RECENT AND POTENTIAL PANDEMICS OF RESPIRATORY VIRAL INFECTIONS AND THEIR PREVENTION AND MANAGEMENT

DM SEMINAR

Dr. Pratap Upadhya

3/2/17

- ✓ Introduction
- ✓ Middle East respiratory syndrome coronavirus-MERS CoV
- ✓ Novel avian influenza A-H7N9
- ✓ Infection control and prevention

INTRODUCTION:

A **pandemic** is an epidemic of infectious **disease** that has spread through human populations across a large region; for instance multiple continents or even worldwide.

- ***Pandemic*** *is different from an* ***epidemic*** *or seasonal outbreak.*
- ***Pandemic*** *covers a much wider geographical area, often worldwide where as an* ***epidemic*** *is specific to one city, region or country.*
- *cause great numbers of* ***hospitalizations*** *and deaths*

http://www.who.int/csr/disease/en/

phases:

Phase 1	No animal virus circulating among animals has been reported to cause infection in humans.
Phase 2	An animal virus is known to have caused infection in humans and is therefore considered a specific potential pandemic threat.
Phase 3	sporadic cases or small clusters of disease in people has not resulted in human-to-human transmission sufficient to sustain community-level outbreaks.
Phase 4	Human-to-human transmission able to sustain community-level outbreaks has been verified.
Phase 5	The same identified virus has caused sustained community level outbreaks atleast 2 countries in 1 WHO region.
Phase 6	sustained community level outbreaks in at least one other country in another WHO region.

http://ecdc.europa.eu/en/healthtopics/pandemic_preparedness/basic_facts/Pages/WHO_pandemic_phases.aspx

Epidemic and pandemic diseases

- **Airborne diseases:** influenza (seasonal, pandemic, avian), severe acute respiratory syndrome (SARS), Middle East respiratory syndrome coronavirus (MERS-CoV)
- **Vector-borne diseases:** yellow fever, chikungunya, Zika fever, West Nile fever
- **Water-borne diseases:** cholera, shigellosis, typhoid fever
- **Epidemic meningitis**
- **Rodent-borne diseases:** plague, leptospirosis, hantavirus, Lassa fever, rickettsia (murine typhus)
- **Haemorrhagic fevers:** Ebola virus disease, Marburg virus disease, Crimean-Congo haemorrhagic fever, Rift Valley fever
- Smallpox, **monkeypox**
- **Other zoonotic diseases:** Nipah virus infection, Hendra virus infection

http://www.who.int/csr/disease/en/

- Acute respiratory infections (ARIs) are the leading cause of morbidity and mortality from infectious disease in the world.
- 4 million deaths/yr
- most common causes are viruses or mixed viral–bacterial infections.
- ARIs that have epidemic or pandemic potential, and may pose a public-health risk, warrant special precautions and preparedness

World Health Organization (WHO). The World Health Report 2004: changing history [electronic resource]
Reviews of Infectious Diseases, 1991, 13 Suppl 6:S454–462

Infectious diseases have spread across populations and regions throughout history, and it is likely that newly emerging infectious diseases will continue to be identified.

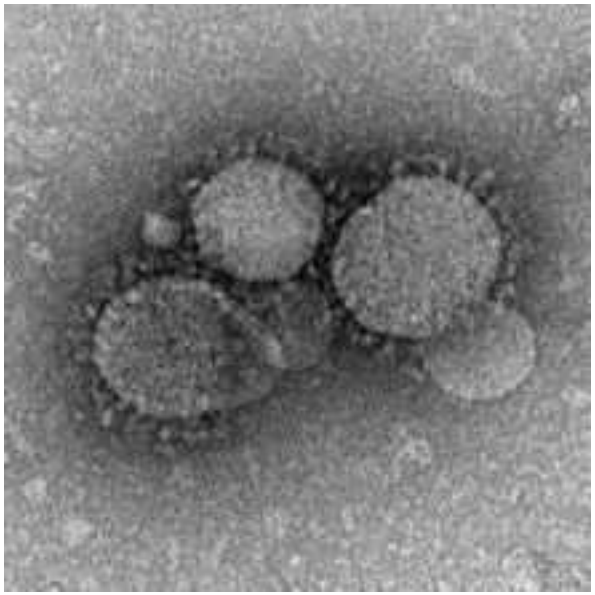
The following factors have been associated with the emergence and spread of infectious diseases

- changes in human demographics and behaviour;
- impact of new technologies and industries;
- economic development and changes in land use;
- increased international travel and commerce;
- microbial adaptation and change;
- poor implementation of public-health measures; and
- sharing an environment with domestic or wild animals, including birds.

Emerging infections: microbial threats to health in the United States. Washington, D.C., The Institute of Medicine, 1992.
Principles and practice of infectious disease. Philadelphia, Elsevier Churchill Livingstone, 2005:173–192.

Middle East respiratory syndrome coronavirus

MERS-CoV



- Introduction
- Virology
- pathology
- Epidemiology
- Clinical manifestations
- Diagnosis
- Treatment
- Prevention

Introduction:

Case1-
Jeddah, Saudi Arabia
13/6/2012

A patient in his sixties presented with 7 days of respiratory complaints

Died after 11 days
[Virus isolated from sputum]

Case2-September 2012

A man in forties with severe respiratory symptoms from QATAR, had travelled to SAUDI, sought medical help in UNITED KINGDOM.

Published Date: 2012-09-20 15:51:26
Subject: PRO/EDR> Novel coronavirus - Saudi Arabia: human isolate
Archive Number: 20120920.1302733

NOVEL CORONAVIRUS - SAUDI ARABIA: HUMAN ISOLATE
****

A ProMED-mail post
http://www.promedmail.org
ProMED-mail is a program of the
International Society for Infectious Diseases
http://www.isid.org

Date: Sat 15 Sep 2012
From: Ali Mohamed Zaki <azaki53@hotmail.com> [edited]

A new human coronavirus was isolated from a patient with pneumonia by Dr Ali Mohamed Zaki at the Virology Laboratory of Dr Soliman Fakeeh Hospital Jeddah Saudi Arabia.

The virus was isolated from sputum of a male patient aged 60 years old presenting with pneumonia associated with acute renal failure. The virus grows readily on Vero cells and LLC-MK2 cells producing CPE in the form of rounding and syncetia formation.

BMJ

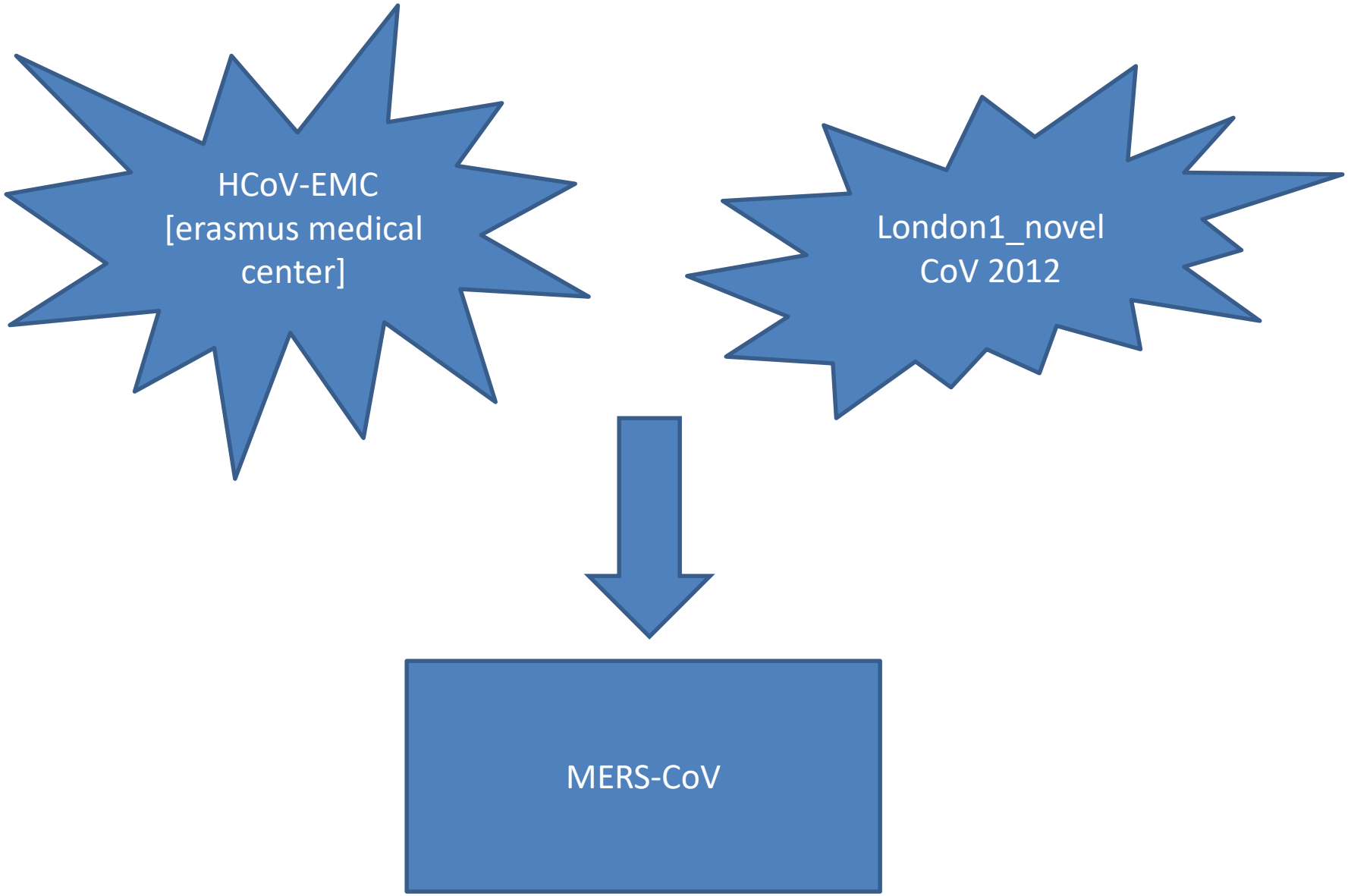
BMJ 2012;345:e6455 doi: 10.1136/bmj.e6455 (Published 24 September 2012)

NEWS

Patient with new strain of coronavirus is treated in intensive care at London hospital

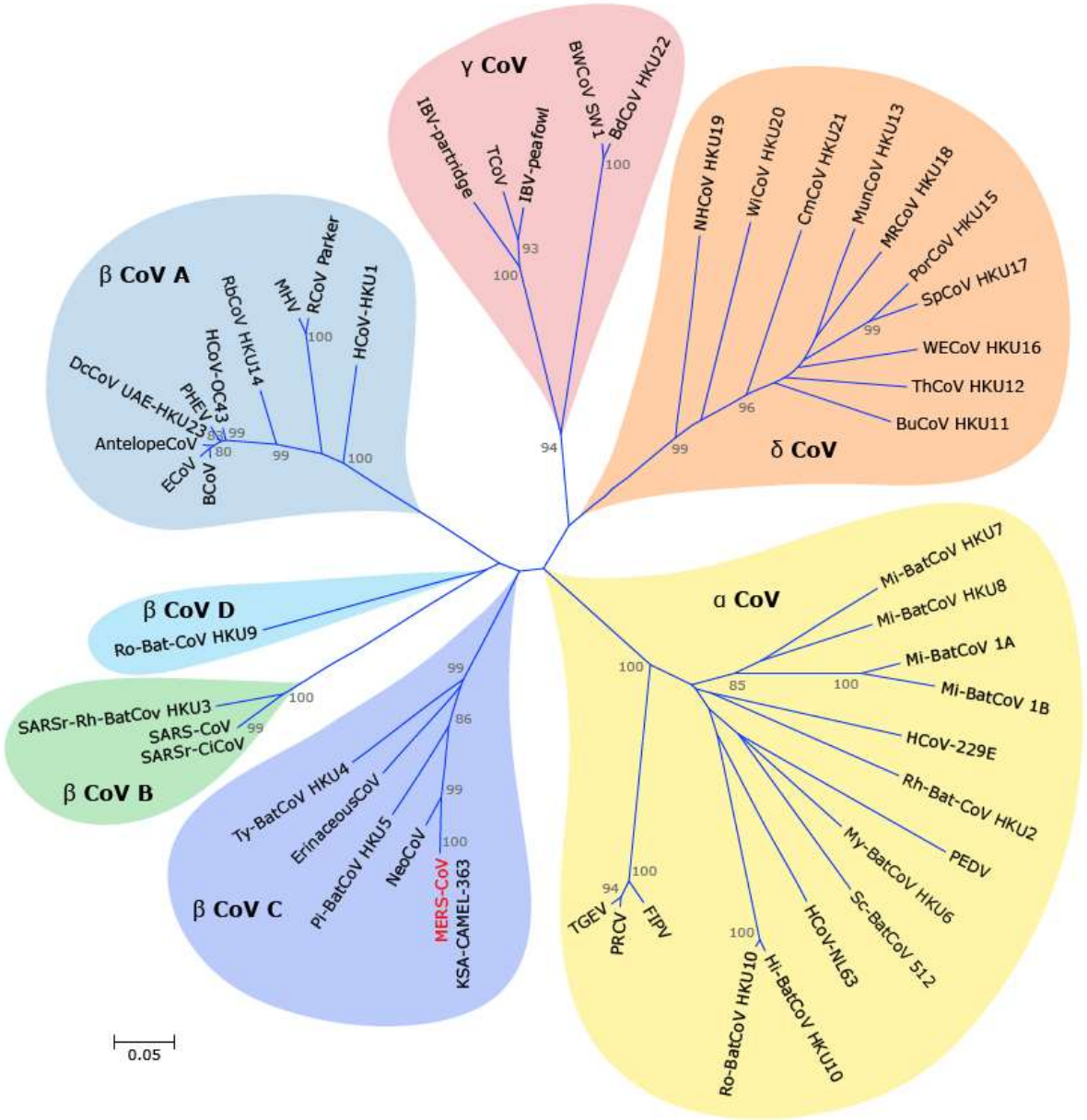
Jacqui Wise

London

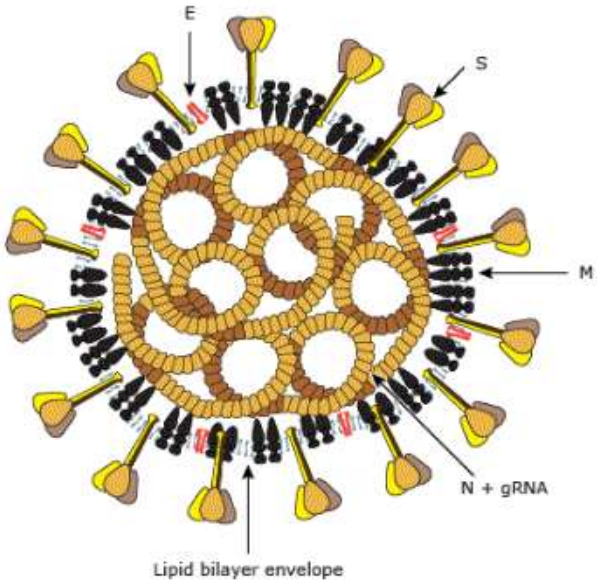

HCoV-EMC
[erasmus medical
center]
London1_novel
CoV 2012
MERS-CoV

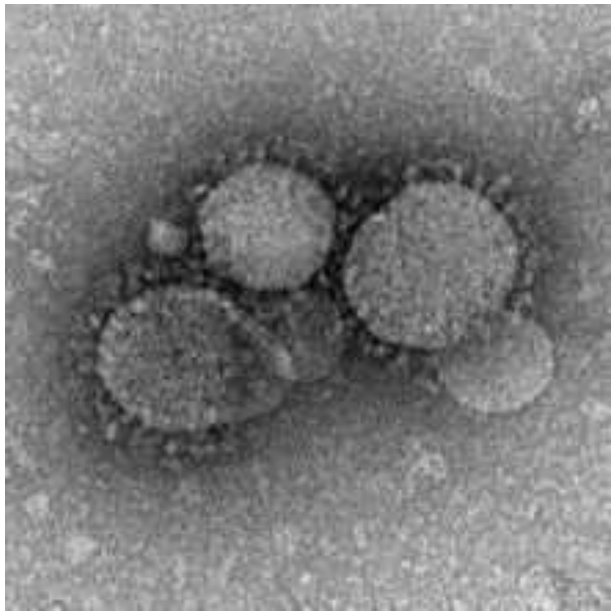
Virology:

- Coronaviruses are important human and animal pathogens.
- 1/3rd-community-acquired upper respiratory tract infections in adults.
- has a role in severe respiratory infections in both children and adults.
- Coronaviruses are classified as a family within the Nidovirales order, viruses that replicate using a nested set of mRNAs ("nido-" for "nest").



Clin Microbiol Rev 2015; 28:465.





Masters PS, Perlman S. Coronaviridae. In: Fields Virology, 6th edition

Pathogenesis: poorly understood

Virus shedding-

Lower respiratory tract samples of symptomatic patients

- For weeks!!
- RNA loads decrease with time
- RNA levels corelate with disease severity
- **Isolated even from environmental samples**

almost all studies of viral shedding have depended on real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) for detection of the MERS coronavirus

Clinical Infectious Diseases

MAJOR ARTICLE

Viral Shedding and Antibody Response in 37 Patients With Middle East Respiratory Syndrome Coronavirus Infection

Victor M. Corman,[1,2] Ali M. Albarrak,[3] Ali Senosi Omrani,[3] Mohammed M. Albarrak,[4] Mohamed Elamin Farah,[5] Malak Almasri,[6] Doreen Muth,[1,2] Andrea Sieberg,[1] Benjamin Meyer,[1] Abdullah M. Assiri,[6] Tabea Binger,[1] Katja Steinhagen,[7] Erik Lattwein,[7] Jaffar Al-Tawfiq,[8,9] Marcel A. Müller,[1] Christian Drosten,[1,2,a] and Ziad A. Memish[6,10,a]

[1]Institute of Virology, University of Bonn Medical Centre, and [2]German Centre for Infection Research, Partner Site Bonn-Cologne, Bonn, Germany; [3]Division of Infectious Diseases, [4]Department of Critical Care, [5]Central Military Laboratory and Blood Bank, Microbiology Division, Prince Sultan Military City, [6]Ministry of Health, Riyadh, Kingdom of Saudi Arabia; [7]Euroimmun AG, Lübeck, Germany; [8]Johns Hopkins Aramco Healthcare, Dhahran, and [9]Indiana University School of Medicine, Indianapolis; and [10]College of Medicine, Alfaisal University, Riyadh, Kingdom of Saudi Arabia

Background. The Middle East respiratory syndrome (MERS) coronavirus causes isolated cases and outbreaks of severe respiratory disease. Essential features of the natural history of disease are poorly understood.

Methods. We studied 37 adult patients infected with MERS coronavirus for viral load in the lower and upper respiratory tracts (LRT and URT, respectively), blood, stool, and urine. Antibodies and serum neutralizing activities were determined over the course of disease.

Results. One hundred ninety-nine LRT samples collected during the 3 weeks following diagnosis yielded virus RNA in 93% of tests. Average (maximum) viral loads were 5×10^6 (6×10^{10}) copies/mL. Viral loads (positive detection frequencies) in 84 URT samples were 1.9×10^4 copies/mL (47.6%). Thirty-three percent of all 108 serum samples tested yielded viral RNA. Only 14.6% of stool and 2.4% of urine samples yielded viral RNA. All seroconversions occurred during the first 2 weeks after diagnosis, which corresponds to the second and third week after symptom onset. Immunoglobulin M detection provided no advantage in sensitivity over immunoglobulin G (IgG) detection. All surviving patients, but only slightly more than half of all fatal cases, produced IgG and neutralizing antibodies. The levels of IgG and neutralizing antibodies were weakly and inversely correlated with LRT viral loads. Presence of antibodies did not lead to the elimination of virus from LRT.

Conclusions. The timing and intensity of respiratory viral shedding in patients with MERS closely matches that of those with severe acute respiratory syndrome. Blood viral RNA does not seem to be infectious. Extrapulmonary loci of virus replication seem possible. Neutralizing antibodies do not suffice to clear the infection.

Keywords. MERS; viral load; antibodies; shedding; clearance.

Visit Date	Symptoms	RT-PCR	Ct Value
24 April 2014	None	Positive	35
29 April 2014	None	Positive	35
9 May 2014	None	Positive	34
21 May 2014	None	Positive	32
29 May 2014	None	Positive	30
30 May 2014	None	Positive	32
5 June 2014	None	Positive	35
12 June 2014	None	Negative	0
14 June 2014	None	Negative	0

Clin Infect Dis. 2015 Mar;60(6):973-4. Epub 2014 Dec 16

Clinical Infectious Diseases

MAJOR ARTICLE

Environmental Contamination and Viral Shedding in MERS Patients During MERS-CoV Outbreak in South Korea

Seo Yu Bin,[1,a] Jung Yeon Heo,[2,a] Min-Suk Song,[3,a] Jacob Lee,[1,a] Eun-Ha Kim,[3] Su-Jin Park,[3,4] Hyeok-il Kwon,[3,4] Se mi Kim,[3,4] Young-il Kim,[3,4] Young-Jae Si,[3,4] In-Won Lee,[3,4] Yun Hee Baek,[3] Won-Suk Choi,[3] Jinsoo Min,[2] Hye Won Jeong,[2] and Young Ki Choi[2,4]

[1]Division of Infectious Diseases, Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, [2]Departments of Internal Medicine, and [3]Microbiology, College of Medicine and Medical Research Institute, and [4]Zoonotic Infectious Diseases Research Center, Chungbuk National University, Seowon-Gu, Cheongju, Republic of Korea

Background. Although Middle East Respiratory Syndrome coronavirus (MERS-CoV) is characterized by a risk of nosocomial transmission, the detailed mode of transmission and period of virus shedding from infected patients are poorly understood. The aims of this study were to investigate the potential role of environmental contamination by MERS-CoV in healthcare settings and to define the period of viable virus shedding from MERS patients.

Methods. We investigated environmental contamination from 4 patients in MERS-CoV units of 2 hospitals. MERS-CoV was detected by reverse transcription polymerase chain reaction (PCR) and viable virus was isolated by cultures.

Results. Many environmental surfaces of MERS patient rooms, including points frequently touched by patients or healthcare workers, were contaminated by MERS-CoV. Viral RNA was detected up to five days from environmental surfaces following the last positive PCR from patients' respiratory specimens. MERS-CoV RNA was detected in samples from anterooms, medical devices, and air-ventilating equipment. In addition, MERS-CoV was isolated from environmental objects such as bed sheets, bedrails, IV fluid hangers, and X-ray devices. During the late clinical phase of MERS, viable virus could be isolated in 3 of the 4 enrolled patients on day 18 to day 25 after symptom onset.

Conclusions. Most of touchable surfaces in MERS units were contaminated by patients and health care workers and the viable virus could shed through respiratory secretion from clinically fully recovered patients. These results emphasize the need for strict environmental surface hygiene practices, and sufficient isolation period based on laboratory results rather than solely on clinical symptoms.

Keywords. MERS-CoV; South Korea; transmission mode; environmental contamination; prolonged viral shedding.

Clin Infect Dis. 2016;62(6):75

Receptor distribution:

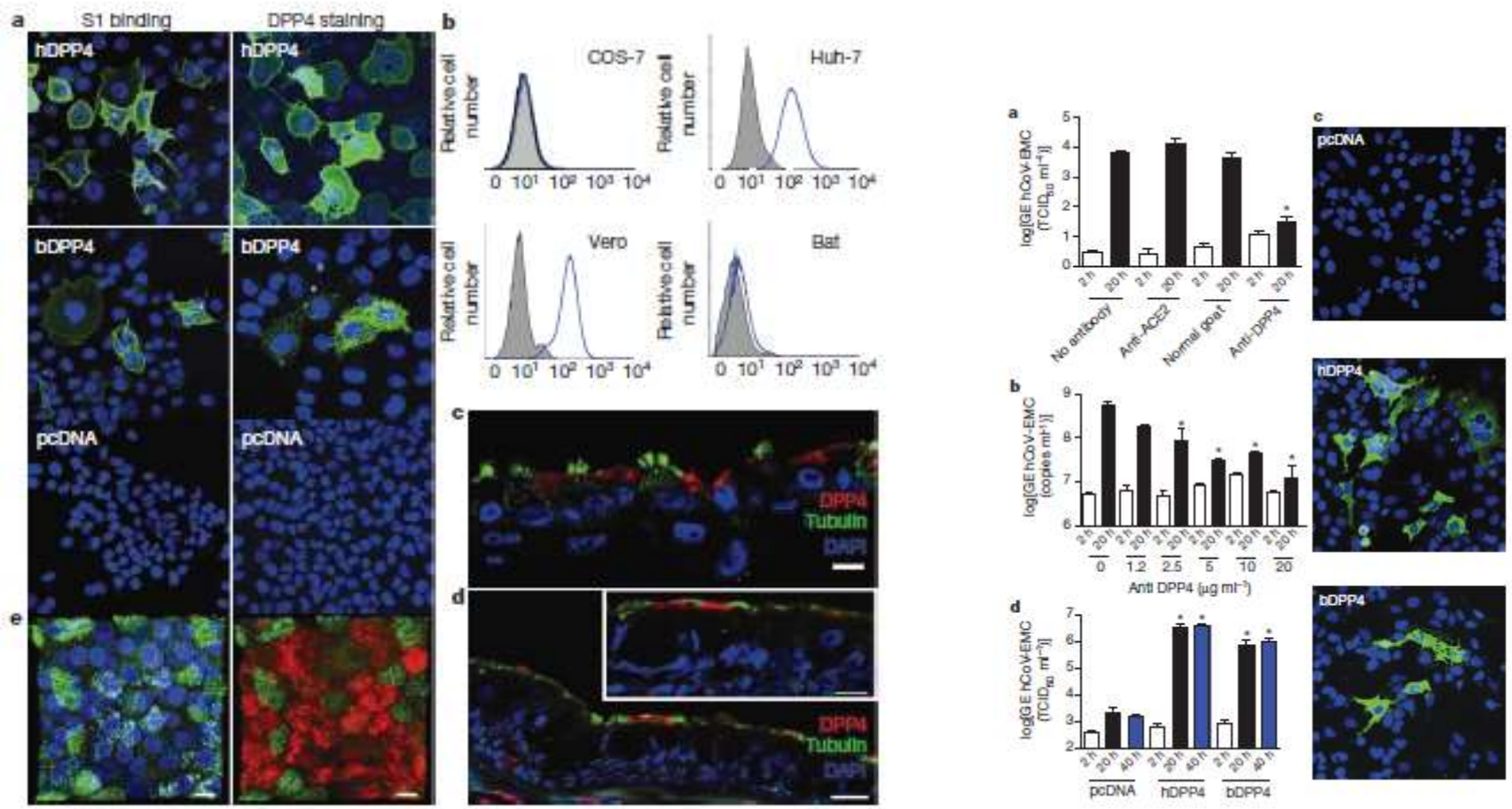
Dipeptidyl peptidase 4 (DPP4), is the the MERS-CoV receptor, is expressed in the upper respiratory tract epithelium of camels, but in humans only in the lower respiratory tract.

- *surfaces of human non ciliated bronchial epithelial cells*
- *DPP4 protein displays high amino acid sequence conservation across different species.*
- *In a cell line susceptibility study, MERS-CoV infected several human cell lines, including lower (but not upper) respiratory, kidney, intestinal, and liver cells as well as histiocytes*

Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC

V. Stalin Raj[1]*, Huihui Mou[2]*, Saskia L. Smits[1,3], Dick H. W. Dekkers[4], Marcel A. Müller[5], Ronald Dijkman[6], Doreen Muth[5], Jeroen A. A. Demmers[4], Ali Zaki[7], Ron A. M. Fouchier[1], Volker Thiel[6,8], Christian Drosten[5], Peter J. M. Rottier[2], Albert D. M. E. Osterhaus[1], Berend Jan Bosch[2] & Bart L. Haagmans[1]

Nature. 2013 Mar;495(7440):251-4.



Nature. 2013 Mar;495(7440):251-4.

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Virology

Differential Expression of the Middle East Respiratory Syndrome Coronavirus Receptor in the Upper Respiratory Tracts of Humans and Dromedary Camels

W. Widagdo,[a] V. Stalin Raj,[a] Debby Schipper,[a] Kimberley Kolijn,[b] Geert J. L. H. van Leenders,[b] Berend J. Bosch,[c] Albert Bensaid,[d] Joaquim Segalés,[e,f] Wolfgang Baumgärtner,[g] Albert D. M. E. Osterhaus,[a,h,i] Marion P. Koopmans,[a] Judith M. A. van den Brand,[a] Bart L. Haagmans[a]

Department of Viroscience, Erasmus MC, Rotterdam, The Netherlands[a]; Department of Pathology, Erasmus MC, Rotterdam, The Netherlands[b]; Virology Division, Department of Infectious Diseases and Immunology, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands[c]; IRTA, Centre de Recerca en Sanitat Animal (CReSA), Campus de la Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain[d]; UAB, Centre de Recerca en Sanitat Animal (CReSA), Unitat Mixta IRTA-UAB, Campus de la Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain[e]; Departament de Sanitat I Anatomia Animals, Facultat de Veterinària, Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain[f]; Department of Pathology, University of Veterinary Medicine, Hannover, Germany[g]; Artemis One Health, Utrecht, The Netherlands[h]; Center for Infection Medicine and Zoonoses Research (FIIZ), University of Veterinary Medicine, Hannover, Germany[i]

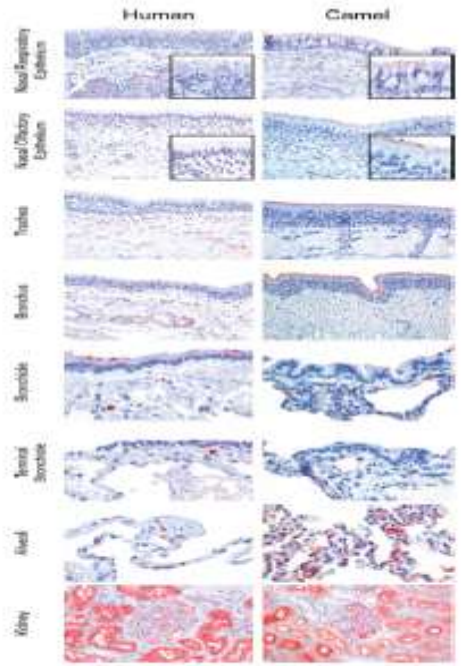
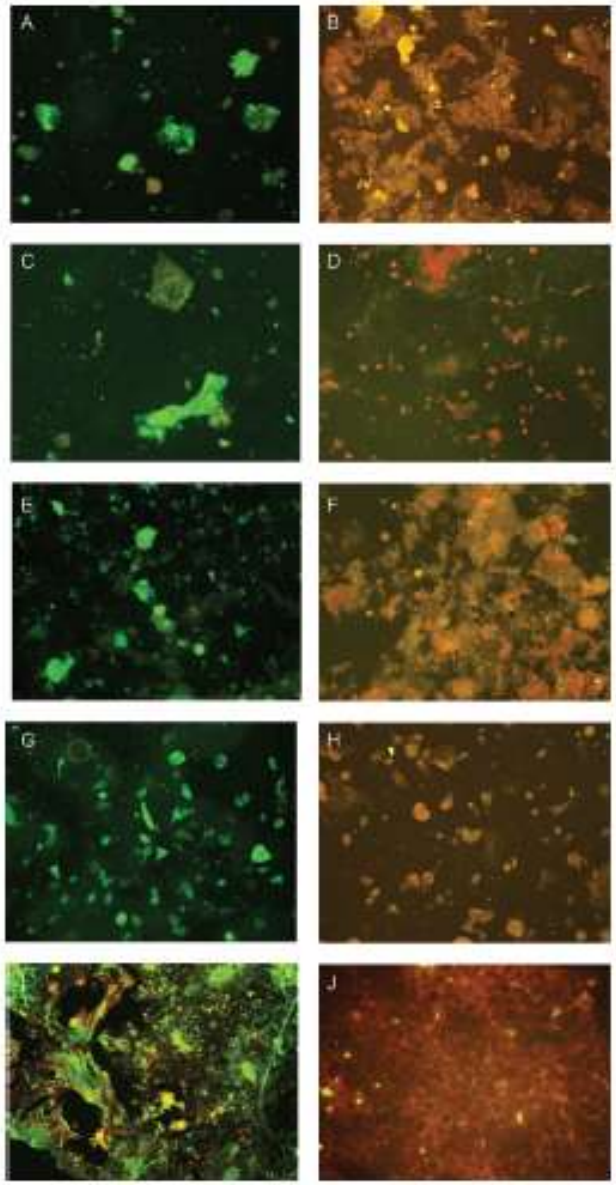


FIG 1 DPP4 expression in the upper respiratory tracts of camels and humans. DPP4 immunohistochemistry staining of human and dromedary camel respiratory tissue samples was performed; kidney tissue was used as the positive control. Nose, trachea, bronchus, and kidney samples, ×200 magnification; bronchiole, terminal bronchiole, and alveolar samples, ×400 magnification. Positive staining is red.

Differential Cell Line Susceptibility to the Emerging Novel Human Betacoronavirus 2c EMC/2012: Implications for Disease Pathogenesis and Clinical Manifestation

Jasper Fuk-Woo Chan,[1,a] Kwok-Hung Chan,[1,a] Garnet Kwan-Yue Choi,[1] Kelvin Kai-Wang To,[1,2,3,4] Herman Tse,[1,2,3,4] Jian-Piao Cai,[1] Man Lung Yeung,[1] Vincent Chi-Chung Cheng,[1] Honglin Chen,[1] Xiao-Yan Che,[5] Susanna Kar-Pui Lau,[1,2,3,4] Patrick Chiu-Yat Woo,[1,2,3,4] and Kwok-Yung Yuen[1,2,3,4]

[1]Department of Microbiology, [2]State Key Laboratory of Emerging Infectious Diseases, [3]Research Centre of Infection and Immunology, [4]Carol Yu Centre for Infection, the University of Hong Kong, Queen Mary Hospital, Hong Kong Special Administrative Region, and [5]Center for Clinical Laboratory, Zhujiang Hospital, Southern Medical University, Guangzhou, China



ure 1. Expression of human betacoronavirus 2c EMC/2012 (HCoV-EMC) nucleoprotein as intense apple green cytoplasmic fluorescence in differen l lines on day 3 after infection stained by monospecific polyclonal serum obtained from a guinea pig infected with His6-tagged HCoV-EMC nucleoprotei ginal magnification ×200). *A*, Infected lower airway (Calu-3) cells. *B*, Uninfected Calu-3 control. *C*, Infected intestinal (Caco-2) cells. *D*, Uninfected Caco ontrol. *E*, Infected liver (Huh-7) cells. *F*, Uninfected Huh-7 control. *G*, Infected histiocytes (His-1). *H*, Uninfected His-1 control. *I*, Infected African green nkey kidney (Vero) cells. *J*, Uninfected Vero control.

Histopathology:

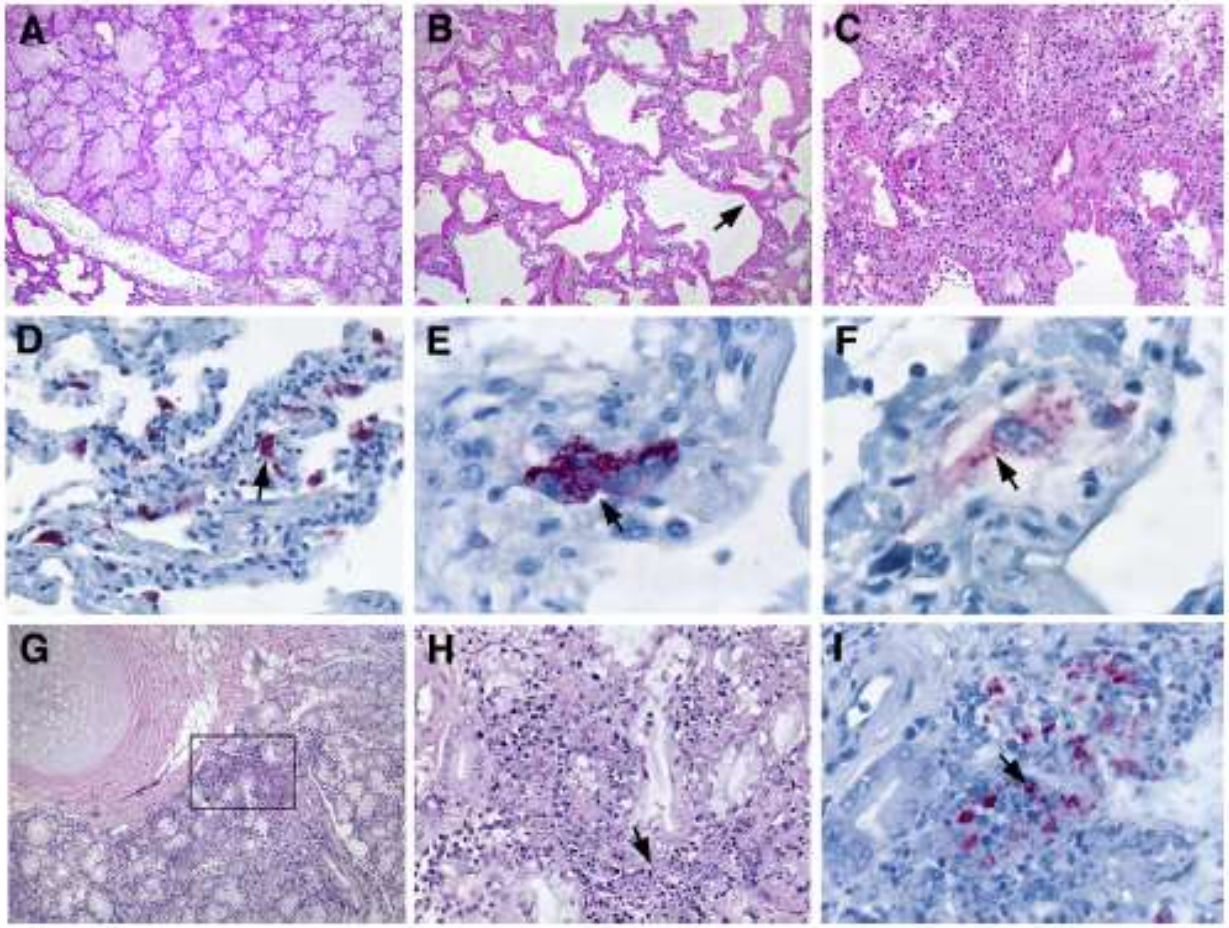
Few reports of biopsies/autopsies from MERS patients.

IMMUNOPATHOLOGY AND INFECTIOUS DISEASES

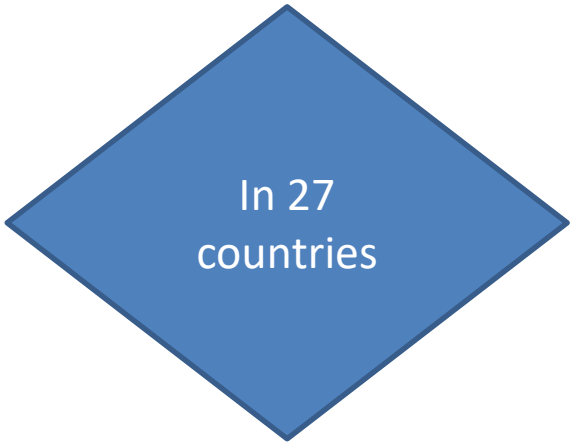
Clinicopathologic, Immunohistochemical, and Ultrastructural Findings of a Fatal Case of Middle East Respiratory Syndrome Coronavirus Infection in the United Arab Emirates, April 2014

Dianna L. Ng,* Farida Al Hosani,† M. Kelly Keating,* Susan I. Gerber,‡ Tara L. Jones,* Maureen G. Metcalfe,* Suxiang Tong,§ Ying Tao,§ Negar N. Alami,¶‖ Lia M. Haynes,** Mowafaq Ali Mutei,†† Laila Abdel-Wareth,‡‡ Timothy M. Uyeki,§§ David L. Swerdlow,¶¶ Maha Barakat,‖‖ and Sherif R. Zaki*

From the Infectious Diseases Pathology Branch, National Center for Emerging and Zoonotic Infectious Diseases, the Epidemiology Branch,‡ the Gastroenteritis and Respiratory Virus Laboratory Branch,§ the Epidemic Intelligence Service,¶ the Influenza Division,§§ the Office of the Director,** the National Center for Immunization and Respiratory Diseases,¶¶ and the International Research and Programs Branch,‖ National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; the Communicable Diseases Department,† and the Emergency and Disaster Department,†† Health Authority-Abu Dhabi,‖‖ Abu Dhabi, United Arab Emirates; and the Pathology and Laboratory Medicine Institute,‡‡ Cleveland Clinic, Abu Dhabi, United Arab Emirates


A
B
C
D
E
F
G
H
I

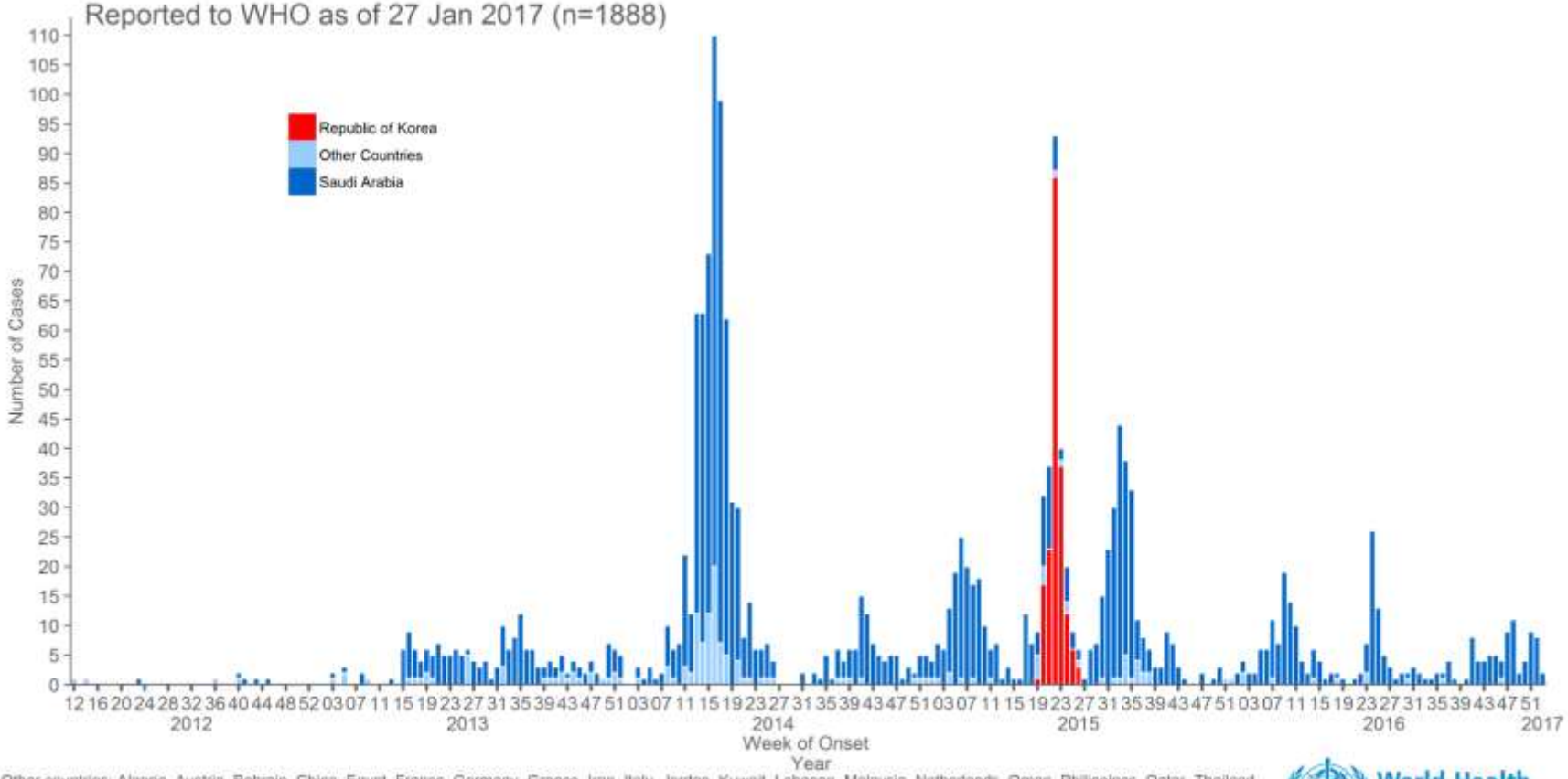
EPIDEMIOLOGY:



16/1/17-31/1/17-15 cases including 2 deaths in Saudi Arabia reported.

Confirmed global cases of MERS-CoV

Reported to WHO as of 27 Jan 2017 (n=1888)



Other countries: Algeria, Austria, Bahrain, China, Egypt, France, Germany, Greece, Iran, Italy, Jordan, Kuwait, Lebanon, Malaysia, Netherlands, Oman, Philippines, Qatar, Thailand, Tunisia, Turkey, United Arab Emirates, United Kingdom, United States of America, Yemen

Please note that the underlying data is subject to change as the investigations around cases are ongoing. Onset date estimated if not available.

World Health Organization

Geographical distribution:

	2012	2013	2014	2015	Total
Algeria	0	0	2	0	**2**
Austria	0	0	1	0	**1**
China	0	0	0	1	**1**
Egypt	0	0	1	0	**1**
France	0	2	0	0	**2**
Germany	1	1	0	1	**3**
Greece	0	0	1	0	**1**
Iran	0	0	5	1	**6**
Italy	0	1	0	0	**1**
Jordan	2	0	10	0	**12**
Kuwait	0	2	1	0	**3**
Lebanon	0	0	1	0	**1**
Malaysia	0	0	1	0	**1**
Netherlands	0	0	2	0	**2**
Oman	0	1	1	4	**6**
Philippines	0	0	0	2	**2**
Qatar	0	7	2	4	**13**
Republic of Korea	0	0	0	185	**185**
Saudi Arabia	5	136	679	217	**1037**
Thailand	0	0	0	1	**1**
Tunisia	0	3	0	0	**3**
Turkey	0	0	1	0	**1**
United Arab Emirates	0	12	57	7	**76**
United Kingdom	1	3	0	0	**4**
United States of America	0	0	2	0	**2**
Yemen	0	0	1	0	**1**
Total	**9**	**168**	**768**	**423**	**1368**

Sources and modes of transmission:

Primary animal host-dromedary camels.

Reservoir- Bats

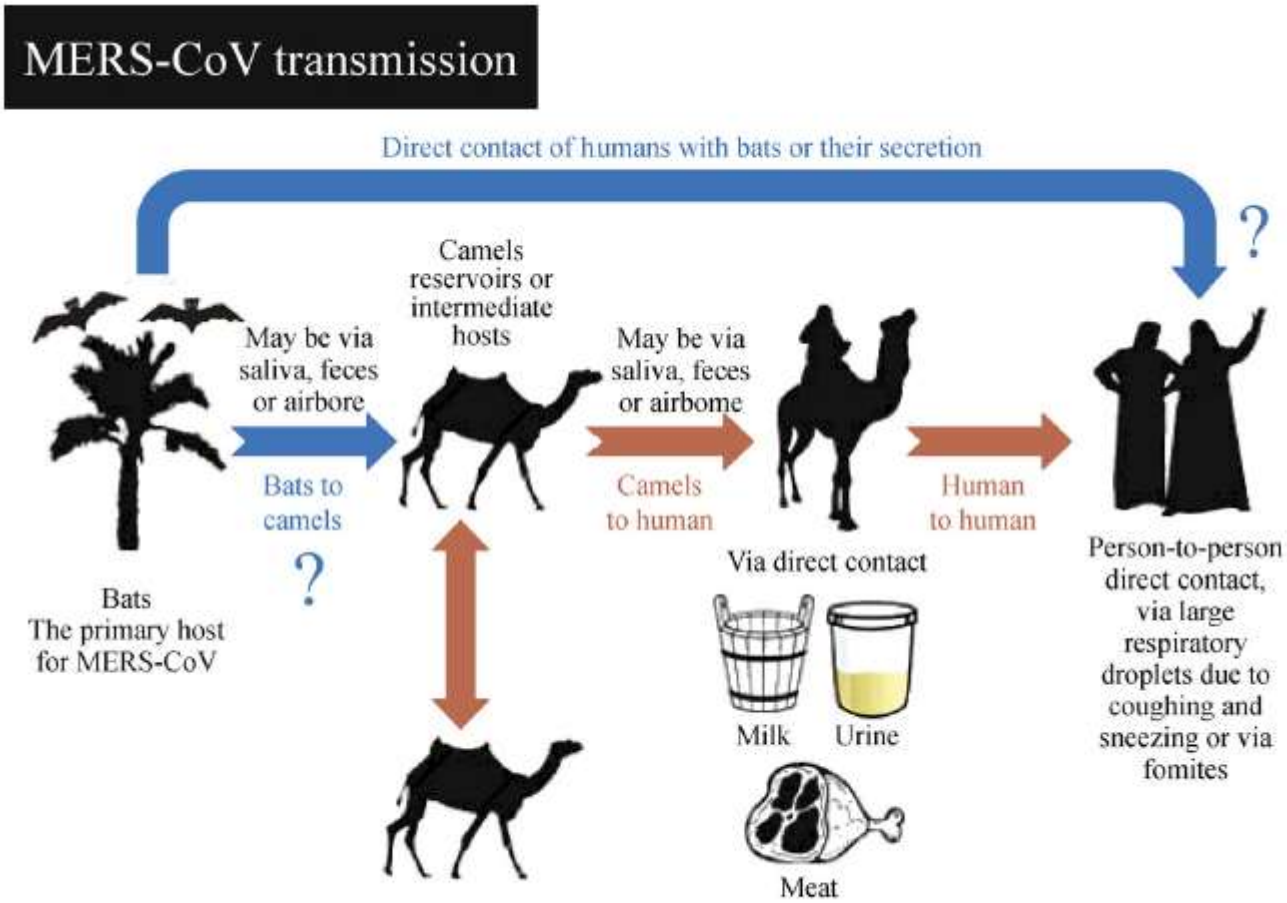
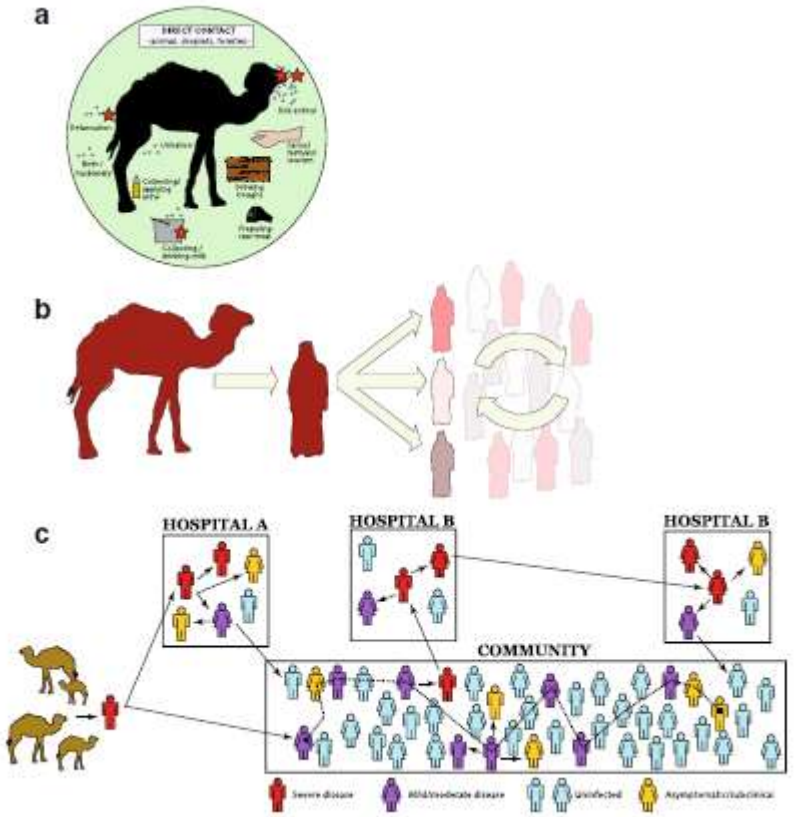


Fig. 2 Zoonotic transmission of newly emerged MERS-CoV.

Front Med. 2016 Jun;10(2):120-36



Virology Journal 2015**12**:222

Humans as reservoirs-unlikely.

Investigation of Anti–Middle East Respiratory Syndrome Antibodies in Blood Donors and Slaughterhouse Workers in Jeddah and Makkah, Saudi Arabia, Fall 2012

Asad S. Aburizaiza,[1,a] Frank M. Mattes,[2,5,a] Esam I. Azhar,[2,3] Ahmed M. Hassan,[3] Ziad A. Memish,[4] Doreen Muth,[5] Benjamin Meyer,[6] Erik Lattwein,[7] Marcel A. Müller,[6] and Christian Drosten[6]

[1]Environmental Science Department, Faculty of Metrology, Environmental Science and Arid Land Agriculture, [2]Special Infectious Agents Unit, King Fahd Medical Research Center, and [3]Medical Laboratory Technology Department, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, and [4]Ministry of Health, Riyadh, Saudi Arabia; [5]German International Cooperation, Eschborn, [6]Institute of Virology, University of Bonn Medical Center, Bonn, and [7]EUROIMMUN AG, Lübeck, Germany

(See the editorial commentary by Hui and Zumla on pages 173–6, and the major article by Yao et al on pages 236–42.)

Middle East respiratory syndrome coronavirus (MERS-CoV) is a novel, potentially zoonotic human coronavirus (HCoV). We investigated MERS-CoV antibodies using a staged approach involving an immunofluorescence assay (IFA), a differential recombinant IFA, and a plaque-reduction serum neutralization assay. In 130 blood donors sampled during 2012 in Jeddah and 226 slaughterhouse workers sampled in October 2012 in Jeddah and Makkah, Saudi Arabia, 8 reactive sera were seen in IFA but were resolved to be specific for established HCoVs by discriminative testing. There is no evidence that MERS-CoV circulated widely in the study region in fall 2012, matching an apparent absence of exported disease during the 2012 Hajj.

Prevalence of MERS-CoV Nasal Carriage and Compliance With the Saudi Health Recommendations Among Pilgrims Attending the 2013 Hajj

Ziad A. Memish,[1,2] Abdullah Assiri,[1] Malak Almasri,[1] Rafat F. Alhakeem,[1] Abdulhafeez Turkestani,[3] Abdullah A. Al Rabeeah,[1] Jaffar A. Al-Tawfiq,[4,5] Abdullah Alzahrani,[1] Essam Azhar,[6] Hatem Q. Makhdoom,[7] Waleed H. Hajomar,[8] Ali M. Al-Shangiti,[9] and Saber Yezli[1]

[1]Global Centre for Mass Gatherings Medicine (GCMGM), Ministry of Health, [2]College of Medicine, Alfaisal University, Riyadh, [3]Makkah Regional Health Affairs, Ministry of Health, Jeddah, [4]Saudi Aramco Medical Services Organization, Dhahran, Kingdom of Saudi Arabia; [5]Indiana University School of Medicine, Indianapolis; [6]Special Infectious Diseases Unit, King Abdualziz University, King Fahad Medical Research Center, Jeddah, [7]Jeddah Regional Laboratory and Blood Bank, Ministry of Health, [8]Riyadh Regional Laboratory and Blood Bank, Ministry of Health, and [9]General Directorate of Laboratory Services, Ministry of Health, Riyadh, Kingdom of Saudi Arabia

Background. Annually, Saudi Arabia is the host of the Hajj mass gathering. We aimed to determine the Middle East respiratory syndrome coronavirus (MERS-CoV) nasal carriage rate among pilgrims performing the 2013 Hajj and to describe the compliance with the Saudi Ministry of Health vaccine recommendations.

Method. Nasopharyngeal samples were collected from 5235 adult pilgrims from 22 countries and screened for MERS-CoV using reverse transcriptase–polymerase chain reaction. Information regarding the participants' age, gender, country of origin, medical conditions, and vaccination history were obtained.

Results. The mean age of the screened population was 51.8 years (range, 18–93 years) with a male/female ratio of 1.17:1. MERS-CoV was not detected in any of the samples tested (3210 pre-Hajj and 2025 post-Hajj screening). According to the vaccination documents, all participants had received meningococcal vaccination and the majority of those from at-risk countries were vaccinated against yellow fever and polio. Only 22% of the pilgrims (17.5% of those ≥65 years and 36.3% of diabetics) had flu vaccination, and 4.4% had pneumococcal vaccination.

Conclusion. There was no evidence of MERS-CoV nasal carriage among Hajj pilgrims. While rates of compulsory vaccinations uptake were high, uptake of pneumococcal and flu seasonal vaccinations were low, including among the high-risk population.

Keywords. Hajj pilgrimage; MERS-CoV; nasal carriage; screening; vaccination.

Presence of Middle East respiratory syndrome coronavirus antibodies in Saudi Arabia: a nationwide, cross-sectional, serological study

Marcel A Müller, Benjamin Meyer, Victor M Corman, Malak Al-Masri, Abdulhafeez Turkestani, Daniel Ritz, Andrea Sieberg, Souhaib Aldabbagh, Berend-J Bosch, Erik Lattwein, Raafat F Alhakeem, Abdullah M Assiri, Ali M Albarrak, Ali M Al-Shangiti, Jaffar A Al-Tawfiq, Paul Wikramaratna, Abdullah A Alrabeeah, Christian Drosten*, Ziad A Memish*

	Year of sampling	Total number	rELISA positive		Stage 1 seropositive		Stage 2 seropositive	
			n (%; 95% CI)	p value	n (%; 95% CI)	p value	n (%; 95% CI)	p value
General population	2012–13	10 009	152 (1·5%; 1·3–1·8)	NA	17 (0·2%; 0·1–0·3)	NA	15 (0·2%; 0·1–0·2)	NA
Camel shepherds	2014	87	6 (6·9%; 2·8–13·8)	p=0·0003	2 (2·3%; 0·3–7·4)	p=0·0009	2 (2·3%; 0·3–7·4)	p=0·0004
Slaughterhouse workers	2013	140	6 (4·3%; 1·8–8·7)	p=0·0224	5 (3·6%; 1·3–7·7)	p<0·0001	5 (3·6%; 1·3–7·7)	p<0·0001

Data are n (%; 95% CI) from a serosurvey, unless otherwise specified. p values refer to comparison with the general population cohort (χ^2 test with Yates correction two-tail test; OpenEpi). rELISA=recombinant ELISA. NA=not applicable.

Table 1: **Middle East respiratory syndrome coronavirus antibodies in the general and subpopulations of Saudi Arabia**

LINK TO BATS:

- Likely reservoir not hosts.
- CoV frequently found in fecal samples resemble MERS-CoV
- one 190 nucleotide sequence in the RNA-dependent RNA polymerase (RdRp) gene from a fecal pellet of a Taphozous perforatus had 100% identity with Mers-CoV isolate.
- widespread but asymptomatic infection of Jamaican fruit bats.

Contacts with **HUMANS IS UNCOMMON.**

LINK TO BATS:

Table 1. Overview of bats tested for 2c betacoronaviruses, Ghana and Europe

Area, bat species	No. bats tested (no. [%] positive)*	Age, juvenile/adult†	Sex, F/M‡	Location§ (no. tested/no. positive)
Ghana				
Coleura afra	108 (0)	2/105	46/59	a, b, e
Hipposideros abae	604 (0)	55/548	207/341	a, b, d, f
H. cf. gigas	28 (0)	7/19	8/11	a, b, d
H. fuliginosus	1 (0)	1/0	Unknown	c
H. jonesi	31 (0)	6/25	1/24	c, d
H. cf. ruber	3,763 (0)	674/3,078	1,109/1,969	a, b, c, d, f, g
Nycteris cf. gambiensis	185 (46 [24.9])	22/161¶	79/82	a# (5/2), b# (65/15), d# (104/29), f (1/0)
Rhinolophus alcyone	4 (0)	2/2	1/1	c
R. landeri	13 (0)	3/10	2/8	b, d, f
Taphozous perforatus	21 (0)	3/18	0/18	e
Total	4,758 (46 [1.0])			
Europe				
Pipistrellus kuhlii	7 (0)	Unknown	3/3	l
P. nathusii	82 (30 [36.6])	15/65	38/43	j (2/0), k# (74/29), l# (6/1)
P. pipistrellus	42 (1 [2.4])	17/25	19/21	i (29/0), k# (7/1), h (6/0)
P. pygmaeus	141 (9 [6.4])	11/127	83/55	j (44/0), k# (91/9), l (6/0)
Total	272 (40 [14.7])			

Emerg Infect Dis. 2013;19(3):456.

SCIENTIFIC REPORTS

OPEN

Replication and shedding of MERS-CoV in Jamaican fruit bats (*Artibeus jamaicensis*)

Received: 28 August 2015
Accepted: 03 February 2016
Published: 22 February 2016

Vincent J. Munster[1], Danielle R. Adney[2], Neeltje van Doremalen[1], Vienna R. Brown[2], Kerri L. Miazgowicz[1], Shauna Milne-Price[1], Trenton Bushmaker[1], Rebecca Rosenke[3], Dana Scott[3], Ann Hawkinson[4], Emmie de Wit[1], Tony Schountz[5] & Richard A. Bowen[2]

The emergence of Middle East respiratory syndrome coronavirus (MERS-CoV) highlights the zoonotic potential of *Betacoronaviruses*. Investigations into the origin of MERS-CoV have focused on two potential reservoirs: bats and camels. Here, we investigated the role of bats as a potential reservoir for MERS-CoV. *In vitro*, the MERS-CoV spike glycoprotein interacted with Jamaican fruit bat (*Artibeus jamaicensis*) dipeptidyl peptidase 4 (DPP4) receptor and MERS-CoV replicated efficiently in Jamaican fruit bat cells, suggesting there is no restriction at the receptor or cellular level for MERS-CoV. To shed light on the intrinsic host-virus relationship, we inoculated 10 Jamaican fruit bats with MERS-CoV. Although all bats showed evidence of infection, none of the bats showed clinical signs of disease. Virus shedding was detected in the respiratory and intestinal tract for up to 9 days. MERS-CoV replicated transiently in the respiratory and, to a lesser extent, the intestinal tracts and internal organs; with limited histopathological changes observed only in the lungs. Analysis of the *innate* gene expression in the lungs showed a moderate, transient induction of expression. Our results indicate that MERS-CoV maintains the ability to replicate in bats without clinical signs of disease, supporting the general hypothesis of bats as ancestral reservoirs for MERS-CoV.

LINK TO CAMELS

Primary hosts likely.

MERS-CoV infects dromedary camels and can be transmitted from them to humans by close contact.

Phylogenetic and serological studies shows evidence for this.

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Evidence for Camel-to-Human Transmission of MERS Coronavirus

Esam I. Azhar, Ph.D., Sherif A. El-Kafrawy, Ph.D., Suha A. Farraj, M.Sc., Ahmed M. Hassan, M.Sc., Muneera S. Al-Saeed, B.Sc., Anwar M. Hashem, Ph.D., and Tariq A. Madani, M.D.

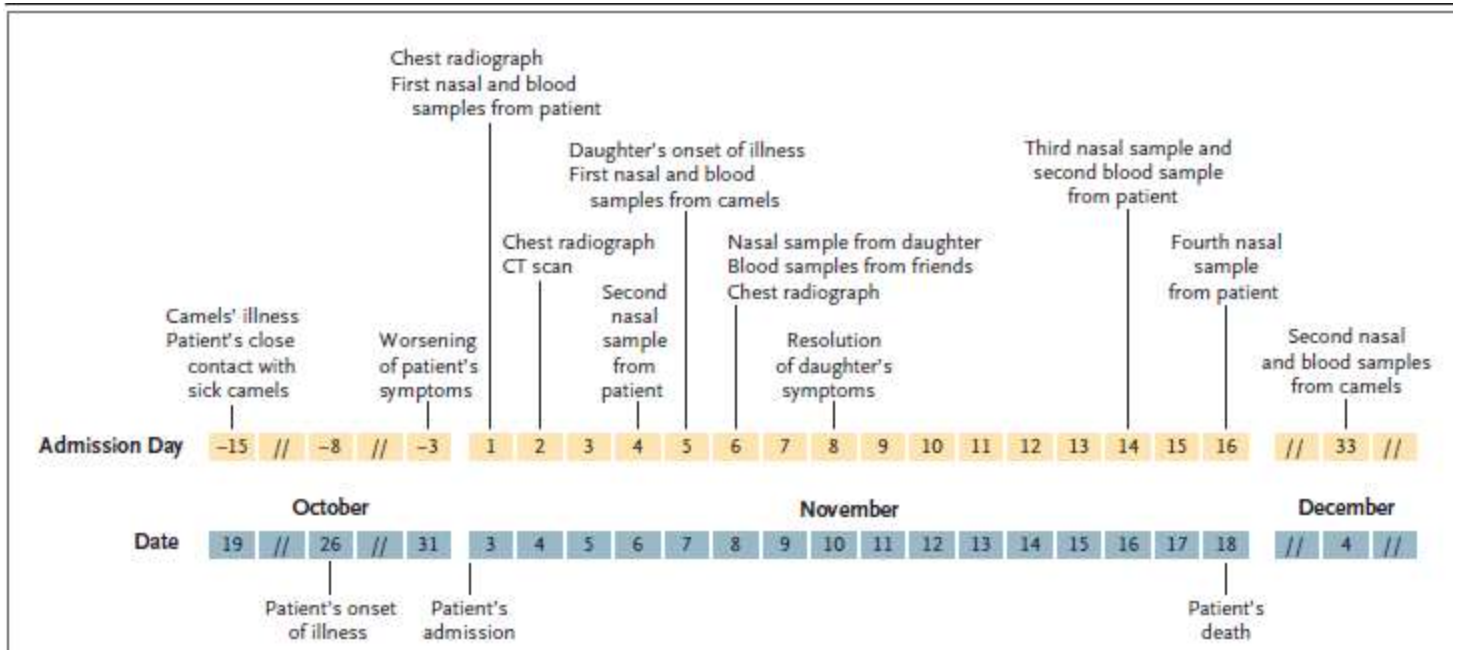


Figure 1. Timeline of the Main Events and Collection of Samples.

Table 1. Identification of MERS-CoV RNA in Nasal Swabs and MERS-CoV Antibodies in Human and Dromedary Samples.*

Host	Age	Real-Time RT-PCR				IFA	
		Original Nasal Samples†			Culture Isolates‡	Serum Sample 1§	Serum Sample 2¶
		upE	ORF1a	ORF1b			
	yr	*cycle threshold*					
Patient	43	27.5	34.7	33.3	13.2	<1:10	1:1,280
Camel A	9	ND	ND	ND	ND	1:51,200	1:51,200
Camel B‖	<1	36.3	36.9	37.5	11.1	1:160	1:1,280
Camel C	10	ND	ND	ND	ND	1:12,800	1:12,800
Camel D	12	ND	ND	ND	ND	1:1,280	1:1,280
Camel E	12	ND	ND	ND	ND	1:640	1:12,800
Camel F‖	<1	ND	ND	ND	ND	1:80	1:1,280
Camel G‖	<1	ND	ND	ND	ND	1:320	1:640
Camel H	12	ND	ND	ND	ND	1:10	1:640
Camel I‖ **	2	ND	ND	ND	ND	1:10	1:1,280

Phylogenetic studies-

MERS Coronaviruses in Dromedary Camels, Egypt

Daniel K.W. Chu,[1] Leo L.M. Poon,[1]
Mokhtar M. Gomaa, Mahmoud M. Shehata,
Ranawaka A.P.M. Perera, Dina Abu Zeid,
Amira S. El Rifay, Lewis Y. Siu, Yi Guan,
Richard J. Webby, Mohamed A. Ali,
Malik Peiris, and Ghazi Kayali

Table 2. Percentage identity between ORFs of dromedary camel MERS-CoV (NRCE-HKU205) and human MERS-CoV (EMC/2012) at the nucleotide and amino acid levels*

	% Identity to HCoV-EMC/2012	
ORF	Nucleotide	Amino acid
ORF1a	99.5	99.2
ORF1b	99.5	99.7
S	99.2	98.9
ORF3	99.0	98.0
ORF4a	99.0	100
ORF4b	99.4	99.1
ORF5	99.4	98.6
E	100	100
M	100	100
N	99.4	99.2
ORF8b	99.1	98.2

*ORF, open reading frame; MERS, Middle East respiratory syndrome; CoV, coronavirus; H, human; E, envelope; M, membrane; N, nucleocapsid.

Serological studies-

Middle East Respiratory Syndrome Coronavirus Infection in Dromedary Camels in Saudi Arabia

Abdulaziz N. Alagaili,[a,b] Thomas Briese,[c] Nischay Mishra,[c] Vishal Kapoor,[c] Stephen C. Sameroff,[c] Emmie de Wit,[d] Vincent J. Munster,[d] Lisa E. Hensley,[e] Iyad S. Zalmout,[a] Amit Kapoor,[c] Jonathan H. Epstein,[f] William B. Karesh,[f] Peter Daszak,[f] Osama B. Mohammed,[a] W. Ian Lipkin[c]

KSU Mammals Research Chair, Department of Zoology, College of Science, King Saud University, Riyadh, Saudi Arabia[a]; Saudi Wildlife Authority, Riyadh, Saudi Arabia[b]; Center for Infection and Immunity, Mailman School of Public Health, Columbia University, New York, New York, USA[c]; Laboratory of Virology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rocky Mountain Laboratories, Hamilton, Montana, USA[d]; Integrated Research Facility, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Frederick, Maryland, USA[e]; EcoHealth Alliance, New York, New York, USA[f]

A.N.A. and T.B. contributed equally to this article.

TABLE 2 Analysis of archived DC sera from the KSA from 1992 to 2010

Yr	Location	Age group	No.	% Seropositive (no. positive/total)
1992	Riyadh	Adult	1	100 (1/1)
1993	Riyadh	Adult	2	100 (2/2)
1994	Empty quarter	Adult	123	93 (114/123)
1996	Riyadh	Adult	6	100 (6/6)
2004	Riyadh	Adult	6	100 (6/6)
2009	Riyadh	Juvenile	56	72 (40/56)
2009	Rumah	Adult	26	92 (24/26)
2010	Riyadh	Juvenile	21	76 (16/21)
2010	Kharj	Adult	23	91 (21/23)

Mbio.2014 Mar-Apr; 5(2): e00884-14.

Fig. 3 (See legend on next page.)

Virology Journal 2015**12**:222

Human-human:

- Case controls in many countries points towards this but number of contacts infected by individuals with confirmed infections is limited
- South Korea outbreak in June 2015, where many secondary and some tertiary cases occurred in which ‘super-spreader’ events were identified.
- Secondary cases are milder than primary cases and occurs in both healthcare settings and household.
- Droplet or contact transmission.

Lack of Transmission among Close Contacts of Patient with Case of Middle East Respiratory Syndrome Imported into the United States, 2014

Lucy Breakwell,[1] Kimberly Pringle,[1] Nora Chea,[1] Donna Allen, Steve Allen, Shawn Richards, Pam Pantones, Michelle Sandoval, Lixia Liu, Michael Vernon, Craig Conover, Rashmi Chugh, Alfred DeMaria, Rachel Burns, Sandra Smole, Susan I. Gerber, Nicole J Cohen, David Kuhar, Lia M. Haynes, Eileen Schneider, Alan Kumar, Minal Kapoor, Marlene Madrigal, David L. Swerdlow, Daniel R. Feikin

Occupation	
Administration	3 (7)
Housekeeping	2 (4)
Medical doctor	3 (7)
Nurse practitioner	1 (2)
Nursing assistant	10 (22)
Phlebotomist	4 (9)
Radiology technician	4 (9)
Respiratory therapist	6 (13)
Registered nurse	11 (24)
Social personnel	1 (2)
Primary employment location in hospital	
Ward	21 (47)
Emergency department	11 (24)
Multiple locations	12 (27)
Computed tomography suite	1 (2)

Laboratory Results

For 60 contacts, both initial and follow-up nasopharyngeal and oropharyngeal swab samples and serum samples were negative for MERS-CoV by rRT-PCR and for MERS-CoV–specific antibodies by serologic testing. For the com-

Table 3. Summary of Serologic Results in Household Contacts, According to Timing of Sampling. *

Variable	Time from Onset of Symptoms in Index Patient until Sampling of Contact			
	Any Time	<2 Wk	2–3 Wk	>3 Wk†
No. of household contacts	280	127	45	108
No. of clusters	26	10	3	13
Positive results — no. (%)				
RT-PCR	7 (2)	7 (6)	0	0
ELISA	20 (7)	8 (6)	3 (7)	11 (10)
IFA	7 (2)	1 (1)	3 (7)	3 (3)
IFA plus PRNT	5 (2)	1 (1)	3 (7)	1 (1)
Household contacts with possible or probable secondary infection — no. (%)				
Possible on basis of RT-PCR or stage 1 seropositivity	14 (5)	8 (6)‡	3 (7)	3 (3)
Positive RT-PCR assay	7 (2)	7 (6)	0	0
Stage 1 seropositivity	7 (2)	1 (1)	3 (7)	3 (3)
Probable on basis of dual positive RT-PCR assays or stage 2 seropositivity	12 (4)	8 (6)	3 (7)	1 (1)
Dual positive RT-PCR assays	7 (2)	7 (6)	0	0
Stage 2 seropositivity	5 (2)	1 (1)	3 (7)	1 (1)
Clusters of household contacts with possible or probable secondary infection — no. (%)				
Possible on basis of RT-PCR or stage 1 seropositivity‡	6 (23)	4 (40)	1 (33)	2 (15)
Positive RT-PCR assay	3 (12)	3 (30)	0	0
Stage 1 seropositivity	4 (15)	1 (10)	1 (33)	2 (15)
Probable on basis of dual positive RT-PCR assays or stage 2 seropositivity	6 (23)	4 (40)	1 (33)	1 (8)
Dual positive RT-PCR assays	3 (12)	3 (30)	0	0
Stage 2 seropositivity	3 (12)	1 (10)	1 (33)	1 (8)

Osong Public Health Res Perspect 2015 6(4), 269–278
http://dx.doi.org/10.1016/j.phrp.2015.08.006
pISSN 2210-9099 eISSN 2233-6052

ORIGINAL ARTICLE

Middle East Respiratory Syndrome Coronavirus Outbreak in the Republic of Korea, 2015

Korea Centers for Disease Control and Prevention*

Korea Centers for Disease Control and Prevention, Cheongju, Republic of Korea.

Characteristics	No. of patients
Sex, *n* (%)	
Male	111 (59.7)
Female	75 (40.3)
Age (y), median (IQR)	55 (42–66)
≥65y, *n* (%)	55 (29.6)
Case classification, *n* (%)	
Healthcare personnel	25 (13.4)
Patient	82 (44.1)
Caregiver	61 (32.8)
Others*	18 (9.7)
Symptoms at presentation, *n* (%)	
Fever/chills	138 (74.2)
Cough	33 (17.7)
Dyspnea	10 (5.4)
Myalgia	47 (25.3)
Headache	16 (8.6)
GI symptoms†	24 (12.9)
Sputum	14 (7.5)
Sore throat	8 (4.3)
Comorbidities, *n* (%)	
Any‡	102 (54.8)
Respiratory disease§	23 (12.4)
Diabetes mellitus	52 (28.0)
Cardiac disease‖	42 (22.6)
Chronic kidney disease	9 (4.8)
Malignancy	43 (23.1)
Known setting of contact, *n* (%)¶	
Healthcare facility	178 (98.0)
Household	1 (0.5)
Ambulance	3 (1.5)
Time from symptom onset to laboratory confirmation in days, median (IQR)	5 (3–9)
Time from symptom onset to death in days, median (IQR)	15 (10–20)
Outcome as of July 13, 2015, *n* (%)	
Recovered	131 (70.4)
Ongoing treatment in hospital	19 (10.2)
Died	36 (19.4)

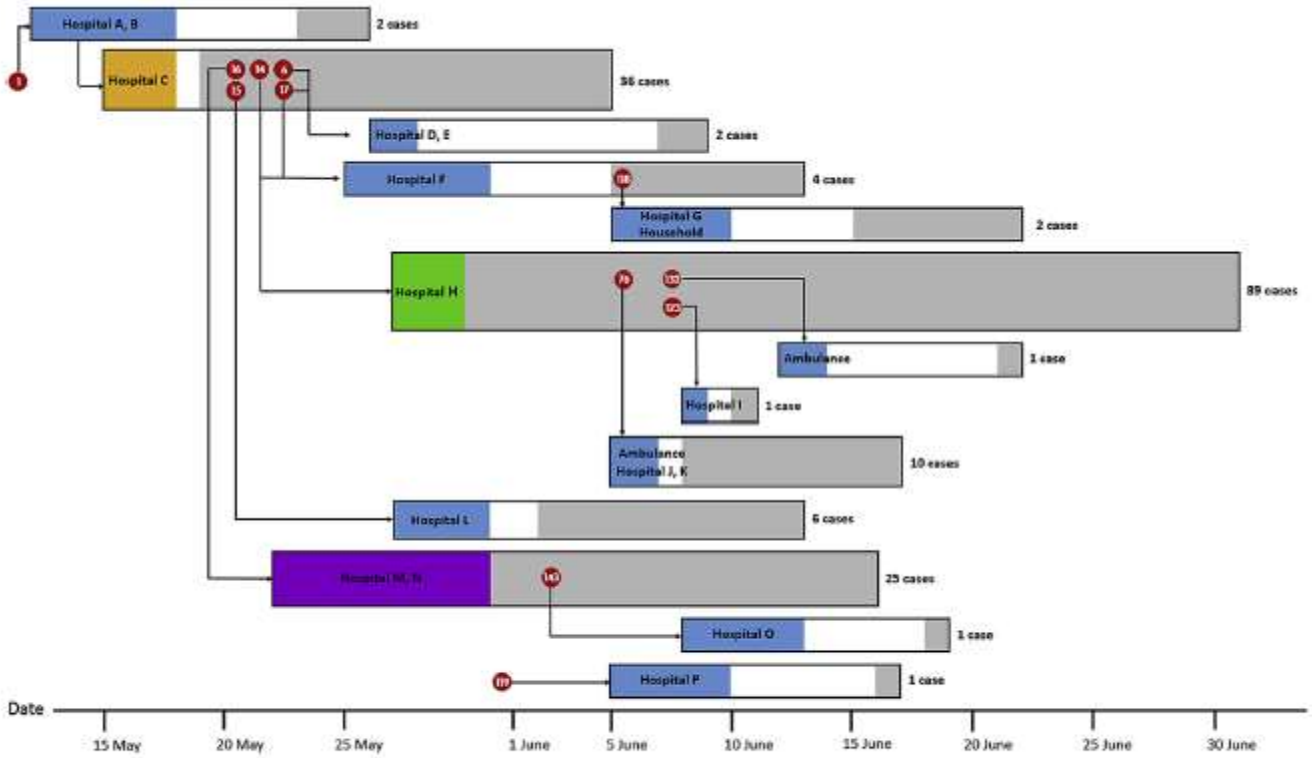


Figure 4. Transmission map of 182 confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in the Republic of Korea. The numbers within the red circles are identifiers of notable patients who caused succeeding MERS-CoV infection. The site and the duration of exposure by these patients are indicated in colored boxes. Gray boxes depict the time periods that new cases occurred by date of symptom onset at each site. Black arrows represent how each spreader moved to the next site of transmission. The transmission route of Patient 119 is uncertain. Four cases still under investigation are excluded.

Table 2. Characteristics of superspreaders of Middle East respiratory syndrome coronavirus infection outbreak in the Republic of Korea, 2015.

Patient number	1	14	15	16	76
Infected no. of patients	28	85	6	23	11
Age (y)	68	35	35	41	75
Sex	Male	Male	Male	Male	Female
Body mass index	27	30	24	24	19
Underlying disease	Hypertension, asthma	No	No	Familial adenomatous polyposis	Diabetes mellitus, multiple myeloma
Exposed duration (d)*	10	9	10	11	2
Exposed setting	GW (27 cases) OPD (1 case)	ER (78 cases) GW (4 cases) Other (3 cases)	GW (6 cases)	GW (22 cases) Other (1 case)	ER (4 cases) GW (3 cases) Other (4 cases)
Number of close contacts	626	594	304	277	805
Personal protective equipment	No	Intermittent	No	No	No
Pneumonia†	Present	Present	Present	Present	Present
Cough	Frequent	Frequent	Rare	Frequent	Rare
Prognosis	Survived	Survived	Survived	Survived	Expired
Aerosol-generating procedure	No	No	No	No	No

*Exposed duration is defined as the period from symptom onset to the date of proper isolation; †Pneumonia detected from chest radiograph at the moment of investigation. ER = emergency room; GW = general ward; OPD = outpatient department.

Clinical manifestations:

CASE DEFENITIONS:

CONFIRMED CASE:

A person with **laboratory** confirmation of infection with MERS-CoV irrespective of clinical signs and symptoms

Probable case:

1-A febrile acute respiratory illness with clinical, radiographic, or histopathologic evidence of pulmonary parenchymal disease (eg, pneumonia or acute respiratory distress syndrome)

And

2-Direct epidemiologic link with a confirmed MERS-CoV case

3-Testing for MERS-CoV is unavailable, negative on a single inadequate specimen, or inconclusive **OR**

4-Testing for MERS-CoV is inconclusive

1-A febrile acute respiratory illness with clinical, radiographic, or histopathologic evidence of pulmonary parenchymal disease (eg, pneumonia or acute respiratory distress syndrome) **and**

2-The person resides in or traveled to the Middle East or countries where MERS-CoV is known to be circulating in dromedary camels or where human infections have recently occurred **and**

3-Testing for MERS-CoV is inconclusive

https://www.cdc.gov/coronavirus/mers/case-def.html
http://www.who.int/csr/disease/coronavirus_infections/case_definition

WHO criteria for laboratory confirmation:

Nucleic acid-

2 sequence specific rRT-PCRs or 1 rRT PCR +direct sequencing

or

Acute and acute and convalescent serology-

demonstration of seroconversion in two samples ideally collected at least 14 days apart using atleast one screening assay (enzyme-linked immunoassay, immunofluorescence assay) and a neutralization assay.

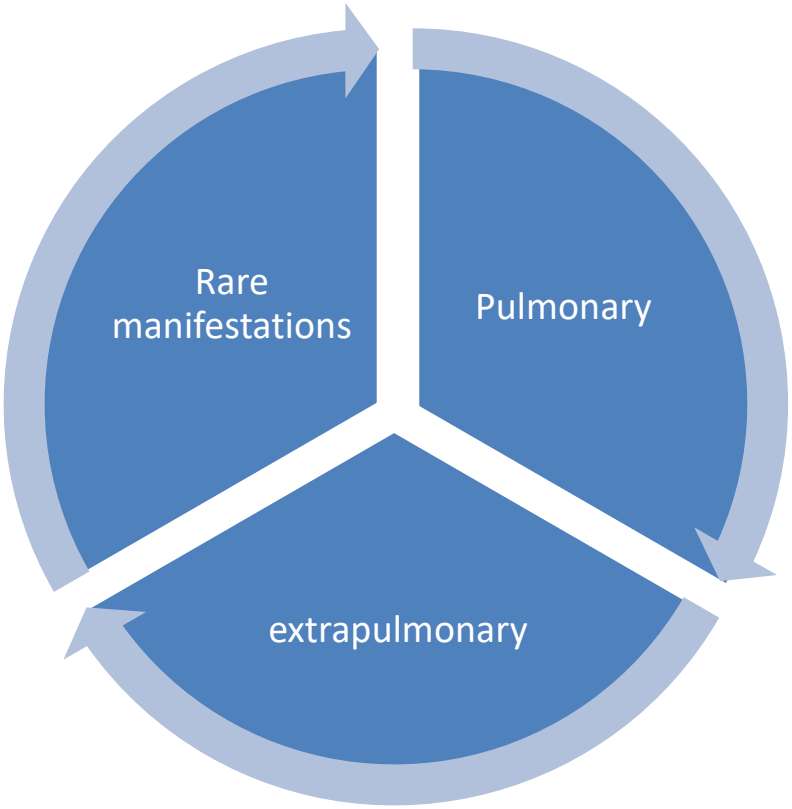
Incubation period:

Median-5 to 7 days

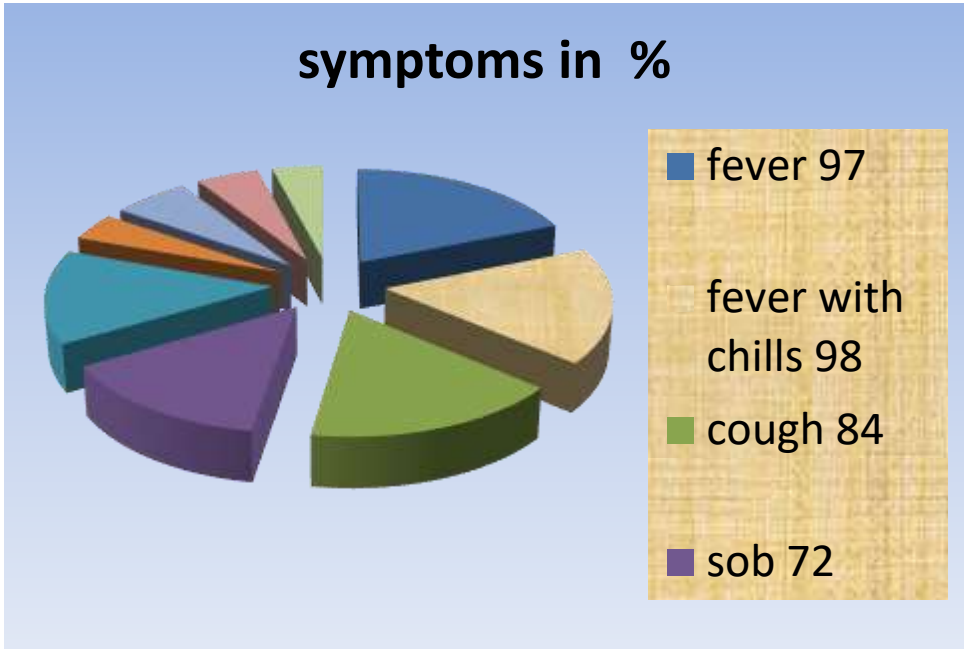
The World Health Organization (WHO) and the United States Centers for Disease Control and Prevention (CDC) ***recommend that an evaluation for MERS-CoV*** *be considered in individuals with a syndrome of MERS who returned from travel to the* ***Arabian*** *peninsula or neighboring countries within the past* ***14 days***

MMWR Morb Mortal Wkly Rep. 2013;62(23):480.

Signs and symptoms-



clinical findings among 47 patients with MERS-CoV infection in Saudi Arabia.



- 42 (89 percent)-intensive care
- 34 (72 percent) required mechanical ventilation.
- The median time from presentation for medical care to mechanical ventilation was 7 days (range 3 to 11 days) and to death was 14 days (range 5 to 36 days).

Lancet Infect Dis 2013; 13:752.

Gastrointestinal symptoms-

- Anorexia
- Nausea
- Vomiting
- abdominal pain
- diarrhea

Pericarditis

Disseminated intravascular coagulation

Annals of Internal Medicine | ORIGINAL RESEARCH

Clinical Course and Outcomes of Critically Ill Patients With Middle East Respiratory Syndrome Coronavirus Infection

Yaseen M. Arabi, MD; Ahmed A. Arifi, MD; Hanan H. Balkhy, MD; Hani Najm, MD; Abdulaziz S. Aldawood, MD; Alaa Ghabashi, MD; Hassan Hawa, MD; Adel Alothman, MB; Abdulaziz Khaldi, MD; and Basel Al Raiy, MD

Table 3. **Main Interventions and Outcomes**

Variable	Value
Noninvasive positive-pressure ventilation, *n (%)*	5 (42)
Invasive ventilation, *n (%)*	12 (100)
Neuromuscular blockade, *n (%)*	4 (33)
High-frequency oscillation ventilation, *n (%)*	2 (17)
Nitric oxide, *n (%)*	6 (50)
Prone positioning, *n (%)*	3 (25)
Barotrauma, *n (%)*	2 (17)
Vasopressors, *n (%)*	11 (92)
Renal replacement therapy, *n (%)*	7 (58)
Tracheostomy, *n (%)*	3 (25)
Median duration of mechanical ventilation (range), *d*	16 (4–30)
Alive at day 28, *n (%)*	7 (58)
Alive at day 90, *n (%)*	5 (42)
ICU survival, *n (%)*	5 (42)
Median ICU length of stay (range), *d*	30 (7–104)
Median hospital length of stay (range), *d*	41 (8–96)*

CASE REPORT

Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV)

Y. M. Arabi · A. Harthi · J. Hussein · A. Bouchama · S. Johani · A. H. Hajeer · B. T. Saeed · A. Wahbi · A. Saedy · T. AlDabbagh · R. Okaili · M. Sadat · H. Balkhy

Finding The three patients presented with severe neurologic syndrome which included altered level of consciousness ranging from confusion to coma, ataxia, and focal motor deficit. Brain MRI revealed striking changes characterized by widespread, bilateral hyperintense lesions on T2-weighted imaging within the white matter and subcortical areas of the frontal, temporal, and parietal lobes, the basal ganglia, and corpus callosum. None of the lesions showed gadolinium enhancement.

Infection (2015) 43:495–501

Children:

ORIGINAL STUDIES

Middle East Respiratory Syndrome Coronavirus Disease in Children

Ziad A. Memish, MD, FRCP, Jaffar A Al-Tawfiq, MD,† Abdullah Assiri, MD,‡ Fahad A. AlRabiah, MD,§ Sami Al Hajjar, MD,§ Ali Albarrak, MD,§ Hesham Flemban, MD,¶ Rafat F. Alhakeem, MD,‖ Hatem Q. Makhdoom, PhD,** Sarah Alsubaie, MD,†† and Abdullah A. Al-Rabeeah, MD, FRCS‡‡*

Only one series

9/11 infections were asymptomatic

2 symptomatic-downs and cystic fibrosis.

Pediatr Infect Dis J. 2014 Sep;33(9):904-6

Effect on pregnant women and fetuses:

8 cases till now

2-still birth.

2-preterm

2 maternal deaths

2-healthy baby/mother

J Infect Dis. 2014;209(12):1870
Emerg Infect Dis. 2016;22(3):515
BMC Infect Dis. 2016;16(1):105

LABORATORY ABNORMALITIES-

- leukopenia
- lymphopenia,
- thrombocytopenia,
- elevated aspartate aminotransferase,
- elevated alanine aminotransferase and
- elevated lactate dehydrogenase.

DIC/HEMOLYSIS-1 case report.

Lancet Infect Dis 2013; 13:752.

Imaging-

Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study

Abdullah Assiri*, Jaffar A Al-Tawfiq*, Abdullah A Al-Rabeeah, Fahad A Al-Rabiah, Sami Al-Hajjar, Ali Al-Barrak, Hesham Flemban, Wafa N Al-Nassir, Hanan H Balkhy, Rafat F Al-Hakeem, Hatem Q Makhdoom, Alimuddin I Zumla*, Ziad A Memish*

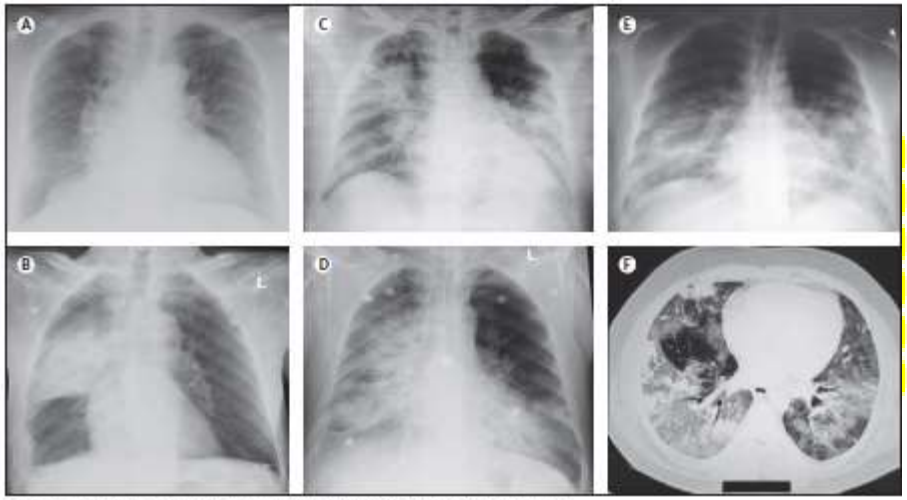


Figure 1: Imaging findings at presentation in Saudi patients with Middle East respiratory syndrome

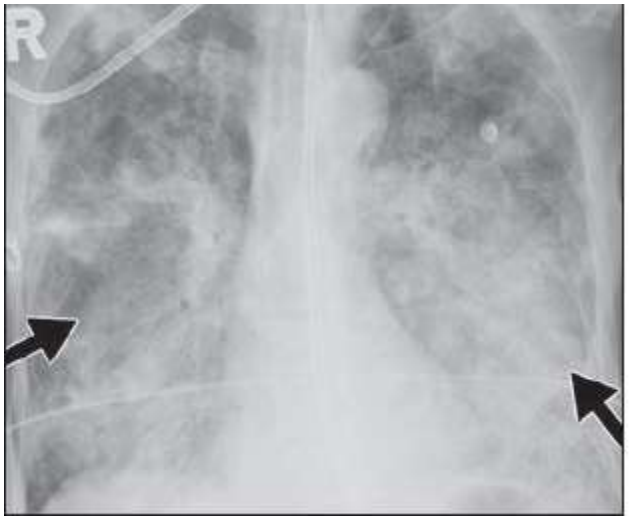
Lancet Infect Dis 2013; 13:752.

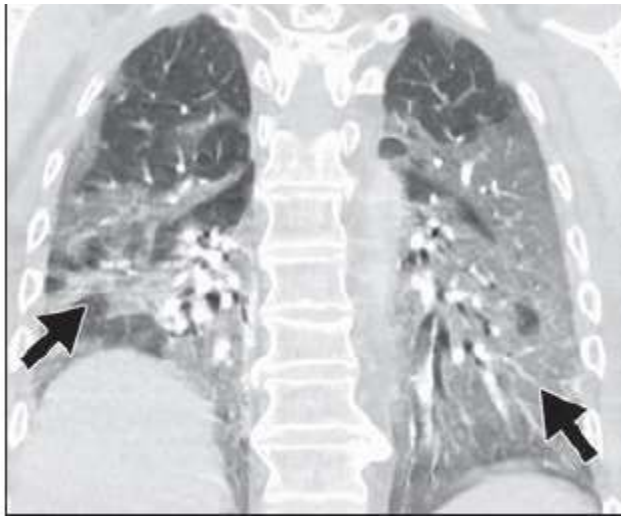
Most common finding in CT:

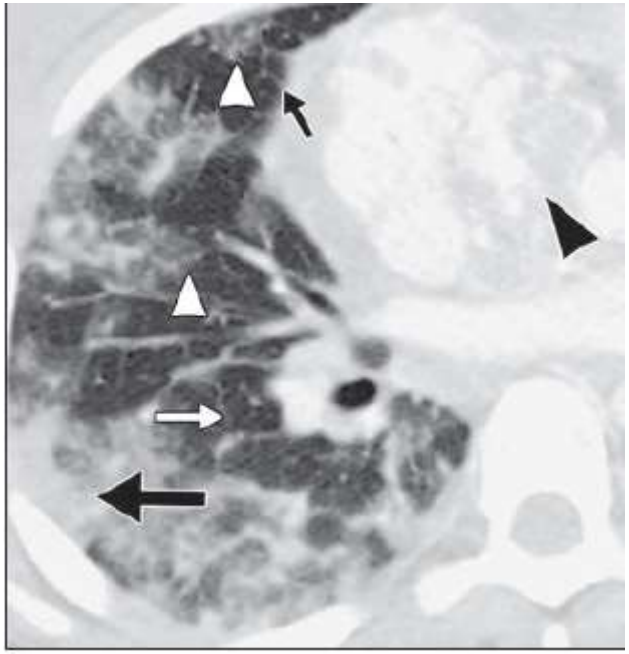
bilateral predominantly peripheral and basilar airspace changes with more extensive ground-glass opacities than consolidation.

CT Correlation With Outcomes in 15 Patients With Acute Middle East Respiratory Syndrome Coronavirus

objective	Methods:	Results
retrospectively analyze chest CT findings for 15 patients with Middle East respiratory syndrome coronavirus and to identify features associated with survival	**group 1** if they died (*n* = 9) and to **group 2** if they made a full recovery (*n* = 6).	Ggo=53% Peripheral=54% Lower lobe>upper,middle


R





Comorbidities:

Remains unclear whether persons with specific comorbidities are disproportionately infected with Middle East respiratory syndrome coronavirus (MERS-CoV) or come to medical attention because they have more severe disease.

	Patients (n=47)	Deaths (%)*
Any comorbidity	45 (96%)	28 (60%)
Diabetes	32 (68%)	21 (66%)
Chronic kidney disease	23 (49%)	17 (74%)
Chronic heart disease	13 (28%)	10 (77%)
Hypertension	16 (34%)	13 (81%)
Chronic lung disease	12 (26%)	10 (83%)
Obesity	8 (17%)	5 (63%)
Smoking	11 (23%)	7 (64%)
Malignant disease	1 (2%)	1 (100%)
Steroid use	3 (6%)	3 (100%)

*Proportion of patients who died according to comorbidity.

***Table 4*: Comorbidities in 47 Saudi cases of Middle East respiratory syndrome**

Comorbid conditions, *n* (%)	
Diabetes	8 (67)
Hypertension	6 (50)
Renal insufficiency	5 (42)
Myocardial infarction	4 (33)
Cardiac surgery	3 (25)
Cerebrovascular accident	3 (25)
Obesity	3 (25)
Congestive heart failure	2 (17)
Peripheral vascular disease	2 (17)
Asthma	1 (8)
Dialysis dependency	1 (8)
Kidney and liver transplant	1 (8)
Malignant melanoma	1 (8)
Neuromuscular disease	1 (8)
Valvular disease	1 (8)

Lancet Infect Dis. 2013;13(9):752.
Ann Intern Med. 2014 Mar 18;160(6):389-97

DIAGNOSIS:

- Preferred tests-PCR and serology
- Whom to test?
- Specimen handling
- Where to ship specimens?

World Health Organization. Laboratory testing for Middle East respiratory syndrome coronavirus - Interim recommendations

Preferred tests-

Case Identification Number:_____

Middle East Respiratory Syndrome Coronavirus (MERS-CoV)
Initial Interview Questionnaire of Cases

Guide for the interviewer

Purpose of form: This interview form is developed as a supplemental tool to accompany the **WHO guidelines for investigation of cases of human infection with MERS-CoV**, which can be found on the WHO website.[1] It is designed to gather initial information about the potential exposures of a suspected or confirmed case of MERS-CoV infection in the 14 days before symptom onset. The interview should be conducted as soon as possible once the patient is suspected of having MERS-CoV infection. If the patient is unable to personally answer questions because of death or severity of illness, a close relative or friend can answer the questions for him or her. This form should be modified according to local needs and experience. It is not intended as a formal study instrument but rather contains many open-ended questions that will allow investigators to develop hypotheses to test during subsequent formal studies. However, the questions about specific exposures are also contained in the WHO **Case-control study to assess potential risk factors related to human illness caused by MERS-CoV,**[1] which may be used for follow-up investigation. The information gathered in this interview could be used in that study as well.

World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). Initial interview questionnaire of cases

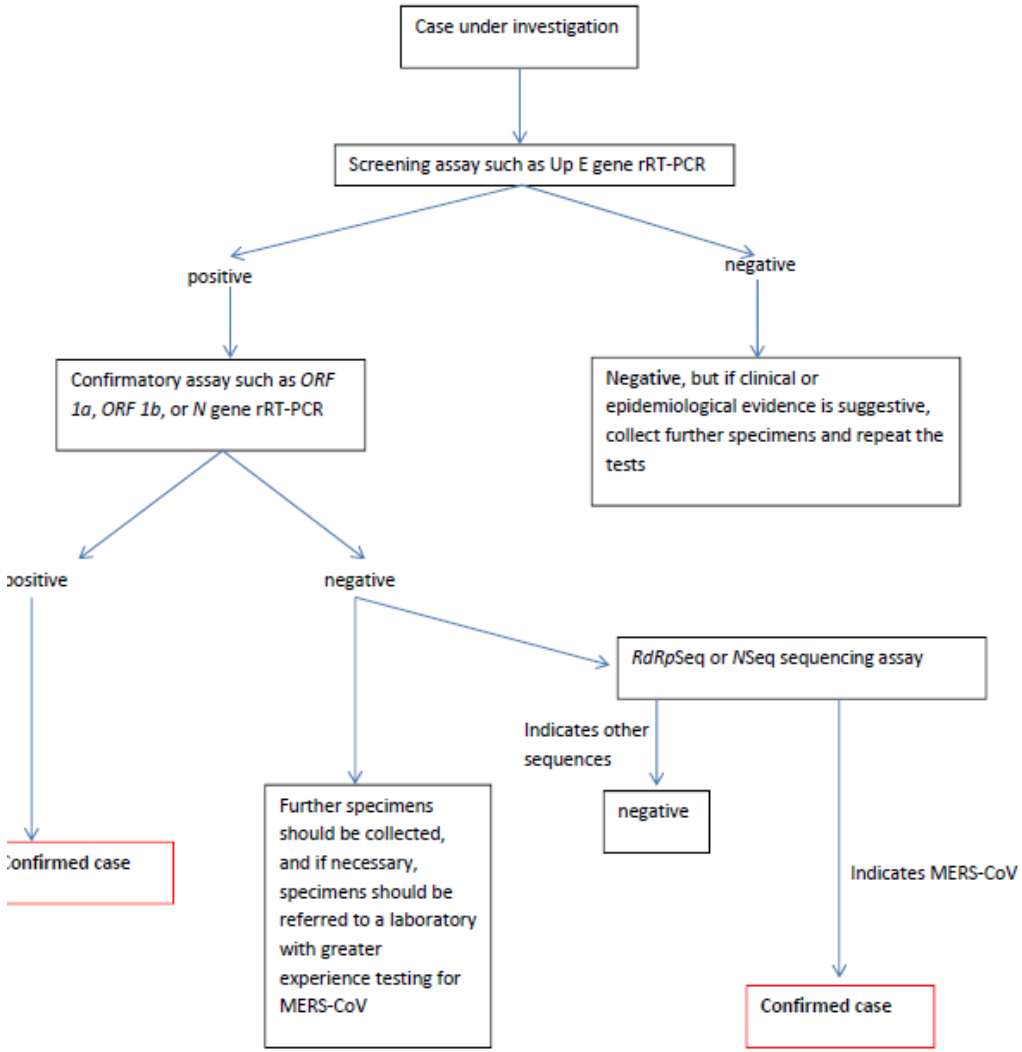
Specimen types:

symptomatic	**PCR**	**Lower Respiratory tract:** sputum, endotracheal aspirate, or bronchoalveolar lavage **Upper Respiratory tract:** Naso pharyngeal oro pharyngeal Swabs Naso pharyngeal wash/naso pharyngeal Aspirate [2-3ml]
symptomatic	serology	Paired samples- 1st week, 2nd-2weeks later
Asymptomatic	PCR	Naso/oropharyngeal swabs, within 14 days
Asymptomatic	serology	Within 14days, 2 weeks later

World Health Organization. Laboratory testing for Middle East respiratory syndrome coronavirus - Interim recommendations

PCR

Figure 1. Algorithm for testing cases under investigation for MERS-CoV by rRT-PCR



World Health Organization. Laboratory testing for Middle East respiratory syndrome coronavirus - Interim recommendations (revised), September 2014

Serology:

1) serology in relation to defining a MERS-CoV case for reporting under the International Health Regulations (IHR)

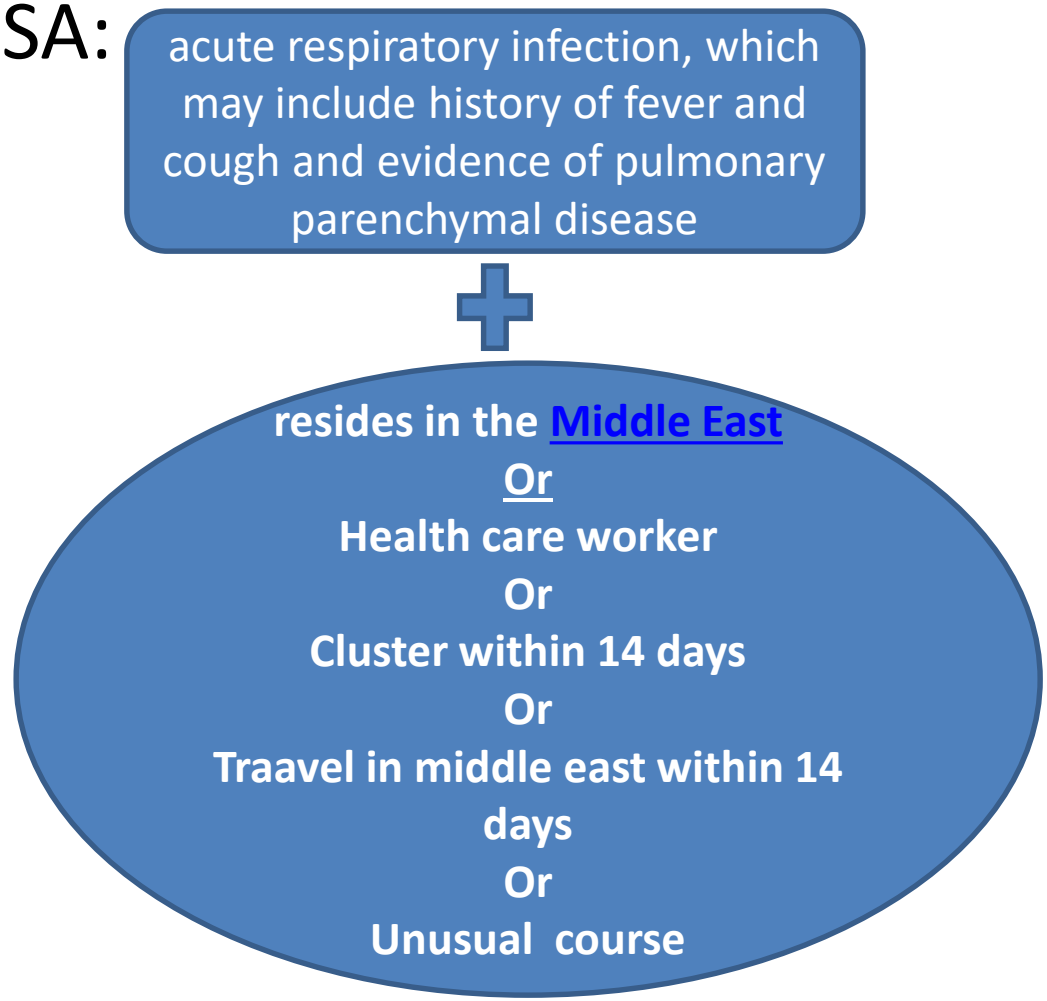
2) serological surveys.

CDC has developed a two-stage approach, which uses an enzyme-linked immunosorbent assay (ELISA) for screening followed by an indirect immunofluorescence test or microneutralization test for confirmation.

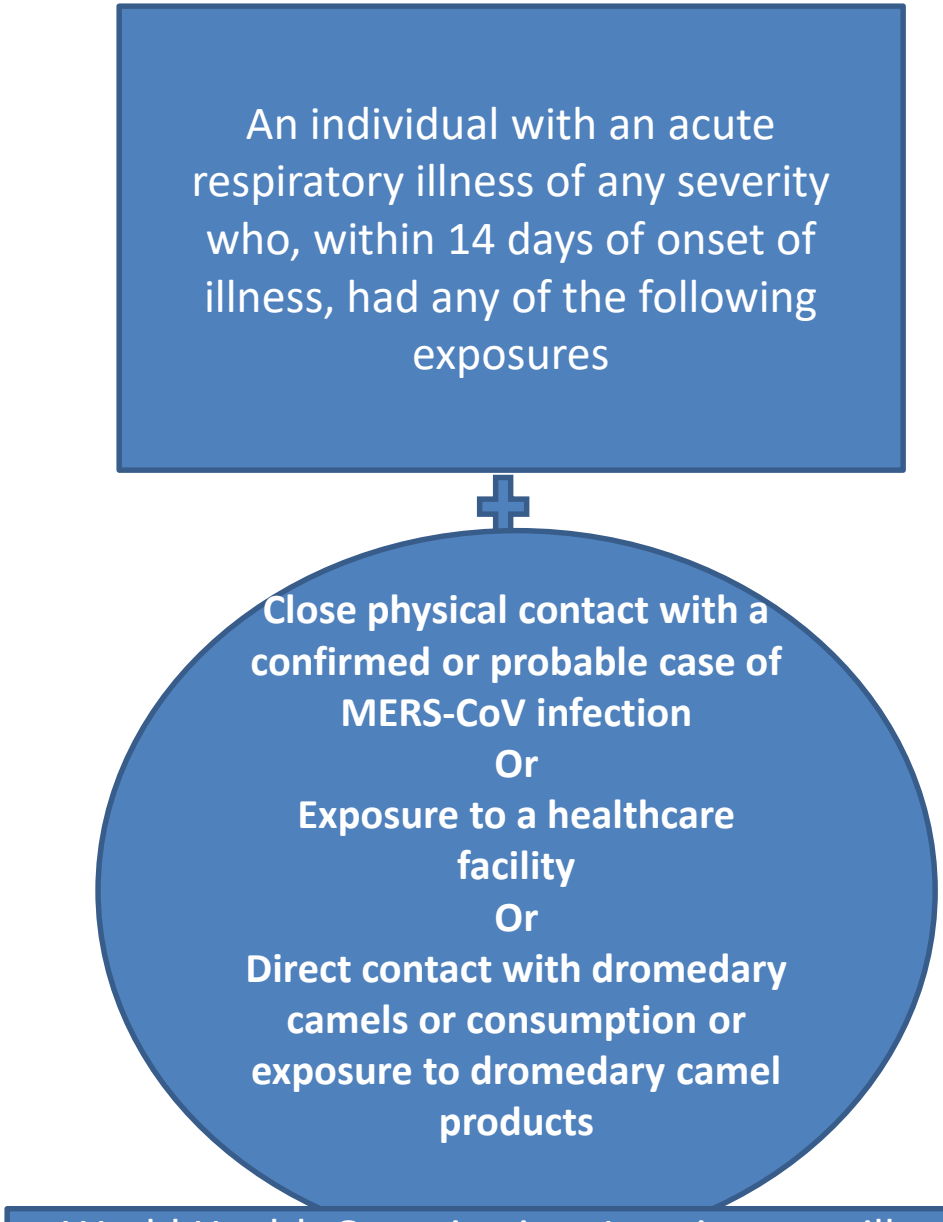
World Health Organization. Laboratory testing for Middle East respiratory syndrome coronavirus - Interim recommendations (revised), September 2014

WHOM TO TEST?

OUTSIDE USA:



World Health Organization. Laboratory testing for Middle East respiratory syndrome coronavirus - Interim recommendations (revised), September 2014



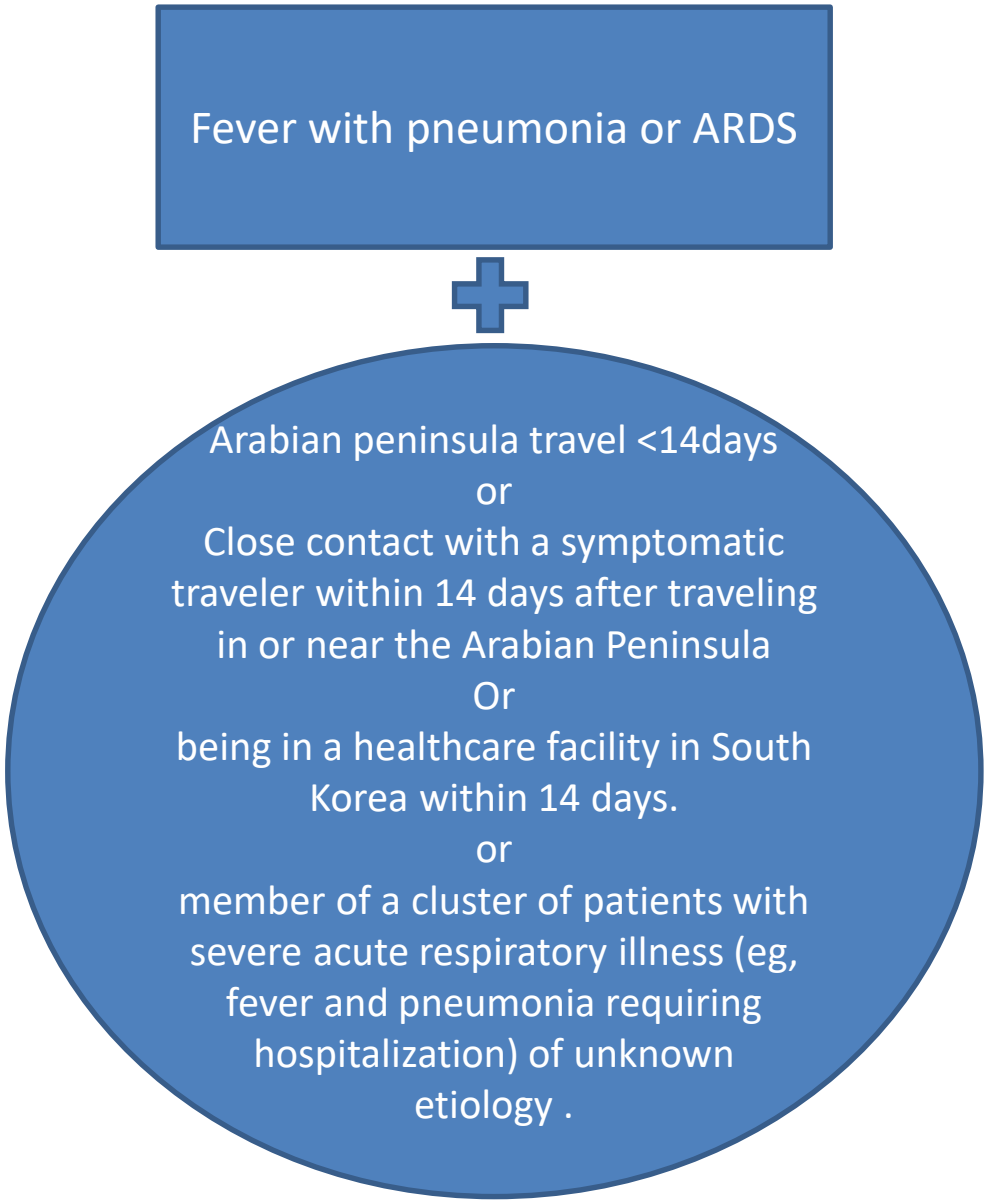
World Health Organization. Interim surveillance recommendations for human infection with Middle East respiratory syndrome coronavirus.

Countries in the Middle East are strongly encouraged to consider adding testing for MERS-CoV to testing algorithms as part of routine sentinel respiratory disease surveillance and diagnostic panels for pneumonia.

Routine testing of asymptomatic contacts of cases is not recommended

World Health Organization. Interim surveillance recommendations for human infection with Middle East respiratory syndrome coronavirus.

USA:



MMWR Morb Mortal Wkly Rep. 2014;63(19):431.
Centers for Disease Control and Prevention. Interim guidance for healthcare professionals

Specimen handling:

- Specimens should reach the laboratory as soon as possible after collection.
- If a delay of more than 72 hours, specimens should be frozen at -80°C and shipped on dry ice.
- Storage of respiratory and serum specimens in domestic frost-free freezers should be avoided, given their wide temperature fluctuations..

Where to ship specimens:

USA:

contact the CDC Emergency Operations Center at 770-488-7100

Outside USA:

follow the recommendations of your own ministry of health regarding diagnostic testing.

TREATMENT:

- NO SPECIFIC TREATMENT with PROVEN BENEFIT
- Anti virals not recommended by WHO.
- Under investigation:

✓ interferon (IFN)-alpha-2b and ribavirin

✓ glucocorticoids

✓ MERS-CoV neutralizing monoclonal antibody-LCA60

WHO recommendations: 2013

- Early recognition and management
- Management of severe respiratory distress, hypoxemia and ARDS
- Management of septic shock
- Prevention of complications

http://www.who.int/csr/disease/coronavirus_infections/InterimGuidance_ClinicalManagement_NovelCoronavirus_11Feb13.pdf

Early recognition and management

DOs	DONTs
Recognize severe manifestations of acute respiratory infections	DO NOT restrict oxygen because of concerns about a patient's respiratory drive.
Initiate infection prevention and control measures-standard, droplet and airborne precautions.	Do not give high-dose systemic corticosteroids or other adjunctive therapies for viral pneumonitis outside the context of clinical trials
Give supplemental oxygen therapy to patients with SARI ->92%	
Give empiric antimicrobials to treat suspected pathogens, including communityacquired pathogens	
Use conservative fluid management in patients with SARI when there is no evidence of shock	
Closely monitor patients with SARI for signs of clinical deterioration	

Management of severe respiratory distress, hypoxemia and ARDS:

DOs	DONTs
mechanical ventilation should be instituted early in patients with increased work of breathing or hypoxemia that persists despite high-flow oxygen therapy	Avoid disconnecting the patient from the ventilator
NIV when immunosuppression is present, or in cases of mild ARDS without impaired consciousness or cardiovascular failure	
lung-protective ventilation strategy (LPV) for patients with ARDS-high peep, permissive hypercapnia, deep sedation	
patients with severe ARDS, consider adjunctive therapeutics early, especially if failing to reach LPV targets-nmB for 48 hrs, proning, recruitment	

Management of septic shock:

DOs	DONTs
early and rapid infusion of crystalloid intravenous fluids for septic shock	Do not give hypotonic or starch-based solutions for resuscitation
vasopressors	Do not use fluid balance as guide to administer volume
administration of intravenous hydrocortisone (up to 200 mg/day) or prednisolone (up to 75 mg/day) to patients with persistent shock who require escalating doses of vasopressors	

http://www.who.int/csr/disease/coronavirus_infections/InterimGuidance_Clinical Management_NovelCoronavirus_11Feb13.pdf

Interferon alpha 2b and ribavarin:

- Retrospective studies-benefit seen
- RCTs required.

study	objective	Methods [n-20]	results
Omrani etal, 2014 [Riyadh, Saudi Arabia]	compare ribavirin and interferon alfa-2a treatment for patients with severe MERS-CoV infection with a supportive therapy only,	oral ribavirin (dose based on calculated creatinine clearance, for 8–10 days) and subcutaneous pegylated interferon alfa-2a (180 µg per week for 2 weeks).	14 (70%) of 20 patients in the treatment group had survived after 14 days, compared with seven (29%) of 24 in the comparator group (p=0·004)

Lancet Infect Dis. 2014 Nov;14(11):1090-5

Steroids:

Not recommended

OPEN ACCESS Freely available online

PLOS MEDICINE

SARS: Systematic Review of Treatment Effects

Lauren J. Stockman[1,2*], Richard Bellamy[3], Paul Garner[4]

1 Centers for Disease Control and Prevention, Respiratory and Enteric Viruses Branch, Atlanta, Georgia, United States of America, **2** Department of Veterans' Affairs, Atlanta Research and Education Foundation, Decatur, Georgia, United States of America, **3** James Cook University Hospital, Middlesbrough, United Kingdom, **4** Liverpool School of Tropical Medicine, Liverpool, United Kingdom

Corticosteroids were commonly prescribed to SARS patients with worsening pulmonary disease or progressing abnormalities on chest X-rays. Treatment regimens varied widely but can be classified into two groups, early treatment and rescue treatment given at a later stage of illness. It is difficult to make a clear recommendation about whether corticosteroids should be used to treat SARS-associated lung injury in any stage of illness, particularly as the drug is immunosuppressive and may delay viral clearance if given

PLoS Med. 2006;3(9):e343

MERS-CoV neutralizing monoclonal antibody:

LCA 60

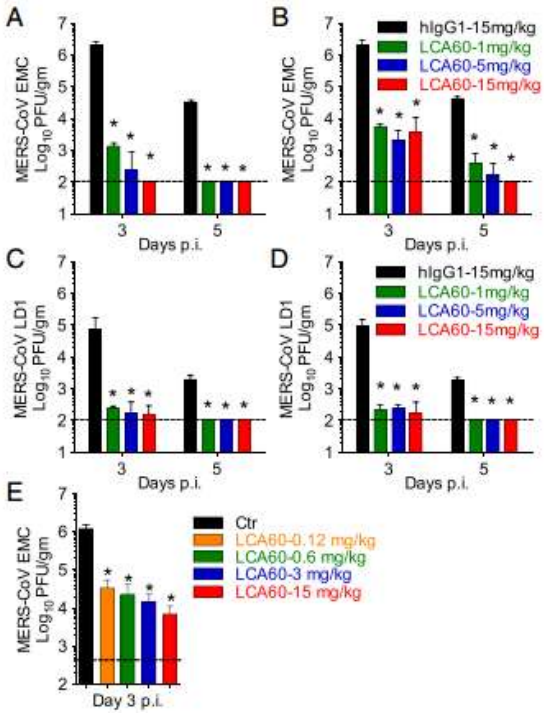
isolated from the memory B cells of an infected patient

Binds to a novel site on the spike protein and neutralizes infection with MERS-CoV by interfering with the binding to the cellular receptor CD26.

Prophylactic and postexposure efficacy of a potent human monoclonal antibody against MERS coronavirus

Davide Corti[a,b,1], Jincun Zhao[c,d,1], Mattia Pedotti[a], Luca Simonelli[a], Sudhakar Agnihothram[e], Craig Fett[e], Blanca Fernandez-Rodriguez[a], Mathilde Foglierini[a], Gloria Agatic[b], Fabrizia Vanzetta[b], Robin Gopal[f], Christopher J. Langrish[g], Nicholas A Barrett[g,h], Federica Sallusto[a], Ralph S. Baric[e,i], Luca Varani[a], Maria Zambon[f], Stanley Perlman[c], and Antonio Lanzavecchia[a,j,2]

[a]Immune Regulation Unit, Institute for Research in Biomedicine, Università della Svizzera Italiana, 6500 Bellinzona, Switzerland; [b]Humabs BioMed SA, 6500 Bellinzona, Switzerland; [c]Department of Microbiology, University of Iowa, Iowa City, IA 52240; [d]State Key Laboratory of Respiratory Diseases, Guangzhou Institute of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, China; [e]Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599; [f]Microbiology Services Colindale, Public Health England, London NW9 5HT, United Kingdom; [g]Guy's and St. Thomas' National Health Service Foundation Trust, London SE1 7EH, United Kingdom; [h]King's College London, Strand, London WC2R 2LS, United Kingdom; [i]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599; and [j]Institute of Microbiology, Eidgenössische Technische Hochschule Zurich, 8093 Zurich, Switzerland

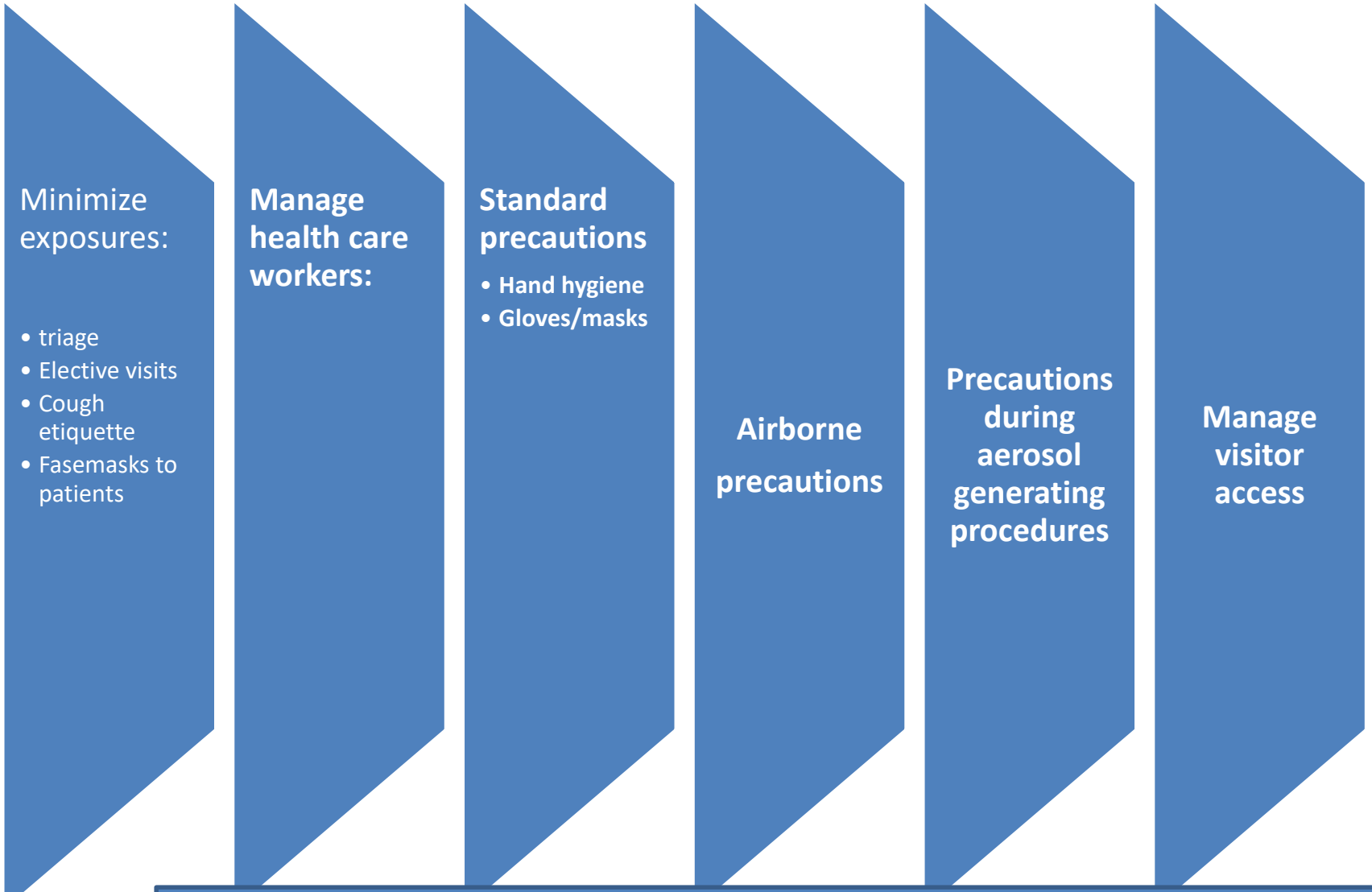


Proc Natl Acad Sci U S A. 2015;112(33):10473

PREVENTION:

- Infection control
- Interim home care and isolation
- Avoiding camels
- Travelling recommendations
- Vaccine development

INFECTION CONTROL:



http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_Update_09_May_2014.pdf?ua=1
Clin Infect Dis. 2015;60(11):1686

Interim home care and isolation:

CDC recommends that ill individuals who are being evaluated for MERS-CoV infection and do not require hospitalization may be cared for and isolated in their home

MMWR Morb Mortal Wkly Rep. 2014;63(19):431

AVOIDING CAMELS:

General:

- Anyone visiting farms, markets, barns or other places where camels are present should practice general hygiene measures

1. regular hand washing after touching animals
2. avoiding touching eyes, nose or mouth with hands
3. avoiding contact with sick animals

- Animal products processed appropriately through proper cooking are safe for consumption but should also be handled with care, to avoid cross-contamination with uncooked foods.

http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_RA_20140424.pdf?ua=1

At risk groups:

People with **diabetes, renal failure, chronic lung disease, and** immunocompromised persons are considered at high risk of severe disease from MERS-CoV infection.

These people should:

- avoid contact with camels,
- should not drink raw camel milk or camel urine, and
- should not eat meat that has not been properly cooked

http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_RA_20140424.pdf?ua=1

Travel:

- WHO does not recommend either special screening for MERS-CoV at points of entry or the application of any travel or trade restrictions.
- WHO recommends that countries outside the affected region maintain a high level of vigilance

World Health Organization. World - travel advice on MERS-CoV for pilgrimages

The Ministry of Health of Saudi Arabia recommended that, in 2014, the following individuals postpone their plans to travel to Mecca, Saudi Arabia, for Hajj and/or Umrah due to the outbreak of MERS-CoV infection:

- Older individuals (>65 years of age)
- Individuals with chronic diseases (eg, heart disease, kidney disease, respiratory disease, nervous system disorders, diabetes)
- Individuals with immunodeficiency (congenital or acquired)
- Patients with malignancy
- Patients with a terminal illness
- Pregnant women
- Children

No cases of MERS-CoV infection were detected during Hajj in 2012 or 2013

Lancet. 2014;383(9934):2073

http://www.moh.gov.sa/en/Hajj/Pages/HealthRegulations.aspx

CDC recommends that:

- all United States travelers to countries in or near the Arabian Peninsula protect themselves by washing their hands often
- avoiding contact with persons who are ill.

If travelers to the region have onset of fever with cough or shortness of breath during their trip or within 14 days of returning to the United States, they should seek medical care.

VACCINES:

There is no licensed MERS-CoV vaccine for use in humans

Using:

- major surface spike protein
- cDNA clone of the MERS-CoV genome
- recombinant modified vaccine Ankara (MVA) vaccine expressing full-length MERS-CoV spike protein
- S1 extracellular domain of S protein using adenovirus vectors

MBio. 2013;4(5):e00650
Vaccine. 2014 Oct;32(45):5975-82
J Virol. 2013;87(21):11950

- An **alternative** approach to vaccinating humans involves immunizing camels against MERS-CoV and in one study, an MVA vaccine expressing the MERS-CoV spike protein conferred mucosal immunity in dromedary camels

The development and deployment of vaccines for MERS pose unique challenges related to the virus particular ecology, the biology of coronaviruses, and the availability and adequacy of animal models for testing.

Int J Infect Dis. 2016;47:23
Science. 2016;351(6268):77

AVIAN INFLUENZA A-H7N9

- Introduction
- Virology and pathogenesis
- Epidemiology
- Clinical manifestations
- Diagnosis
- Treatment
- Prevention

INTRODUCTION:

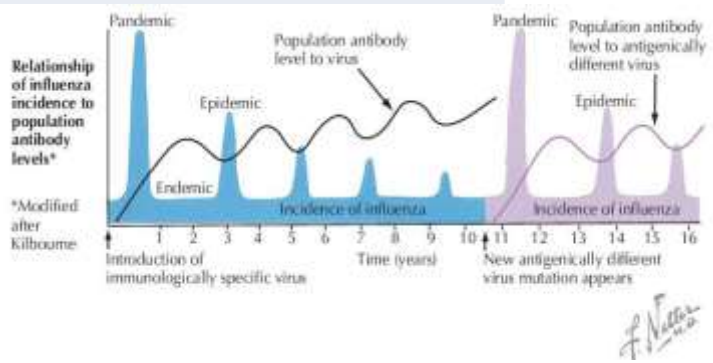
Enveloped orthomyxovirus, negative sense RNA (segmented), with 3 types, A,B,C

	Influenza A	*Influenza B*	*Influenza C*
Genetics	8 gene segments	8 gene segments	7 gene segments
Structure	10 viral proteins M2 unique	11 viral proteins NB unique	9 viral proteins HEF unique
Host range	Humans, swine, equine, avian, marine mammals*	Humans only	Humans and swine
Epidemiology	Antigenic shift and drift	Antigenic drift only; two main lineages cocirculate	Antigenic drift only; multiple variants
Clinical features	May cause large pandemics with significant mortality in young persons	Severe disease generally confined to older adults or persons at high risk; pandemics not seen	Mild disease without seasonality

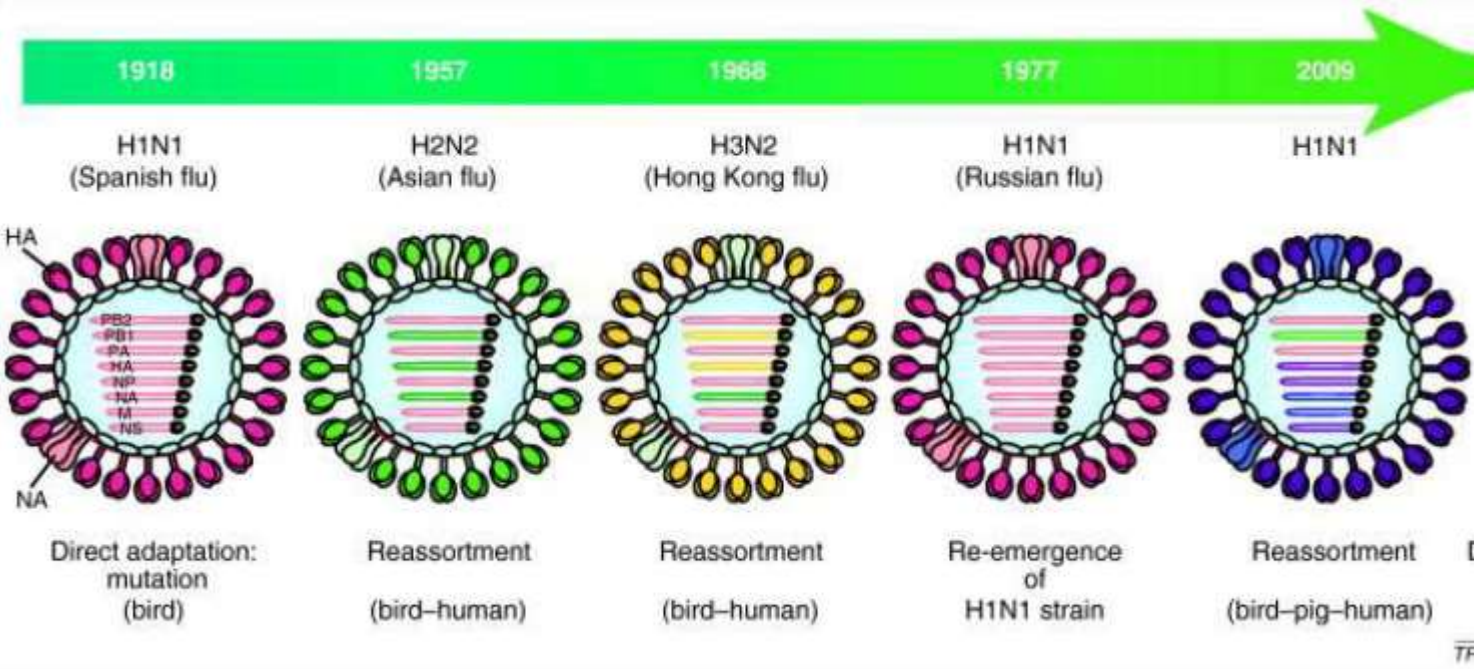
Mandell's Infectious diseases

- Of the 16 HA subtypes, 6 have been found in human infections (H1, H2, H3, H5, H7, and H9).
- So far, only 3 subtypes of HA (H1, H2, H3) and 2 subtypes of NA (N1, N2) have caused pandemics in humans.

Antigenic drift	Antigenic shift
Drift- relatively minor antigenic changes within the HA or NA of the virus	These are "new" viruses, for which the population has no immunity
immunologic selection takes place, and the variant sup-plants previous strains as the predominant virus in the epidemic.	



Influenza pandemics so far:



Why to worry H7N9?

- Humans not exposed to H7, hence susceptible
- Genome analysis suggests, mammalian adaptation possible, hence the fear of human to human transmission
- Low pathogenicity in birds make it difficult to recognize.

H7N9:

The influenza A(H7N9) virus is one subgroup among the larger group of H7 viruses, which normally circulate among birds.

February 19, 2013, 1st human case of novel avian influenza A H7N9 infection in China were reported to the World Health Organization.

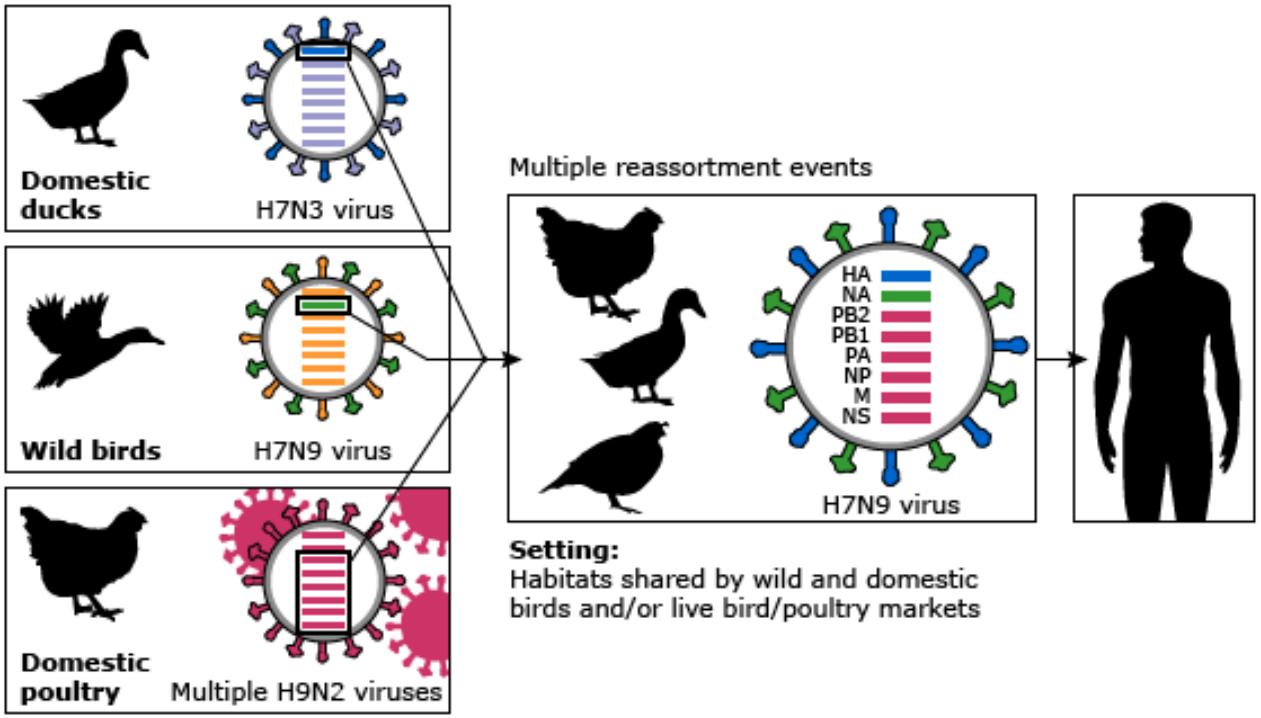
initial wave-from February to May 2013-133 cases detected.

September 2015–August 2016-4th epidemic-118 patients
11/1/17-12/1/17-2 cases in HK,China.

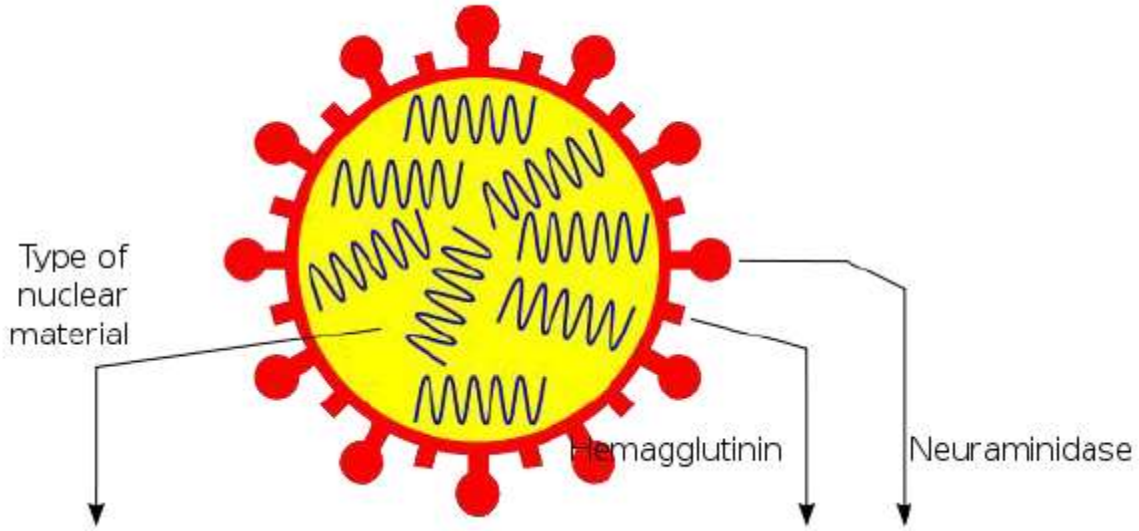
N Engl J Med. 2013;368(20):1888
N Engl J Med. 2014;370(6):520
http://www.who.int/csr/don/18-january-2017-ah7n9-china/en/

Virology:

Sources:



Lancet. 2013;381(9881):1926



A/Shanghai/1/2013 [H7N9]

Virus type | Geographic origin | Strain number | Year of isolation | Virus subtype

N Engl J Med 2013; 368:1888-1897

PATHOGENESIS:

Receptor and tissue tropism

- **Human upper respiratory tract tissues and trachea-** alpha 2-6 galactose receptors
- **human lung tissues-** mixture of alpha 2-3 galactose and alpha 2-6 galactose receptors

Transmission

no evidence of sustained human-to-human transmission

Chemokines and cytokines

- interferon inducible protein-10 [IP-10],
- monocyte chemoattractant protein
- IL-6,
- IL-8

Transmembrane protease S2 (TMPRSS2) is a host protease that cleaves and activates the hemagglutinin of influenza viruses in the human respiratory tract and a polymorphism that upregulates **TMPRSS2 expression was associated with severe H7N9 influenza infection.**

MAJOR ARTICLE

Identification of *TMPRSS2* as a Susceptibility Gene for Severe 2009 Pandemic A(H1N1) Influenza and A(H7N9) Influenza

Zhongshan Cheng,[1,a] Jie Zhou,[1,2,3,a] Kelvin Kai-Wang To,[1,2,3,4] Hin Chu,[1,2,3] Cun Li,[1] Dong Wang,[1] Dong Yang,[1] Shufa Zheng,[5] Ke Hao,[7] Yohan Bossé,[8] Ma'en Obeidat,[9] Corry-Anke Brandsma,[10] You-Qiang Song,[5] Yu Chen,[6] Bo-Jian Zheng,[1,2,3] Lanjuan Li,[6] and Kwok-Yung Yuen[1,2,3,4]

[1] Department of Microbiology, [2]Research Centre of Infection and Immunology, [3]State Key Laboratory of Emerging Infectious Diseases, [4]Carol Yu Centre for Infection, and [5]Department of Biochemistry, The University of Hong Kong, Pok Fu Lam; [6]State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, First Affiliated Hospital, College of Medicine, Zhejiang University, China; [7]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York; [8]Department of Molecular Medicine, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Laval University, and [9]University of British Columbia Center for Heart Lung Innovation, St Paul's Hospital, Vancouver, Canada; and [10]Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen Research Institute for Asthma and COPD, The Netherlands

The genetic predisposition to severe A(H1N1)2009 (A[H1N1]pdm09) influenza was evaluated in 409 patients, including 162 cases with severe infection and 247 controls with mild infection. We prioritized candidate variants based on the result of a pilot genome-wide association study and a lung expression quantitative trait locus data set. The GG genotype of rs2070788, a higher-expression variant of *TMPRSS2*, was a risk variant (odds ratio, 2.11; 95% confidence interval, 1.18–3.77; $P = .01$) to severe A(H1N1)pdm09 influenza. A potentially functional single-nucleotide polymorphism, rs383510, accommodated in a putative regulatory region was identified to tag rs2070788. Luciferase assay results showed the putative regulatory region was a functional element, in which rs383510 regulated *TMPRSS2* expression in a genotype-specific manner. Notably, rs2070788 and rs383510 were significantly associated with the susceptibility to A(H7N9) influenza in 102 patients with A(H7N9) influenza and 106 healthy controls. Therefore, we demonstrate that genetic variants with higher *TMPRSS2* expression confer higher risk to severe A(H1N1)pdm09 influenza. The same variants also increase susceptibility to human A(H7N9) influenza.

Keywords. TMPRSS2; genetic variation; lung eQTL; A(H1N1)pdm09 influenza; A(H7N9) influenza.

Genetic characteristics:

HA cleavage sequence:

- single basic amino acid
- low pathogenicity in avian species
- "silent" epidemics in poultry

HA receptor binding site:

- amino acid sequence alpha 2-6 galactose with the Q226L mutation increases the binding of avian influenza viruses to human-type receptors.

Euro Surveill. 2013;18(15):20453.

Epidemiology:

1st case-Feb 19, 2013

Total cases-> 900 cases

Last case-Jan 2017-2 cases

http://www.who.int/csr/don/en/

Case definitions:

Confirmed: → confirmed by the CDC's Influenza Laboratory or a CDC-certified public health laboratory

Probable: → Illness compatible with influenza in a patient meeting any exposure criteria and
+
laboratory diagnostic testing is positive for influenza A, negative for H1, negative for H1pdm09, and negative for H3 by real-time reverse transcription polymerase chain reaction (RT-PCR)

Case under investigation → Illness compatible with influenza in a patient meeting any of the exposure criteria and
+
laboratory confirmation is not known or pending or for whom test results do not provide a sufficient level of detail to confirm novel influenza A virus infection

Close contact → within about 6 feet (2 meters) or
within the room or care area or
direct contact with infectious secretions

Role of avian species:

avian influenza A H7N9 has been transmitted to humans from the secretions or excretions of infected poultry.

During visiting or working at a live animal market.

Case-control study of risk factors for human infection with influenza A(H7N9) virus in Jiangsu Province, China, 2013

J Ai[1], Y Huang[2,3], K Xu[1], D Ren[3,4], X Qi[1], H Ji[1], A Ge[1], Q Dai[1], J Li[1], C Bao[1], F Tang[4], G Shi[3], T Shen[3], Y Zhu (jszyf@jscdc.cn)[1], M Zhou[1], H Wang[4]
1. Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, Jiangsu, China
2. Tongling Center for Disease Control and Prevention, Tongling, Anhui, China
3. Chinese Field Epidemiology Training Program, Chinese Center for Disease Control and Prevention, Beijing, China
4. Tongren Center for Disease Control and Prevention, Tongren, Guizhou, China

Citation style for this article:
Ai J, Huang Y, Xu K, Ren D, Qi X, Ji H, Ge A, Dai Q, Li J, Bao C, Tang F, Shi G, Shen T, Zhu Y, Zhou M, Wang H. Case-control study of risk factors for human infection with influenza A(H7N9) virus in Jiangsu Province, China, 2013. Euro Surveill. 2013;18(26):pii=20510. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20510

Article submitted on 01 June 2013 / published on 27 June 2013

Characteristics	Cases (n=25) n (%)	Controls (n=93) n (%)	OR (95% CI)	P*
Chronic medical conditions	15 (60)	39 (42)	3.2 (1.2-10.1)	0.052
Hypertension	10 (40)	31 (33)	1.7 (0.6-5.4)	0.334
Chronic medical conditions (hypertension excluded)	12 (48)	19 (20)	5.2 (1.5-16.3)	0.008
Body Mass Index (BMI) (p25)	5 (20)	32 (34)	0.4 (0.1-1.3)	0.147
Having ever smoked	12 (48)	51 (55)	0.6 (0.2-1.9)	0.421
Frequent hand washing	17 (68)	83 (89)	0.2 (0.07-0.6)	0.008
Direct contact with poultry or birds[a]	10 (40)	6 (6)	13.7 (3.9-64.8)	0.001
Direct contact with poultry or birds in live poultry market[a]	7 (28)	1 (1)	23.3 (2.8-192.2)	0.003
Prepared and cooked poultry or birds at home	7 (28)	4 (4)	8.1 (2.1-31.7)	0.003
Occupational contact with poultry[a]	3 (12)	1 (1)	NA[c]	
Environment-related exposures[b]	20 (80)	45 (48)	4.8 (1.5-15.3)	0.003
Visited the market where live poultry was commercialised	15 (60)	35 (38)	3.4 (1.1-8.3)	0.017
Frequency of visits to the market, mean (±SD), days	9.3 ± 5.4	6.4 ± 5.0		
Never	10 (40)	58 (62)	Reference	
1-5 times	5 (20)	17 (18)	1.5 (0.4-5.2)	0.547
6-10 times	1 (4)	9 (10)	0.8 (0.1-3.4)	0.822
>10 times	9 (36)	9 (10)	8.8(2.2-35.1)	0.002
Bought freshly slaughtered poultry or birds in live poultry market	13 (52)	18 (19)	7.3 (2.3-25.8)	0.001
Raise poultry or birds	1 (4)	4 (4)	0.7 (0.1-6.7)	0.752
Travel history[a]	3 (12)	8 (9)	1.2 (0.2-7.2)	0.850
Exposed to persons with fever and respiratory symptoms	0 (0)	1 (1)	NA[c]	

CLINICAL FEATURES:

Incubation peroid-3 to 10 days

Presents with respiratory tract infections

Signs and symptoms may include fever, cough, dyspnea, headache, myalgias, and malaise.

Mild to moderate	severe
➢ Few cases ➢ Fever+ URTi symptoms	➢ fulminant pneumonia ➢ respiratory failure, ➢ acute respiratory distress syndrome (ARDS), ➢ septic shock, ➢ multiorgan failure, rhabdomyolysis, ➢ disseminated intravascular coagulation, ➢ and encephalopathy

Clin Infect Dis. 2013;57(10):1506.
Lancet. 2013;382(9887):129
Lancet. 2013;381(9881):1916

FAST TRACK

Detection of mild to moderate influenza A/H7N9 infection by China's national sentinel surveillance system for influenza-like illness: case series

Dennis KM Ip,[1] Qiaohong Liao,[2] Peng Wu,[1] Zhancheng Gao,[3] Bin Cao,[4] Luzhao Feng,[2] Xiaoling Xu,[5] Hui Jiang,[2] Ming Li,[2] Jing Bao,[3] Jiandong Zheng,[2] Qian Zhang,[2] Zhaorui Chang,[2] Yu Li,[2] Jianxing Yu,[2] Fengfeng Liu,[2] Michael Y Ni,[1] Joseph T Wu,[1] Benjamin J Cowling,[1] Weizhong Yang,[6] Gabriel M Leung,[1] Hongjie Yu[2]

Main results

Of 130 people with laboratory confirmed A/H7N9 infection as of 27 May 2013, five (4%) were detected through the routine sentinel surveillance system for influenza-like

Asymptomatic:

One case report

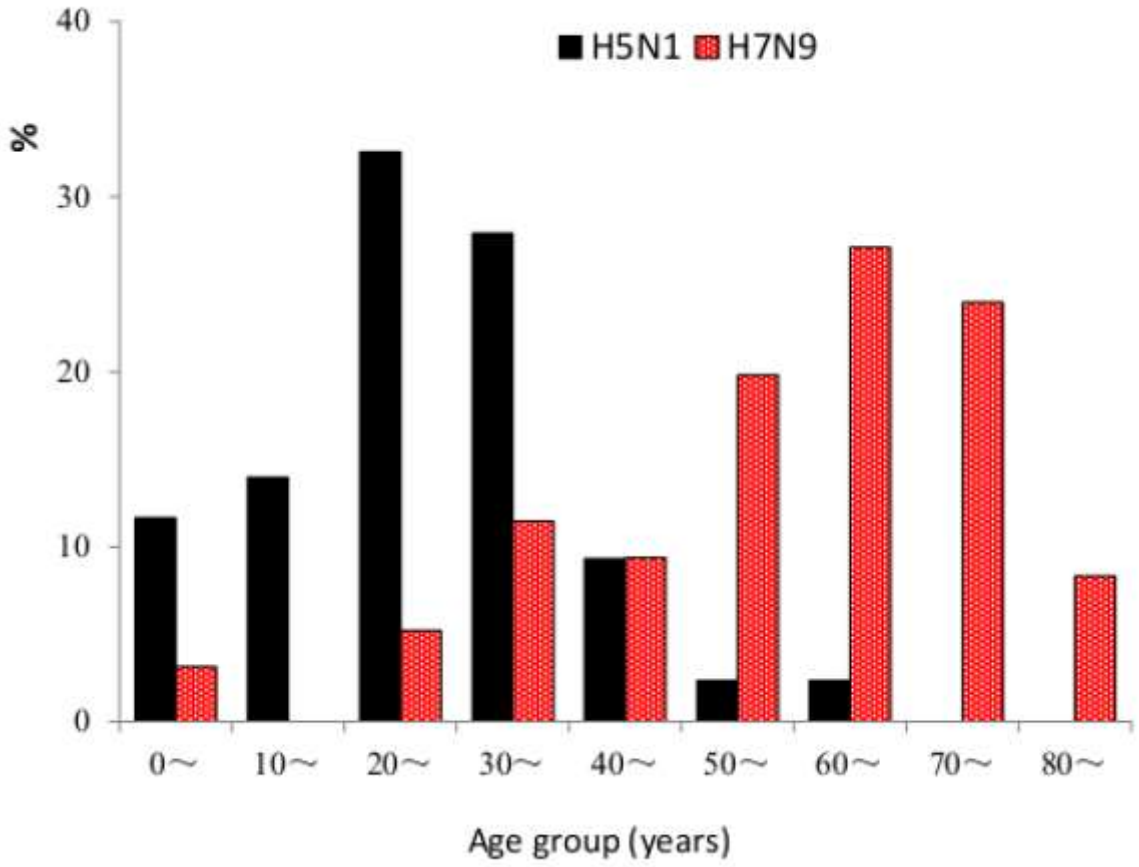
H7N9 spreads to central China as asymptomatic case reported

Filed Under: Avian Influenza (Bird Flu); H7N9 Avian Influenza
By: Lisa Schnirring | Apr 14, 2013

Apr 14, 2013 (CIDRAP News) – In quickly evolving H7N9 influenza developments, the virus has spread to a new part of China—as two illnesses were reported today in Henan province—and Beijing officials have reported the outbreak's first asymptomatic case.

Meanwhile, the H7N9 hot spot in the eastern part of the country reported 9 more cases, spiking the case count to 61, according to official sources and media reports. Shanghai also reported 2 deaths of previously announced cases, which pushes the fatality total to 13.

The asymptomatic case is in a child who apparently tested positive during risk-group surveillance.



Urban elderly males more affected

China mission report 2013.

Characteristics	%
ICU admission	76.6
>65 years	42%
Underlying medical condition	61%
mortality	27%
lymphopenia	88.3%
Exposure to poultry	55.5%

Lancet.2013 Jul 13;382(9887):138-45

DIAGNOSIS:

1-Whom to test?

who meet **both:**

Clinical illness criteria	Exposure criteria:
➢ Patients with new-onset severe acute respiratory infection requiring hospitalization **and** ➢ Patients for whom no alternative infectious etiology is identified	had recent travel (within 10 days of illness onset) to areas where human cases of avian influenza A H7N9 infection have been detected **Or** Patients who have had recent close contact (within 10 days of illness onset) with confirmed cases of human infection with avian influenza A H7N9.

http://www.cdc.gov/flu/avianflu/h7n9/specimen-collection.htm?s_cid=seasonalflu-govd-003

Specimen type-

A nasopharyngeal swab
or
A nasal aspirate or wash
or
Two swabs combined into one viral transport media vial (eg, combined nasal swab with oropharyngeal swab or combined nasopharyngeal swab with oropharyngeal swab)

Choice of diagnostic test-

rRT-PCR-real time REVERSE TRANSCRIPTION-POLYMERASE CHAIN REACTION

Viral culture is not recommended

http://www.cdc.gov/flu/avianflu/h7n9/specimen-collection.htm?s_cid=seasonalflu-govd-003

Timing of testing :

IDEALLY <7 DAYS

Specimen handling:

synthetic tip (eg, polyester or Dacron) and an aluminum or plastic shaft.

collection vials should contain 1 to 3 mL of viral transport medium

4°C for no longer than three days

http://www.cdc.gov/flu/avianflu/h7n9/specimen-collection.htm?s_cid=seasonalflu-govd-003

TREATMENT:

1-General:

- resistant to the adamantanes
- all confirmed cases, probable cases, and cases under investigation receive antiviral treatment with a neuraminidase inhibitor
- even if more than 48 hours has elapsed since illness onset.
- should **not** be delayed for laboratory confirmation

http://www.cdc.gov/flu/avianflu/h7n9-antiviral-treatment.htm

Hospitalized patients:	Uncomplicated illness in outpatients:
As early as possible Laboratory testing simultaneously Oral oseltamivir IV zanamavir to those who cant tolerate oseltamivir	Early If at high risk even in healthy If COPD/ASTHMA-avoid ZANAMAVIR

Oseltamivir Treatment chemoprophylaxis	 75 mg twice daily for five days 75 mg once daily
Zanamivir Treatment chemoprophylaxis	 10 mg (two inhalations) twice daily for five days 10 mg (two inhalations) once daily

http://www.cdc.gov/flu/avianflu/h7n9-antiviral-treatment.htm

A higher dose of oseltamivir (150 mg orally twice daily in adults with normal renal function) is recommended in immunocompromised patients and in severely ill hospitalized patients, although the possible benefit of higher doses remains unknown

PREVENTION:

oseltamivir or inhaled zanamavir chemoprophylaxis should be provided to close contacts of a confirmed or probable H7N9 case.

- High, moderate risk-give
- Low risk-not given

http://www.cdc.gov/flu/avianflu/h7n9-antiviral-treatment.htm

If a close contact tests positive inhalations] twice daily) as soon as possible, and oseltamivir should be stopped because some avian influenza A H7N9 viruses may rapidly become oseltamivir-resistant and remain zanamivir-susceptible for avian influenza A H7N9 virus after taking osaltamivir chemoprophylaxis for more than two days, zanamivir should be started (10 mg [2

Vaccine-

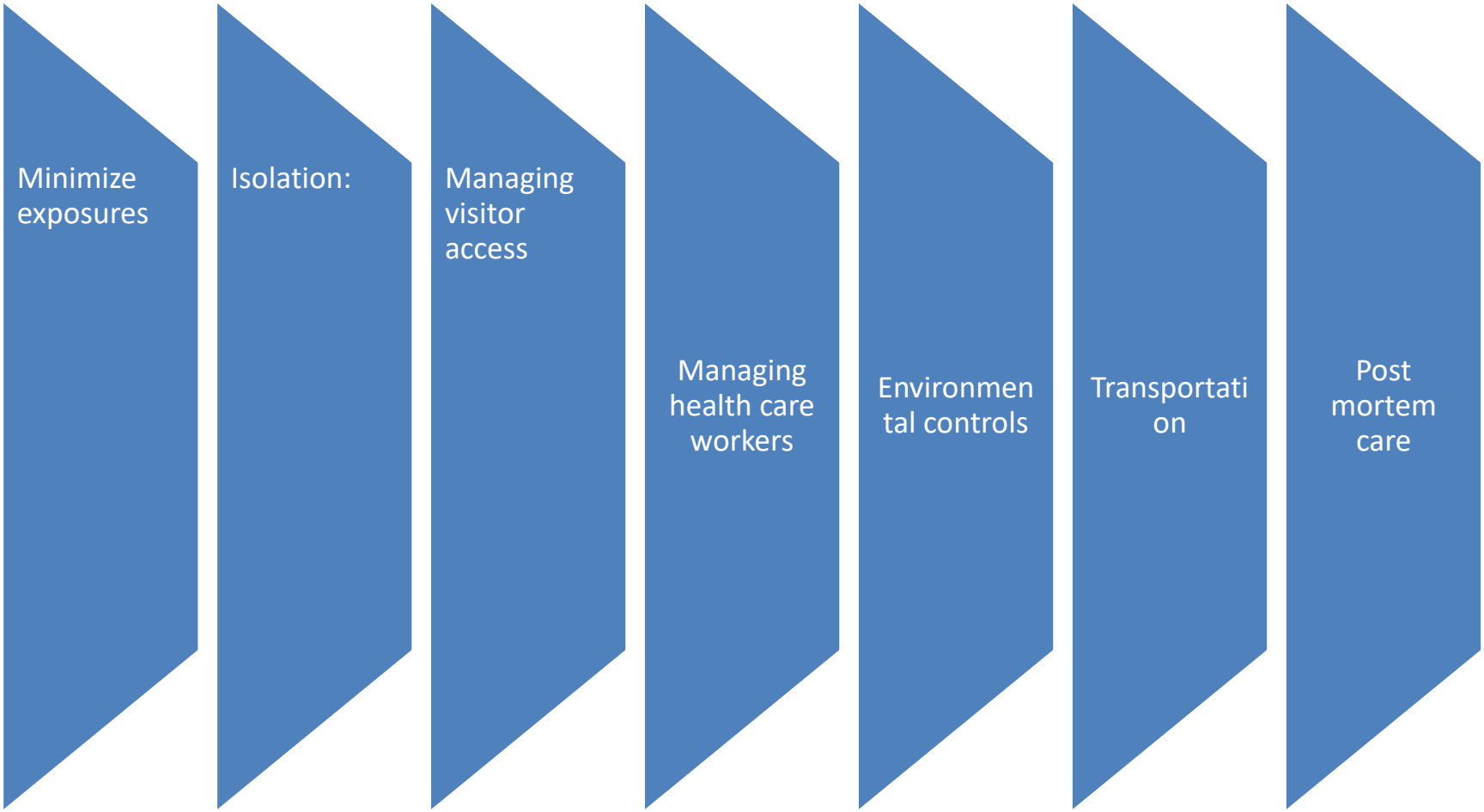
World Health Organization (WHO) recommends to use A/Anhui/1/2013-like virus be used for vaccine development.

<9months of pandemic treat.

Travel:

No restrictions

INFECTION CONTROL and PREVENTION



Minimizing exposures:

Triage/ screening

Patients informing during appointments

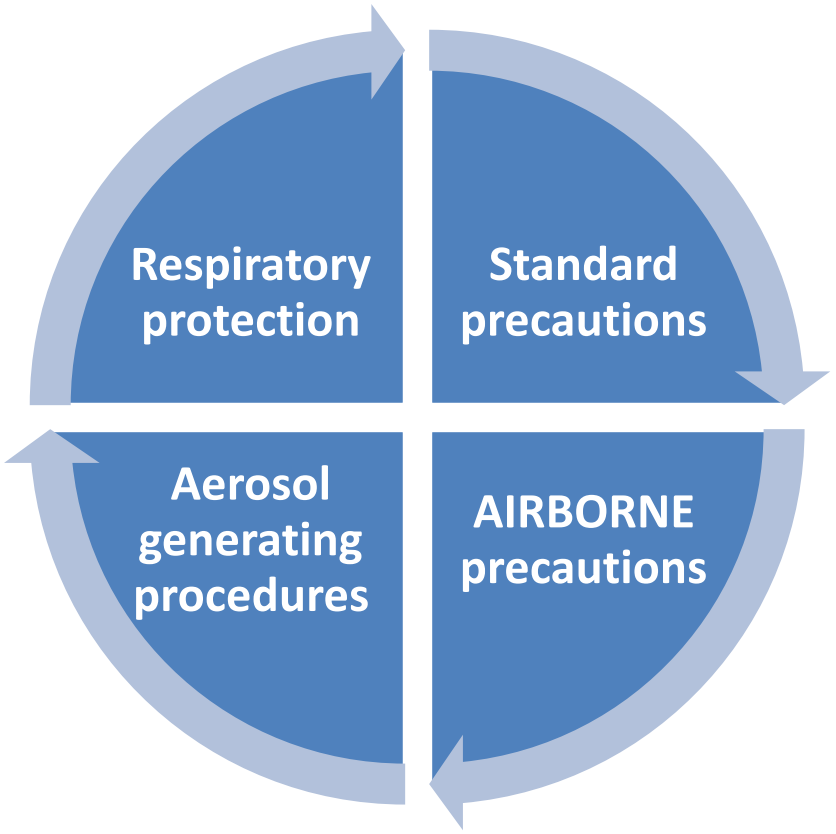
Minimize elective visits-

Telephone consultations

respiratory hygiene, cough etiquette, and hand hygiene

- Posting visual alerts (eg, signs, posters) in strategic locations
- Providing facemasks to patients
- Providing ethanol-based hand sanitizers
- Providing space and encouraging patients with respiratory symptoms

ISOLATION PRECAUTIONS:



Standard precautions:

Hand hygiene-

- before and after every patient contact, contact with potentially infectious material, and before putting on and after taking off personal protective equipment, including gloves.
- soap and water or by using alcohol-based hand rubs
- Healthcare workers with direct patient contact should have fingernails that are short, clean, and free from false nails and nail polish

Gloves:

Gloves should be used for any contact with potentially infectious material, followed by hand hygiene immediately after glove removal.

provide a protective barrier for the healthcare worker as well as the patient.

Wearing gloves does not replace the need for hand hygiene as gloves may have unapparent tears, and hands predictably become contaminated during glove removal.

Gowns:

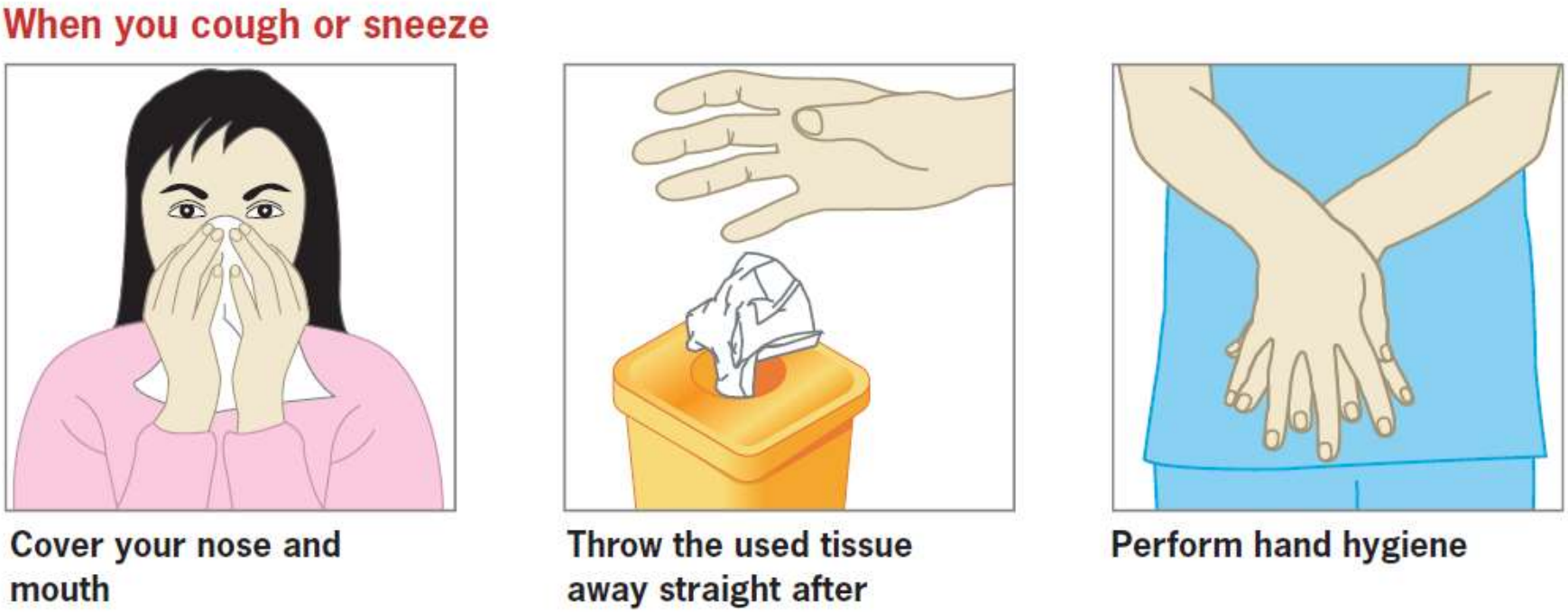
- Reusable/non reusable
- Gowns are used in addition to gloves if there is risk of fluids or blood from the patient splashing onto the health-care worker’s body.
- Re-usable gowns must be laundered after every use.

AIRBORNE PRECAUTIONS:

<5u

remain suspended in the air for extended periods.

<3-6 feet exposure+.



- Cough etiquette

Aerosol generating procedures:

procedures **include endotracheal intubation and extubation, bronchoscopy, sputum induction, cardiopulmonary resuscitation, open suctioning of airways, and autopsies**

- each healthcare worker should wear an N95 respirator
- conduct procedure in an airborne infection isolation room
- Limit the number of healthcare personnel present during the procedure
- Environmental surface cleaning following these procedures

Respiratory protection:

1. Suspected/confirmed-facial masks
2. During airborne generating procedures-N95 masks or its equivalents.

N95 equivalents-

- powered air purifying respirator
- elastomeric

n95
N=not resistant to oil
95=95% efficiency in filtering out <0.3u size particles

N95 vs surgical masks: ~~aerosol~~

ORIGINAL CONTRIBUTION JAMA-EXPRESS

Surgical Mask vs N95 Respirator for Preventing Influenza Among Health Care Workers

A Randomized Trial

Context Data about the effectiveness of the surgical mask compared with the N95 respirator for protecting health care workers against influenza are sparse. Given the likelihood that N95 respirators will be in short supply during a pandemic and not available in many countries, knowing the effectiveness of the surgical mask is of public health importance.

Objective To compare the surgical mask with the N95 respirator in protecting health care workers against influenza.

Design, Setting, and Participants Noninferiority randomized controlled trial of 446 nurses in emergency departments, medical units, and pediatric units in 8 tertiary care Ontario hospitals.

Intervention Assignment to either a fit-tested N95 respirator or a surgical mask when providing care to patients with febrile respiratory illness during the 2008-2009 influenza season.

Main Outcome Measures The primary outcome was laboratory-confirmed influenza measured by polymerase chain reaction or a 4-fold rise in hemagglutinin titers. Effectiveness of the surgical mask was assessed as noninferiority of the surgical mask compared with the N95 respirator. The criterion for noninferiority was met if the lower limit of the 95% confidence interval (CI) for the reduction in incidence (N95 respirator minus surgical group) was greater than −9%.

Results Between September 23, 2008, and December 8, 2008, 478 nurses were assessed for eligibility and 446 nurses were enrolled and randomly assigned the intervention; 225 were allocated to receive surgical masks and 221 to N95 respirators. Influenza infection occurred in 50 nurses (23.6%) in the surgical mask group and in 48 (22.9%) in the N95 respirator group (absolute risk difference, −0.73%; 95% CI, −8.8% to 7.3%; $P = .86$), the lower confidence limit being inside the noninferiority limit of −9%.

JAMA. 2009 Nov 4;302(17):1865-71

For respiratory protection to be effective, it is crucial to achieve a proper fit!!

MAJOR ARTICLE

Mask Use, Hand Hygiene, and Seasonal Influenza-Like Illness among Young Adults: A Randomized Intervention Trial

Allison E. Aiello,[1,2] Genevra F. Murray,[3] Vanessa Perez,[1,2] Rebecca M. Coulborn,[1,2] Brian M. Davis,[1,2] Monica Uddin,[1,2] David K. Shay,[4] Stephen H. Waterman,[4] and Arnold S. Monto,[1]

[1]Department of Epidemiology and [2]Center for Social Epidemiology and Population Health, School of Public Health, University of Michigan, Ann Arbor, Michigan; [3]Department of Sociology, Anthropology, and Social Work, University of South Alabama; [4]Centers for Disease Control and Prevention, Atlanta, Georgia

(See the editorial commentary by Daniels and Talbot, on pages 483–5.)

Background. During the influenza A(H1N1) pandemic, antiviral prescribing was limited, vaccines were not available early, and the effectiveness of nonpharmaceutical interventions (NPIs) was uncertain. Our study examined whether use of face masks and hand hygiene reduced the incidence of influenza-like illness (ILI).

Methods. A randomized intervention trial involving 1437 young adults living in university residence halls during the 2006–2007 influenza season was designed. Residence halls were randomly assigned to 1 of 3 groups—face mask use, face masks with hand hygiene, or control— for 6 weeks. Generalized models estimated rate ratios for clinically diagnosed or survey-reported ILI weekly and cumulatively.

Results. We observed significant reductions in ILI during weeks 4–6 in the mask and hand hygiene group, compared with the control group, ranging from 35% (confidence interval [CI], 9%–53%) to 51% (CI, 13%–73%), after adjusting for vaccination and other covariates. Face mask use alone showed a similar reduction in ILI compared with the control group, but adjusted estimates were not statistically significant. Neither face mask use and hand hygiene nor face mask use alone was associated with a significant reduction in the rate of ILI cumulatively.

Conclusions. These findings suggest that face masks and hand hygiene may reduce respiratory illnesses in shared living settings and mitigate the impact of the influenza A(H1N1) pandemic.

Trial Registration. ClinicalTrials.gov identifier: NCT00490633.

J Infect Dis (2010) 201 (4): 491-498

Step 1
- Cup the respirator in your hand with the noseplece at your fingertips allowing the headbands to hang freely below your hand.

Step 2
- Position the respirator under your chin with the noseplece up.

Step 3
- Pull the top strap over your head resting it high at the back of your head. Pull the bottom strap over your head and position it around the neck below the ears.

Step 4
- Place fingertips of both hands at the top of the metal noseplece. Mould the noseplece (USING TWO FINGERS OF EACH HAND) to the shape of your nose. Pinching the noseplece using one hand may result in less effective respirator performance.

Step 5
- Cover the front of the respirator with both hands, being careful not to disturb the position of the respirator.

Step 5a: Positive seal check
- Exhale sharply. A positive pressure inside the respirator – no leakage. If leakage, adjust the position and/or tension straps. Retest the seal.
- Repeat the steps until the respirator is secured properly.

Step 5b: Negative seal check
- Inhale deeply. If no leakage, negative pressure will make respirator cling to your face.
- Leakage will result in loss of negative pressure in the respirator due to air entering through gaps in the seal.

WHO/CDS/EPR/2007.8

Step 1
- Identify hazards & manage risk. Gather the necessary PPE.
- Plan where to put on & take off PPE.
- Do you have a friend? Mirror?
- Do you know how you will deal with waste?

Step 2
- Put on a gown.

Step 3
- Put on mask.

Step 4
- Put on eye protection e.g. visor, face shield, goggles (consider anti-fog drops or fog-resistant goggles). Caps are optional: if worn, put on after eye protection.

Step 5
- Put on gloves (over cuff).

WHO/CDS/EPR/2007.8

MANAGING VISITOR ACCESS:

limited to individuals who are necessary for the patient's **care and well-being**.

When visits are planned, the following measures should be taken:

- screened for symptoms of acute respiratory illness before entering the facility.
- instruction before visitors enter the patient's room on hand hygiene, limiting surfaces touches, and use of personal protective equipment.
- use respiratory hygiene and cough etiquette.
- Absent for aerosol-generating procedures.
- limit their movement within the facility.
- Vaccines if available.

http://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm

MANAGING HEALTHCARE WORKERS:

Chemoprophylaxis

Ill health workers with fever and respiratory complaints:

- Not report to work or, if already at work, stop patient-care activities, wear a facemask, and promptly notify their supervisor and infection control or occupational health
- adherence to respiratory hygiene, cough etiquette, and hand hygiene
- If symptoms such as coughing and sneezing are still present, wear a facemask after returning to work during patient care activities
- Be excluded from work until at least 24 hours after fever has abated
- Be considered for temporary reassignment or exclusion from work for seven days after symptom onset or until resolution of symptoms, whichever is longer, if returning to care for patients in a protected environment, such as hematopoietic cell transplant recipients.

http://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm

ENVIRONMENTAL CONTROLS:

- well-ventilated rooms which removes the contaminated air reduce risk of infection being transmitted through respiratory aerosols
- The recommended minimal ventilation rate is 12 air changes per hour (ACH).
- Only reduces the risk of infection and not eliminate the risk.

www.tbcindia.nic.in/showfile.php?lid=2858

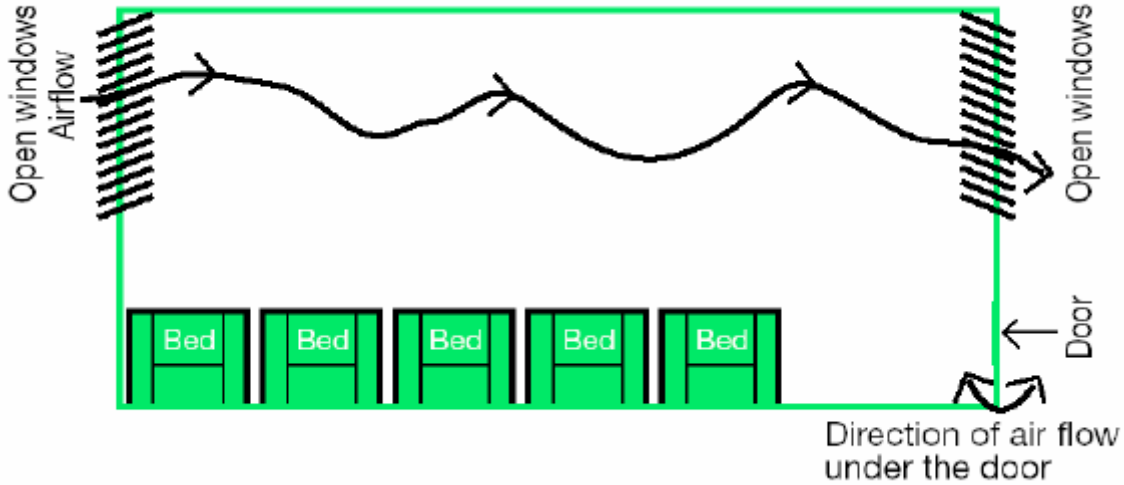
mechanical	natural	Mixed [hybrid]
Fan used to drive air flow. To be effective: ➢ 12 ach minimum. ➢ Doors/windows closed	External airflows generated by natural forces such as wind. air should be directed to flow from patient-care areas towards transit-free areas.	exhaust fan used. useful in places were natural ventilation is not suitable (e.g. very cold weather) and fully mechanically ventilated airborne precautions rooms are not available.
Suitable for all climates and weather More controlled and comfortable environment	Suitable for warm and temperate climates Capable of achieving very high ventilation rates Low costs	Energy saving, relative to mechanical Ventilation flexible
Noise, expensive, faulty	Easily affected by outdoor climate	Difficult to design

www.tbcindia.nic.in/showfile.php?lid=2858

Table 4: Minimum air-changes per hour required for various health care settings

Type of Health-Care Setting	Minimum Air-Changes per Hour (ACH)	Minimum hourly averaged ventilation rates (liters/second/patient)
Registration areas	>6 ACH[3]	>40 l/s/patient
Outpatient departments and their waiting areas	>6 ACH	>40 l/s/patient
Inpatients departments	>6 ACH	>40 l/s/patient
High-risk settings and their waiting areas ART centres	>12 ACH[4]	80–160 l/s/patient

on both sides allow for adequate air exchange.



www.tbcindia.nic.in/showfile.php?lid=2858

TRANSPORTATION:

- Should wear a medical mask when being transported or when being provided with care outside of isolation or cohorting areas.
- Health-care workers designated to receive patients of potential concern should be alerted in advance.
- Transport them via routes that minimize the opportunities for exposure.

WHO/CDS/EPR/2007.8

Post mortem:

- After death of a patient with potential concern, the body should be placed in a fully sealed, impermeable body bag before it is removed from the isolation room for transportation to the mortuary.
- PPE are of sufficient strength to withstand any damage during lifting body.
- Those involved with performing or assisting with autopsies must wear appropriate PPE.

WHO/CDS/EPR/2007.8

TAKE HOME MESSAGE:

- Mers Cov-is a novel lineage C betacoronavirus causing severe pneumonia, kidney injury which has no specific treatment, diagnosed by rRT-PCR and further cases can be prevented by increases level of infection control precautions

- H7N9-is a novel avian influenza virus. Genetic re assortment can lead a future pandemic of a avian influenza virus.

- Infection control precautions should be carried out as a team with a collective effort from everyone including administrators, doctors and nursing.

THANK YOU.