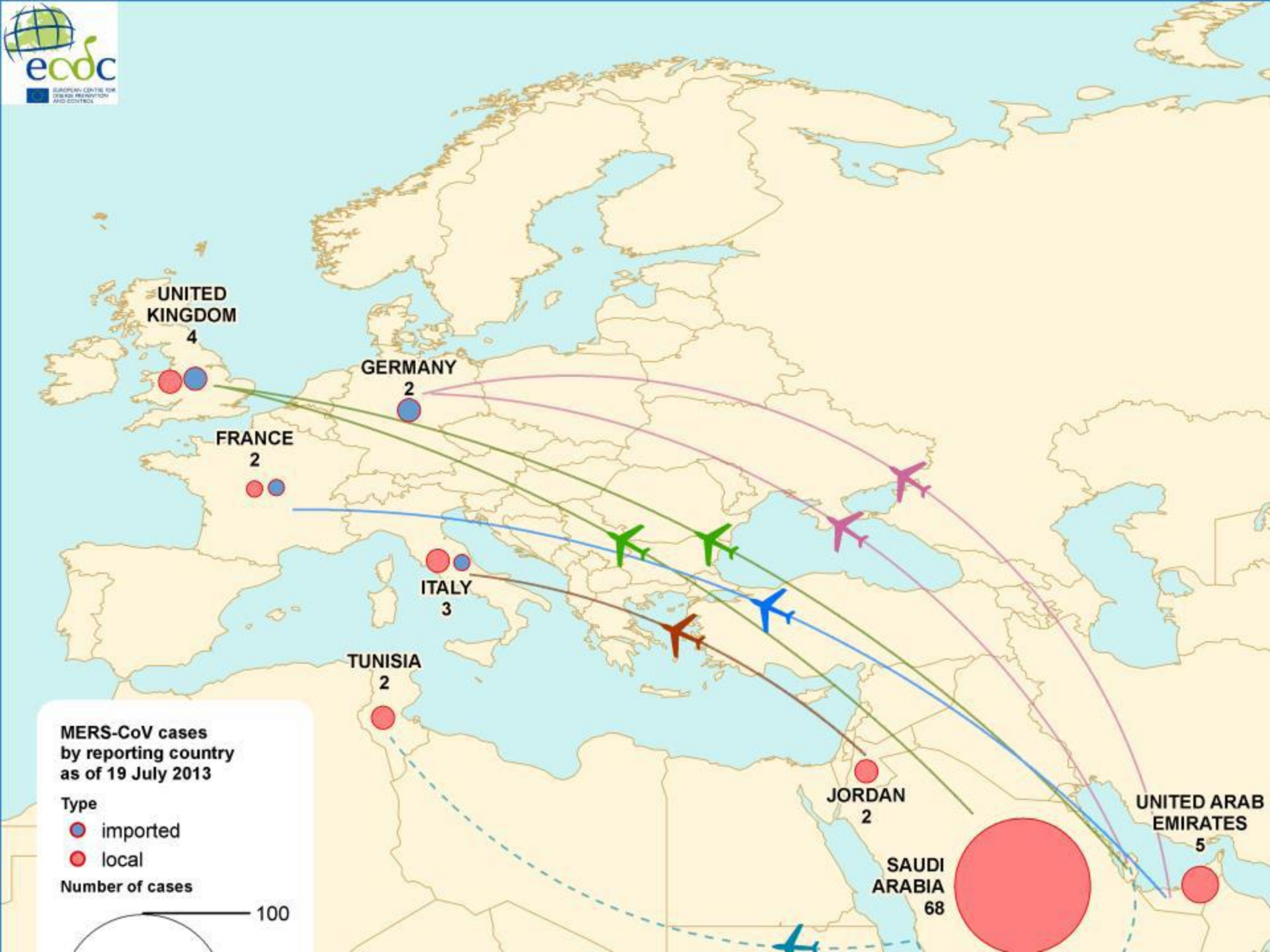
MERS world totals

Infections: **55**

Deaths: **31**

Mortality: **Around 60 percent** of those infected die

Sources: CDC, World Health Organization, MCT


UNITED KINGDOM
4
GERMANY
2
FRANCE
2
ITALY
3
TUNISIA
2
JORDAN
2
SAUDI ARABIA
68
UNITED ARAB EMIRATES
5
MERS-CoV cases by reporting country as of 19 July 2013
Type
imported
local
Number of cases
100

Immunity

As with other respiratory viruses, immunity develops but is not absolute.

Immunity against the surface projection antigen is probably most important for protection.

Resistance to reinfection may last several years, but reinfections with similar strains are common.

Most patients (>95%) with SARS developed an antibody response to viral antigens detectable by a fluorescent antibody test or ELISA.

It was important that the convalescent serum be collected more than 28 days after symptom onset.

Figure 5. Schematic representation of key responses to MERS-CoV related to outcome.

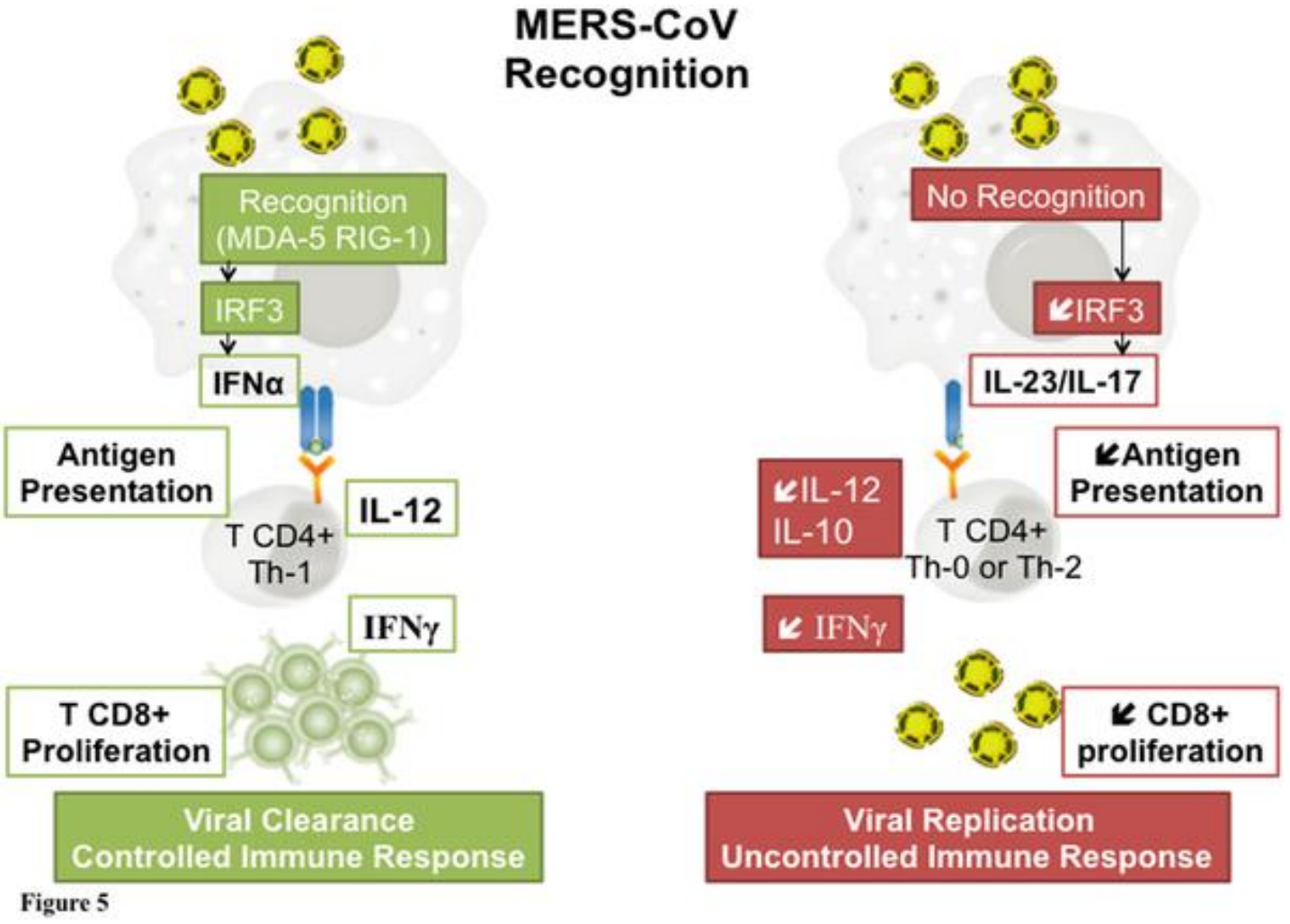


Figure 5

Faure E, Poissy J, Goffard A, Fournier C, et al. (2014) Distinct Immune Response in Two MERS-CoV-Infected Patients: Can We Go from Bench to Bedside?. PLoS ONE 9(2): e88716. doi:10.1371/journal.pone.0088716
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0088716

Laboratory Diagnosis of coronaviruses

DIRECT DETECTION:

- **Antigen detection in cells of respiratory secretions by IF or ELISA**
- **NA detection in respiratory secretions by RT-PCR**

The detection of MERS-CoV in the first reported case was performed by a pan-coronavirus RT-PCR assay.This assay targets the gene of the RNA-dependent RNA polymerase

ISOLATION:

- **CoV are difficult to grow in CC.**
- **Reliable isolation of the virus is accomplished using human embryonic tracheal organ cultures.**
- **These methods are not routinely available.**

Serology:

- **Serologic tests are not routinely available.**

  An alternative diagnostic approach is the detection of an antibody response against MERS-CoV, by immunofluorescence microscopy

  Practical means to confirm coronavirus infection using paired sera to detect rising or stationary high antibody level by:

  - **PASSIVE HAEMAGGLUTINATION TEST**

  - **ELISA**

TREATMENT

- TREATMENT TRAILS
- TRAILS FOR PRODUCTION OF MERS-COV VACCINE

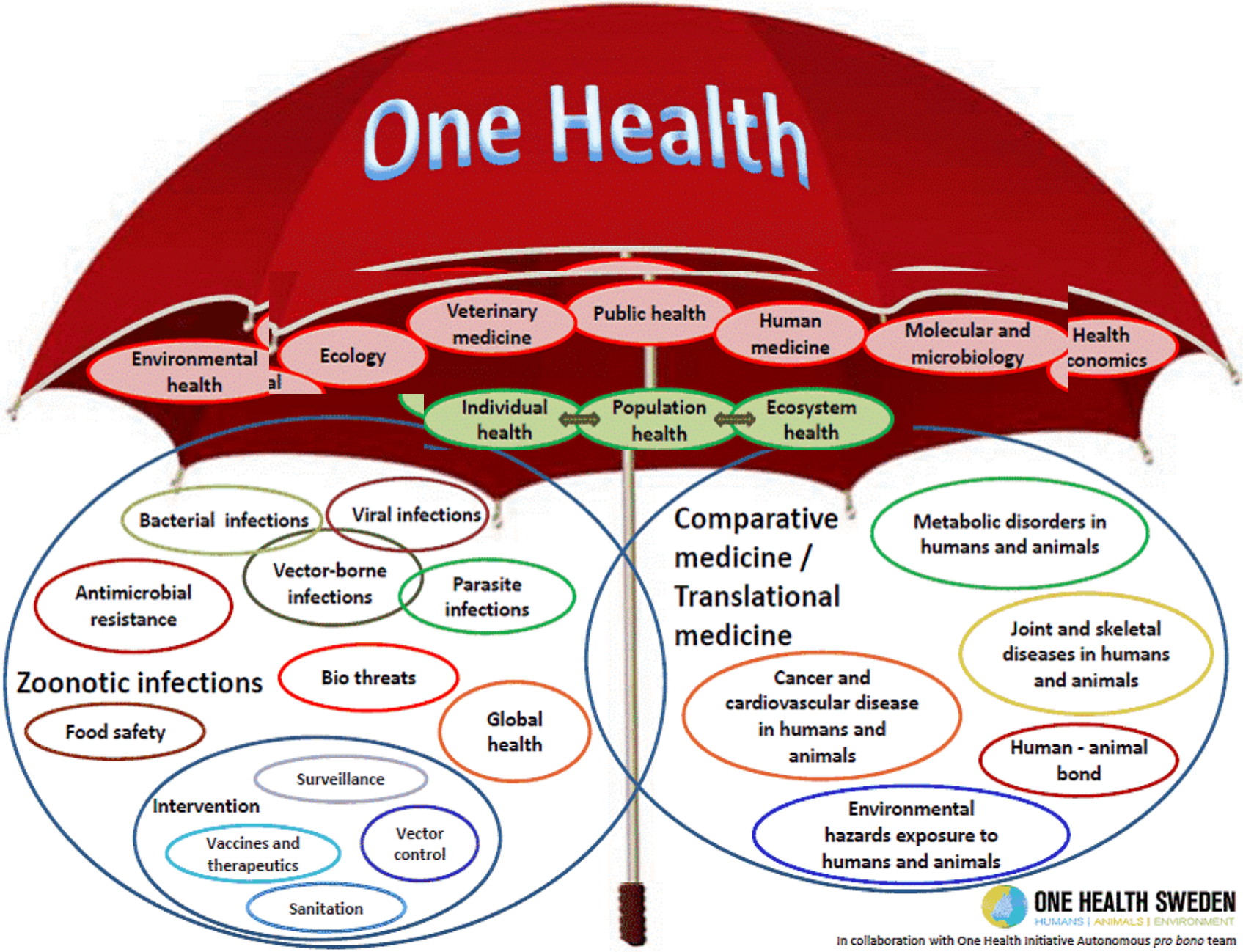
VACCINE STUDIES IN MICE.

Compounds that have been suggested as possible drug candidates against MERS-CoV infections

Drug candidate	Observed effect	Study
INF-α	Reduction of MERS-CoV replication in pseudo-stratified HAE cultures	Kindler *et al.* (2013)[50]
pegylated IFN-α	Inhibition of MERS-CoV-induced CPE and reduction of the viral RNA levels in human lung epithelial and monkey kidney cell lines	de Wilde *et al.* (2013)[52]
INF-β	Reduction of the viral load in MERS-CoV-infected human lung epithelial and monkey kidney cell lines	Zielecki *et al.* (2013)[48]
INF-λ3	Reduction of MERS-CoV replication in pseudo-stratified HAE cultures	Kindler *et al.* (2013)[50]
INF-α2b	Reduction of the MERS-CoV-induced CPE and the viral protein levels in monkey kidney cell lines (more efficient when combined with Ribavirin)	Falzarano *et al.* (2013)[72]
Ribavirin	Reduction of the MERS-CoV-induced CPE and the viral protein levels in monkey kidney cell lines (more efficient when combined with INF-α2b)	Falzarano *et al.* (2013)[72]
Corticosteroids	Significant improvement of the respiratory condition of a MERS-CoV patient (no direct effect has been proved)	Guberina *et al.* (2013)[65]
Cyclosporin A	Inhibition of the MERS-CoV-induced CPE in monkey kidney and a human liver cell lines	de Wilde *et al.* (2013)[52]
SB203580	Reduction of the viral load in a human lung epithelial cell line	Josset *et al.* (2013)[54]
ADS-J1	Inhibition of MERS-CoV pseudo-virus infection in human liver and mink lung cell lines	Zhao *et al.* (2013)[29]
HP-HAS	Inhibition of MERS-CoV pseudo-virus infection in human liver and mink lung cell lines	Zhao *et al.* (2013)[29]
MDL28170	Inhibition of MERS-CoV-S-mediated transduction of a human fetal lung fibroblast cell line	Gierer *et al.* (2013)[25]
NH4Cl	Inhibition of MERS-CoV-S-mediated transduction of a human fetal lung fibroblast cell line	
Camostat	Inhibition of MERS-CoV-S-mediated transduction of a human colon cell line	Gierer *et al.* (2013)[25]
N3	Inhibition of the proteolytic activity of MERS-CoV 3CLpro	Ren *et al.* (2013)[73]
CE-10	Inhibition of the proteolytic activity of MERS-CoV 3CLpro	Kilianski *et al.* (2013)[74]
MERS-CoV RBD	Reduction of the viral load in a MERS-CoV-infected monkey kidney cell line	Chen

YET STOPPING THE SPREAD OF INFECTION WAS POSSIBLE THROUGH

EFFECTIVE CONTROL MEASURES


One Health
Environmental health
Ecology
Veterinary medicine
Public health
Human medicine
Molecular and microbiology
Health economics
Individual health
Population health
Ecosystem health
Bacterial infections
Viral infections
Vector-borne infections
Parasite infections
Antimicrobial resistance
Zoonotic infections
Bio threats
Food safety
Global health
Surveillance
Intervention
Vaccines and therapeutics
Vector control
Sanitation
Comparative medicine / Translational medicine
Metabolic disorders in humans and animals
Joint and skeletal diseases in humans and animals
Cancer and cardiovascular disease in humans and animals
Human - animal bond
Environmental hazards exposure to humans and animals
ONE HEALTH SWEDEN
HUMANS | ANIMALS | ENVIRONMENT
In collaboration with One Health Initiative Autonomous *pro bono* team

KEY POINTS IN CONTROL OF ANY COMMUNICABLE DISEASE

- Early case detection
- Swift isolation
- Thorough control of infection measures
- Vigorous identification and management of close contacts
- Public information for those at risk of infection
- Education of health care professionals

Prevention Measures

✓ Because there are no treatments and no vaccine ,

✓Keep away from someone with a heavy cough, use a tissue to cover the nose/mouth when coughing

✓ Sneezing, wiping and blowing noses, if a tissue isn't available, cough or sneeze into the inner elbow rather than the hand

✓ Wash hands with hot water and soap at least six or seven times a day

✓ Disinfect common surfaces as frequently as possible.

✓ Wash hands or use a sanitizer when in contact with common surfaces like door handles.

MERS Resources

- MERS overview: http://www.cdc.gov/coronavirus/mers/index.html
- Case definitions and guidance: http://www.cdc.gov/coronavirus/mers/case-def.html
- Additional MERS resources: http://www.cdc.gov/coronavirus/mers/related-materials.html

MERS-COV RESOURCES