MERS Co-V

Avian Flu

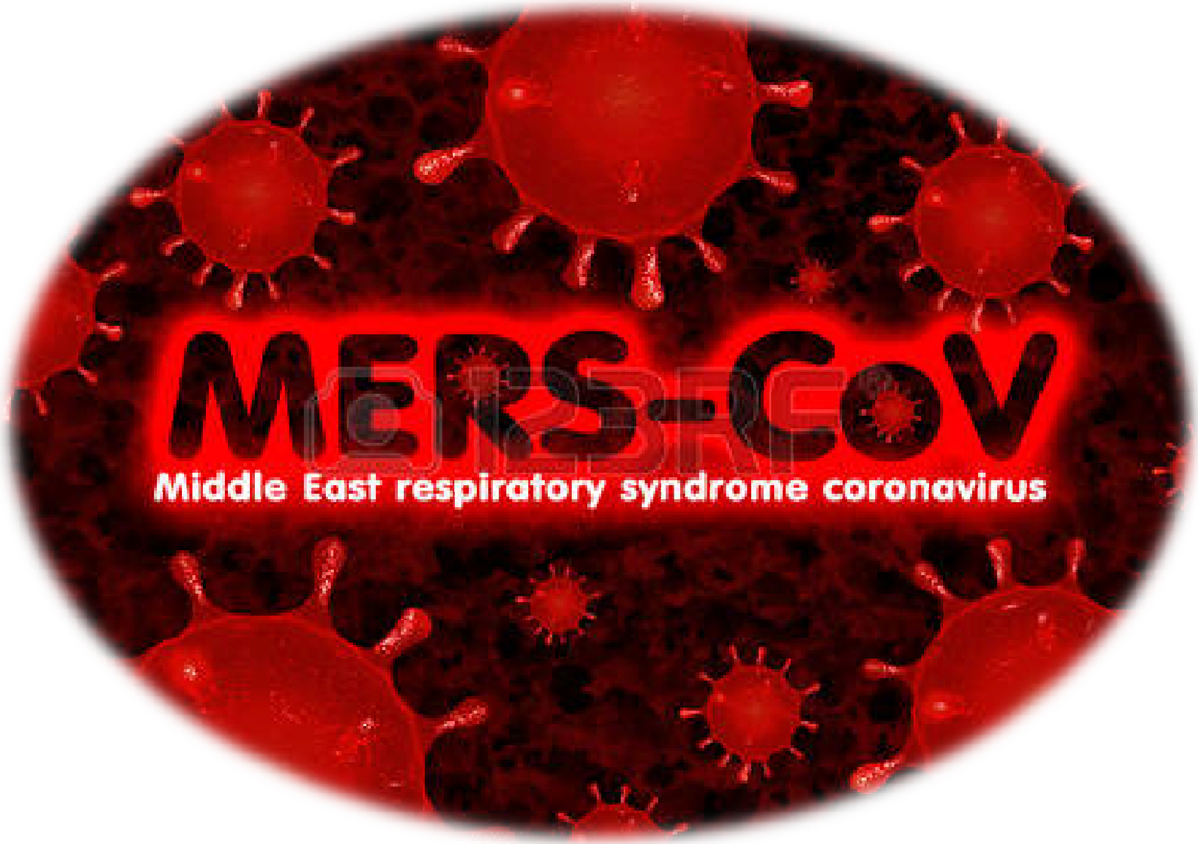
Anilawati Mat Jelani

Hospital Raja Perempuan Zainab II

Kota Bharu

ASMEIT2017

ANNUAL SCIENTIFIC MEETING ON EMERGING INFECTIOUS THREAT


MERS-CoV
Middle East respiratory syndrome coronavirus

How it began….

The NEW ENGLAND JOURNAL of MEDICINE

13th June 2012

BRIEF REPORT

N ENGL J MED 367;19 NEJM.ORG NOVEMBER 8, 2012

Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia

Ali Moh Zaki, M.D., Ph.D., Sander van Boheemen, M.Sc., Theo M. Bestebroer, B.Sc., Albert D.M.E. Osterhaus, D.V.M., Ph.D., and Ron A.M. Fouchier, Ph.D.

ProMED mail

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.

[The clinical isolate] was initially tested for influenza virus A, influenza virus B, parainfluenza virus, enterovirus and adenovirus, with negative results. Testing with a **pancoronavirus** RT-PCR yielded a band at a molecular weight appropriate for a coronavirus. The virus RNA was tested also in Dr. Ron Fouchier's laboratory in the Netherlands and was confirmed to be a new member of the beta group of corononaviruses, closely related to bat coronaviruses. Further analysis is being carried out in the Netherlands.

The Virology Laboratory at the Dr Fakeeh Hospital will be happy to collaborate with others in studies of this virus.

--
Ali Mohamed Zaki
Professor of Microbiology
Dr Fakeeh hospital Jeddah Saudi Arabia

The virus

- Enveloped, single-stranded, positive-sense RNA virus
- Betacoronavirus, related to SARS CoV and other coronaviruses
- Origin is likely bats? 
- Camels a likely virus reservoir, or at least a liaison host 
- MERS-CoV has zoonotic potential

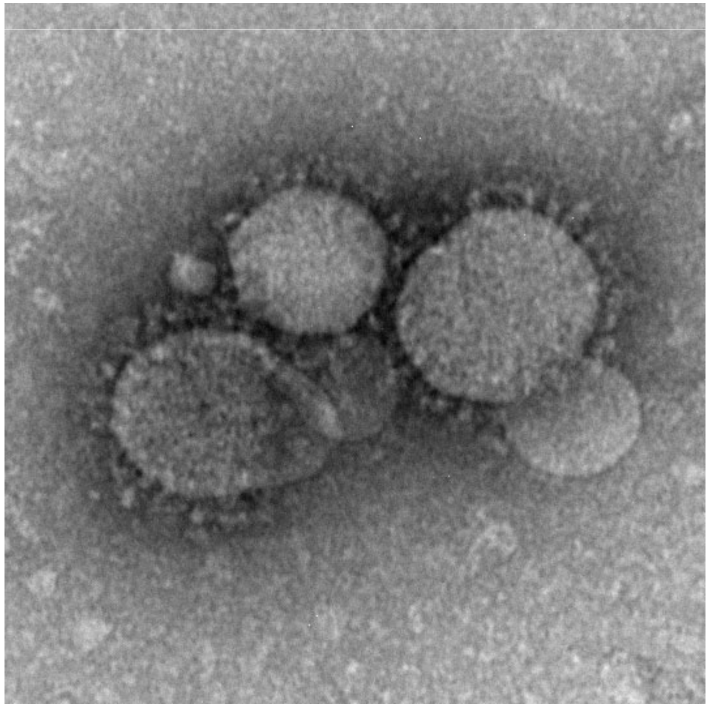


Image source: Cynthia Goldsmith/Maureen Metcalfe/Azaibi Tamin

MERS-CoV particles as seen by negative stain electron microscopy. Virions contain characteristic club-like projections emanating from the viral membrane

SARS Co-V vs MERS Co-V		
	SARS Co-V	MERS Co-V
Lineage	Lineage B/Betacoronaviridae	Lineage B/ Betacoronaviridae
Receptor	ACE2	DPP4

The changing case demography

- Early on in the outbreak :
  - Predominance of male patients and those with comorbidities
  - most cases had severe illness

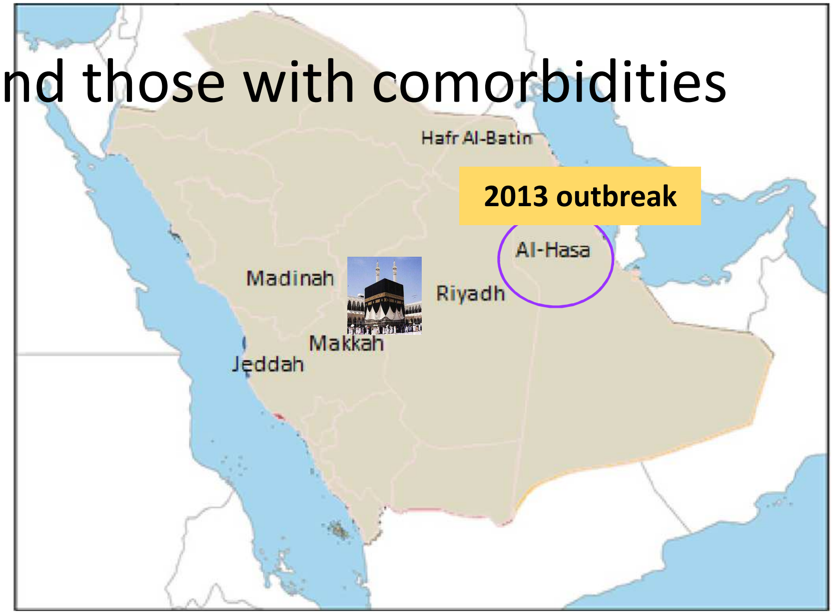


Table 1 A summary of demographics of major MERS-CoV studies

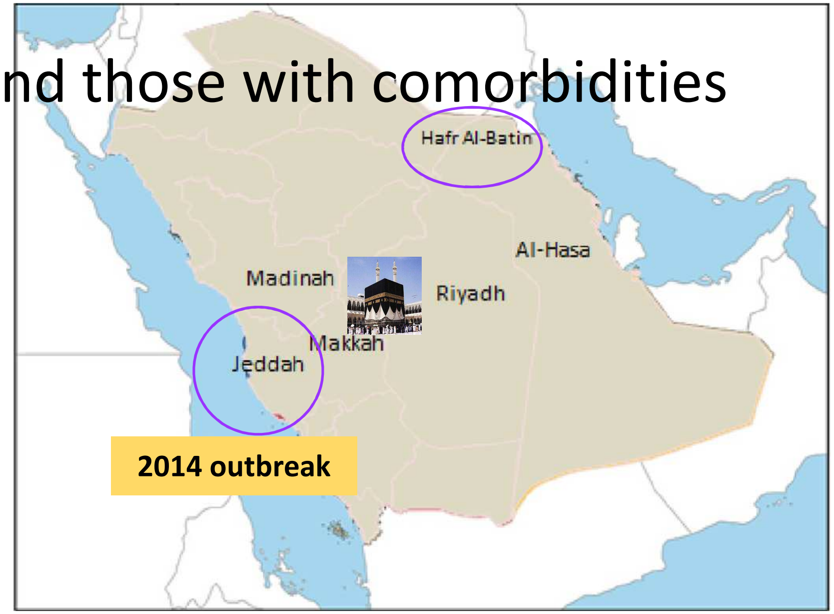
Number of cases	Median age (range) years	Male-to-female ratio	Percentage asymptomatic	Percentage severe cases	Case fatality rate (%)	Reference
23	56 (24–94)	2.8:1	0	100	65	6
47	NA	3.3:1	0	100	60	7
133	NA	1.5:1	13.5	86.5	45	9
161	50 (14–94)	1.8:1	11.1	63.4	–	10
402	46 (0.75–94)	1.4:1	28.6	44.5	28.3	11
113	41 (0.25–89)	1.3:1	28.9	NA	30	12

Abbreviations: MERS-CoV, Middle East respiratory syndrome coronavirus; NA, not available.

Al-Tawfiq et al. Infect Drug Resist 2014

The changing case demography

- Early on in the outbreak :
  - Predominance of male patients and those with comorbidities
  - most cases had severe illness
- As more data collected :
  - spectrum of illness is more clear
  - ↓ percentage of severe cases
  - ↑ asymptomatic cases
  - ↓ in M:F , median age, and CFR



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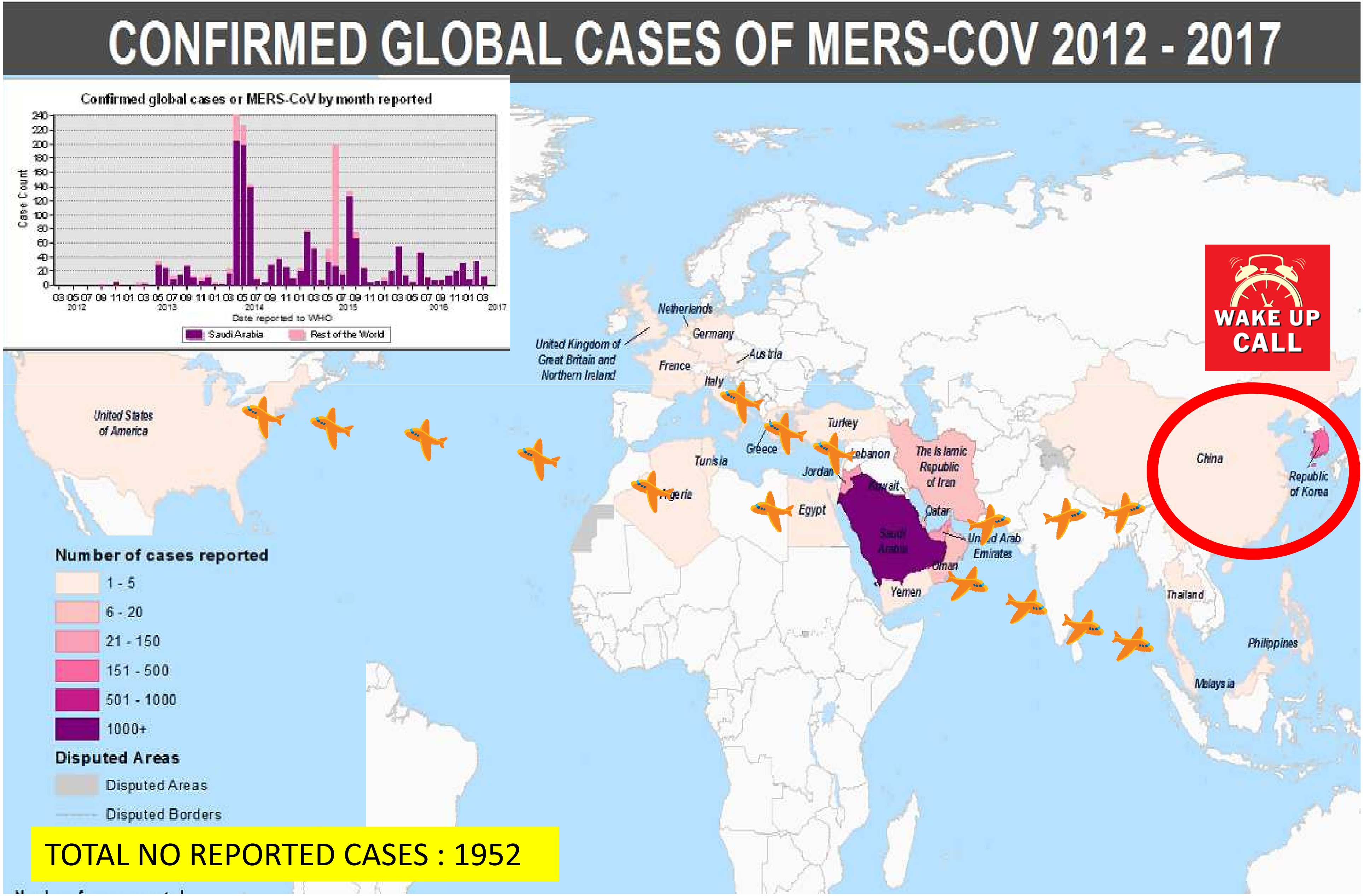
Al-Tawfiq et al. Infect Drug Resist 2014

The clinical syndrome

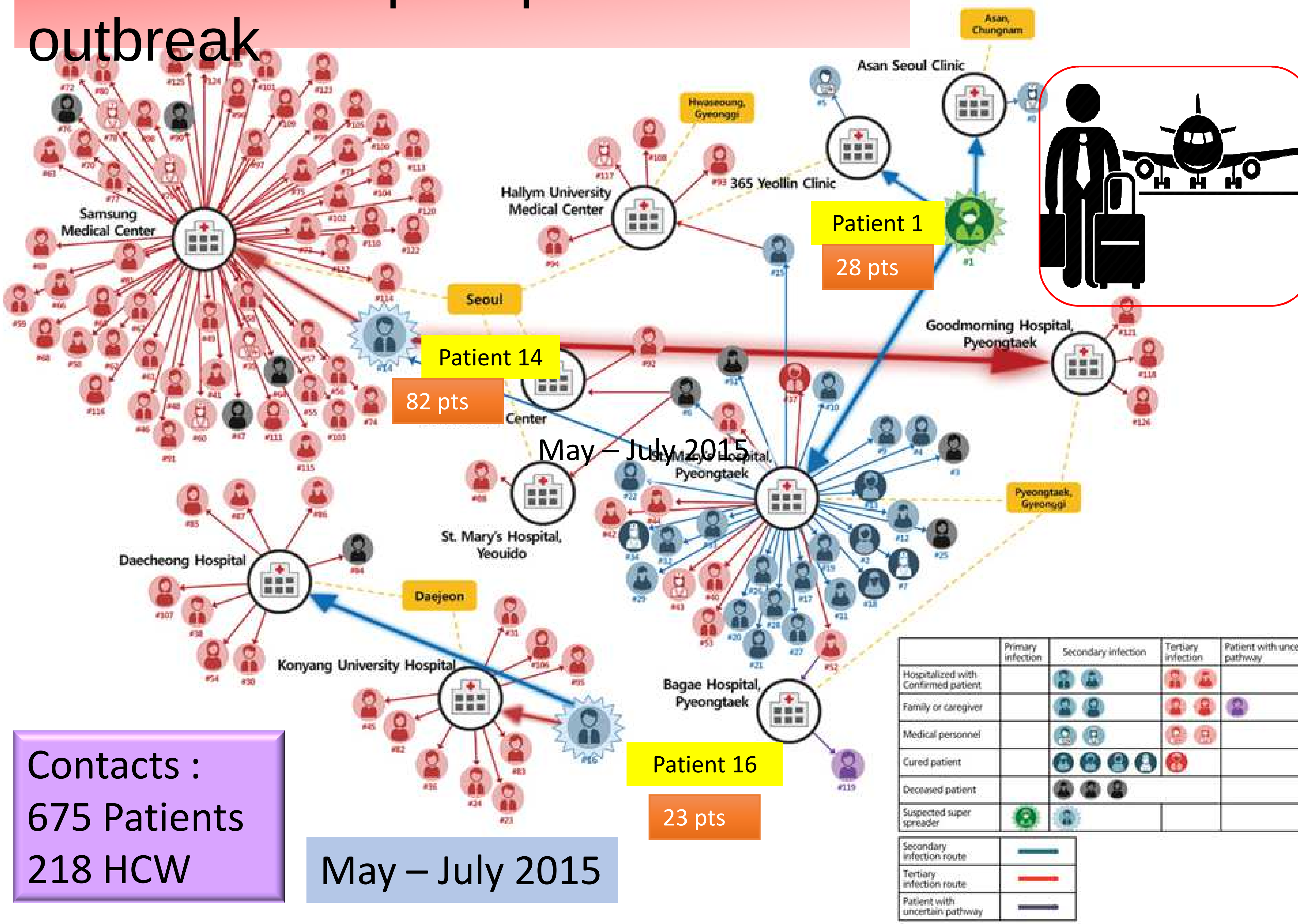
- Incubation period 2-14 days
- “Severe acute hypoxemic respiratory failure and considerable extra pulmonary organ dysfunction”
- Contagious and nosocomial infection is reported
- Higher mortality rate compared to SARS
- Asymptomatic cases (Positivity of contacts by PCR)
    - Up to 15.4%
    - Largest screening from Saudi Arabia – HCW (1.12%) and family contacts (3.6%)
- Imaging - organizing pneumonia vs. bronchiolitis obliterans organizing pneumonia-like pattern in SARS.”
- No known effective treatments or preventive vaccines

Memish ZA et al Clin Microbiol Infect. 2014
Mailles A et al . Euro Surveill. 2013
(HPA) UK Novel Coronavirus Investigation team. Euro Surveill. 2
Pebody RG et al Euro Surveill. 2012

The global spread of MERS



The Korea super spreader outbreak



Contacts :
675 Patients
218 HCW

May – July 2015

The Korea super spreader outbreak

- 186 patients infected
- 99.4% nosocomial acquired
- 38 deaths (19.9%)
- Intra-hospital & inter-hospital transmission
- No intra-community transmission
- Main risk factor for transmission – overcrowding, gaps in infection control measures

Lesson Learnt :-

- Importance of early case detection
- Role of super-spreaders of the virus – quarantine failure
- Breach of infection control – isolation practice , visitors restriction
- Crisis management communication

*1.Cho, Sun Young et al. **MERS-CoV outbreak following a single patient exposure in an emergency room in South Korea: an epidemiological outbreak study**. The Lancet , Volume 388 , Issue 10048 , 994 – 1001*

2.Kim KH, Tandi TE, Choi JW, Moon JM, Kim MS, Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in South Korea, 2015: Epidemiology, characteristics and public health implications, Journal of Hospital Infection (2016)

Transmission

MERS-CoV transmission is not fully understood

Healthcare associated

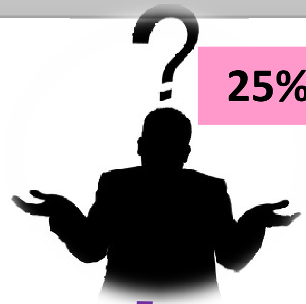
- Most of human-human infections
- 25% are HCW
- involved in aerosol generating procedures

Direct contact

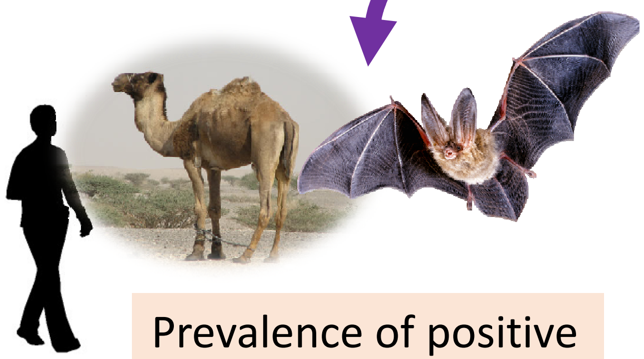
- Community outbreak
- Intra-familial
- 2° attack rate – 3%

Travel related

1° Infection



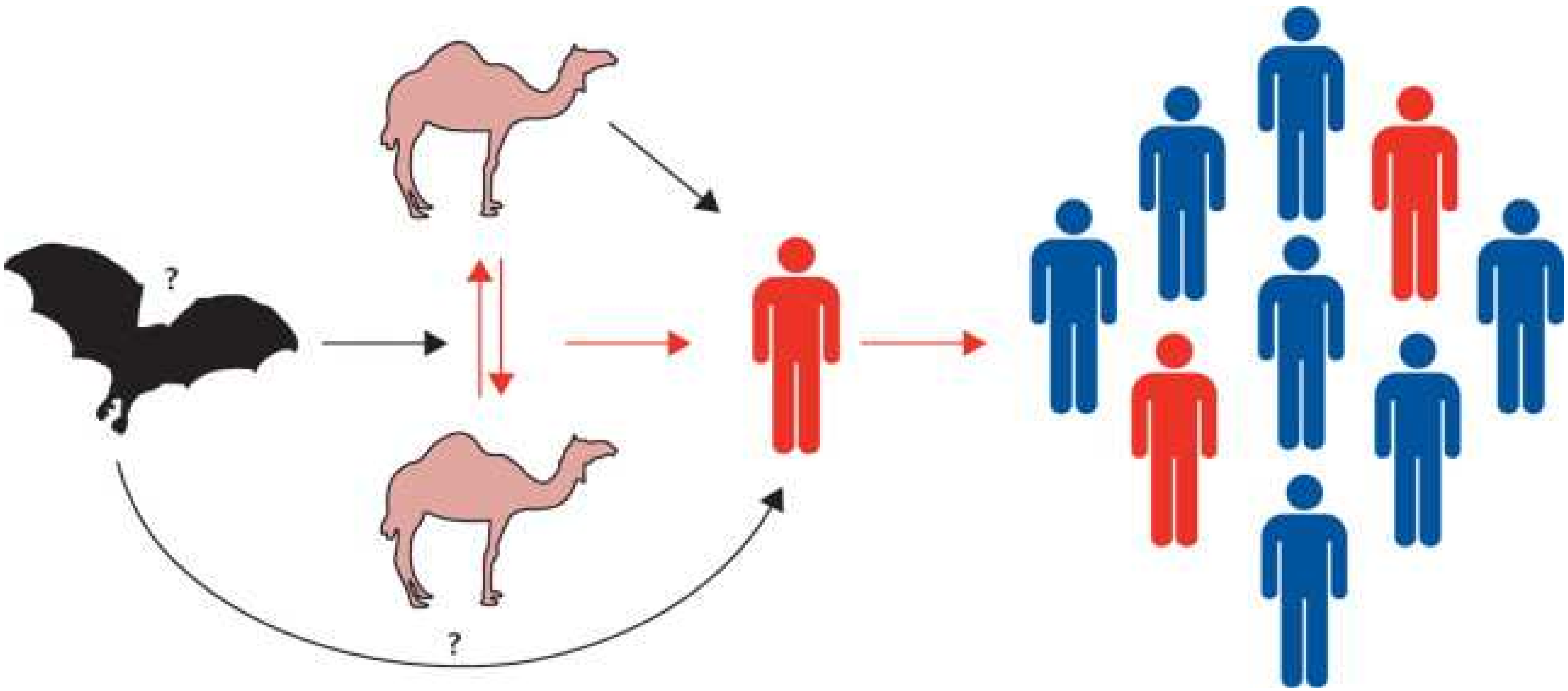
25%



Prevalence of positive MERS COV antibody among human 0.15%[1]

1.Muller MA etal Lancet Infectious Disease 2015

Animals and MERS CoV



REVIEW Open Access

CrossMark

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) origin and animal reservoir

Hamzah A. Mohd[1], Jaffar A. Al-Tawfiq[2,3] and Ziad A. Memish[1,4*]

Review

Middle East respiratory syndrome coronavirus (MERS-CoV): animal to human interaction

Ali S. Omrani[1], Jaffar A. Al-Tawfiq[2,3], Ziad A. Memish[4]

Bat and MERS-CoV

REVIEW | Open Access

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) origin and animal reservoir

Hamzah A. Mohd[1], Jaffar A. Al-Tawfiq[2,3] and Ziad A. Memish[1,4*]

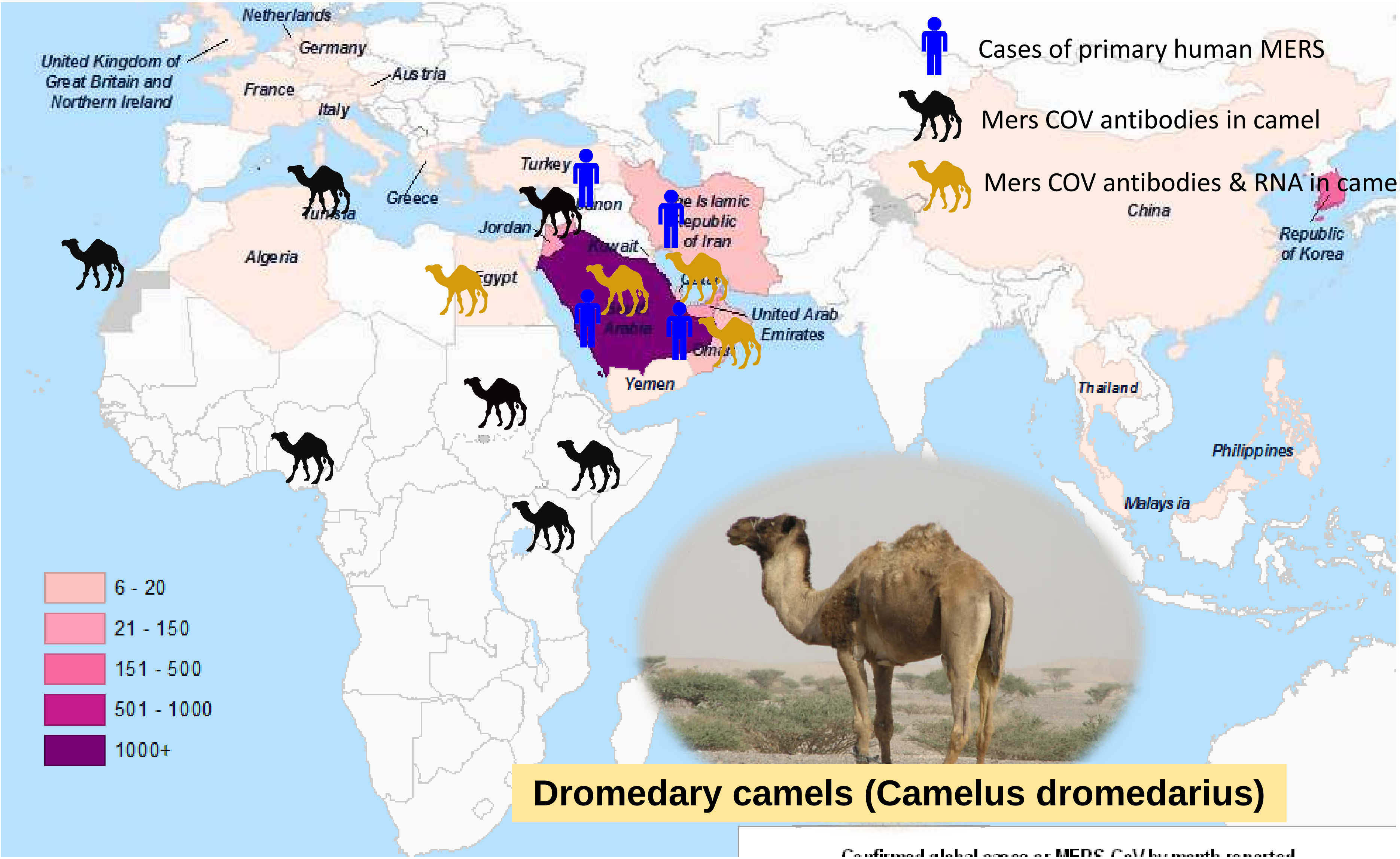
Table 1 Summary of important studies that screened bats for beta-coronaviruses and MERS-CoV

Location	Year	Species	Number	Specimen	Virus	% Positive
Ghana [8]	2009–2011	*Nycteris cf. gambiensis*	185	Fecal	2c betacoronaviruses (closely related to MERS-CoV)	24.9 %
Ghana [8]	2009–2011	9 different species[a]	4573	Fecal		0 %
Europe [8] (Germany, Netherland, Romania, Ukraine)	2009–2011	*Pipistrellus kuhlii, P. nathusii, P. pipistrellus, P. pygmaeus*	272	Fecal		14.7 %
South Africa [9]	2011–2012	13 different species[b]	62	Fecal pellets	bat related-alphacoronaviruses betacoronavirus	6.4 % 1.6 %
Saudi Arabia [10]	2012	*Rhinopomahardwickii, R.microphyllum, Taphozous perforatus, P. kuhlii, Eptesicus bottae, Eidolon helvum, and Rosettus aegyptiacus*	96	Throat swab, serum, urine, rectal swab or fecal pellets	MERS-CoV	1 %
Saudi Arabia [10]	2013	*R.hardwickii, T.perforates, P.kuhlii*	14	Throat swabs, roost feces	MERS-CoV	0 %
Egypt [11]	2013–2015	*T. perforatus*	82	Serum/rectal (alive)	MERS-CoV	0 %
		P. deserti	31			
		R. aegyptiacus	257			
Lebanon [11]	2013–2015	*R. hipposideros*	4	Homogenized lung and liver material (if died or euthanized upon capture)		0 %
		Miniopterus schribersii	6			
		R. ferrumequinm	3			
		R. aegyptiacus	438			

[a]Coleura afra, Hipposiderosabae, H. cf. gigas, H. fuliginosus, H. jonesi, H. cf. ruber, Rhinolophus alcyone, R. landeri, Taphozous perforates
[b]*Chaerephonpumilus, Mops condylurus, Tadaridaaegyptiaca, H.caffer, Miniopterus natalensis, Nycteristhebaica, R.clivosus, R. darlingi, Neoromicia capensis, N. nana, N. cf. zuluensis, Scotophilus viridis, Rousettus aegyptiacus*

- **MERS-CoV, or its immediate ancestor, could have likely originated in bats**
- **Bats may serve as ideal reservoir**
- **Bats are NOT the direct source of human disease**

The camel connection :
Where is human and camel MERS on the map?



Dromedary camels (Camelus dromedarius)

The camel connection : Is there any evidence ?

- Studies found epidemiological association between dromedary camels & human cases in Middle East
- Seroprevalence of MERS-CoV antibodies >90% in dromedary camels in Eastern Africa & Arabian Peninsula
- MERS-CoV RNA and viable virus isolated from dromedary camels
  - Respiratory secretions, camel milk, urine
- MERS-CoV may have been circulating in dromedaries > 20 years
- Near-identical strains of MERS-CoV isolated from epidemiologically linked Saudi Arabian patient and camels

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Evidence for Camel-to-Human Transmission of MERS Coronavirus

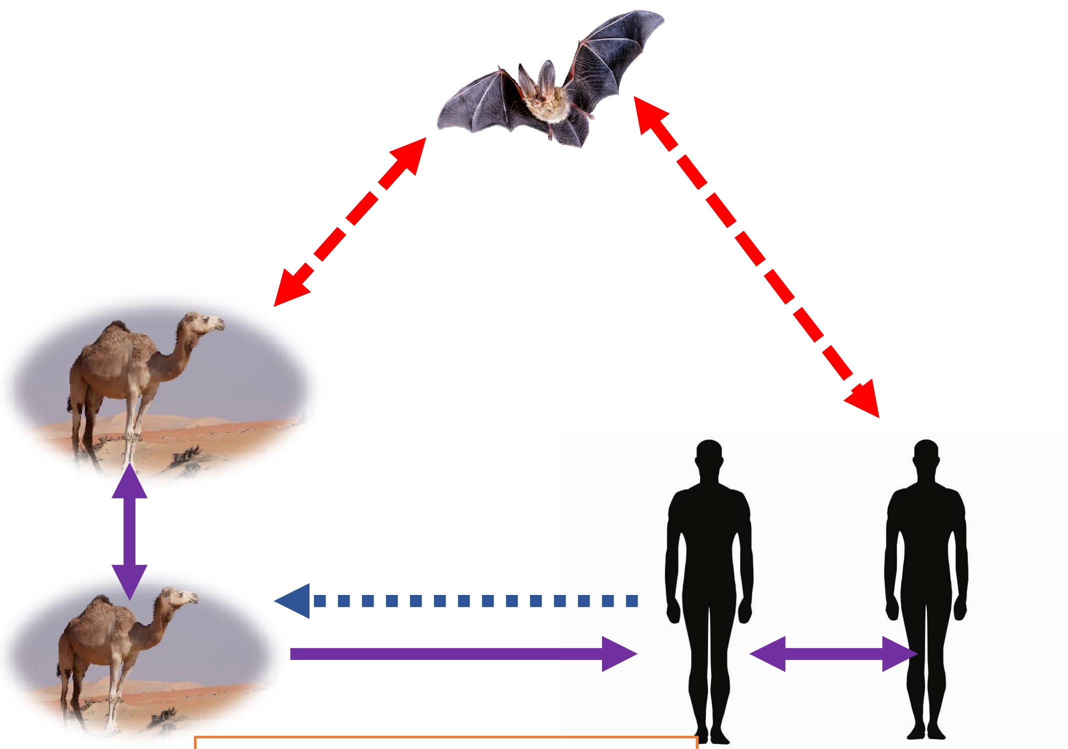
Esam I. Azhar, Ph.D., Sherif A. El-Kafrawy, Ph.D., Suha A. Farraj, M.Sc., Ahmed M. Hassan, M.Sc., Muneera S. Al-Saeed, B.Sc., Anwar M. Hashem, Ph.D., and Tariq A. Madani, M.D.

REVIEW ARTICLE

Dromedary Camels and the Transmission of Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

M. G. Hemida[1,2], A. Elmoslemany[3,4], F. Al-Hizab[5], A. Alnaeem[3], F. Almathen[6], B. Faye[7], D. K. W. Chu[8], R. A. P. M. Perera[8] and M. Peiris[8]

Is it a camel flu ??



Droplets, aerosol, milk, urine and/or feces ?

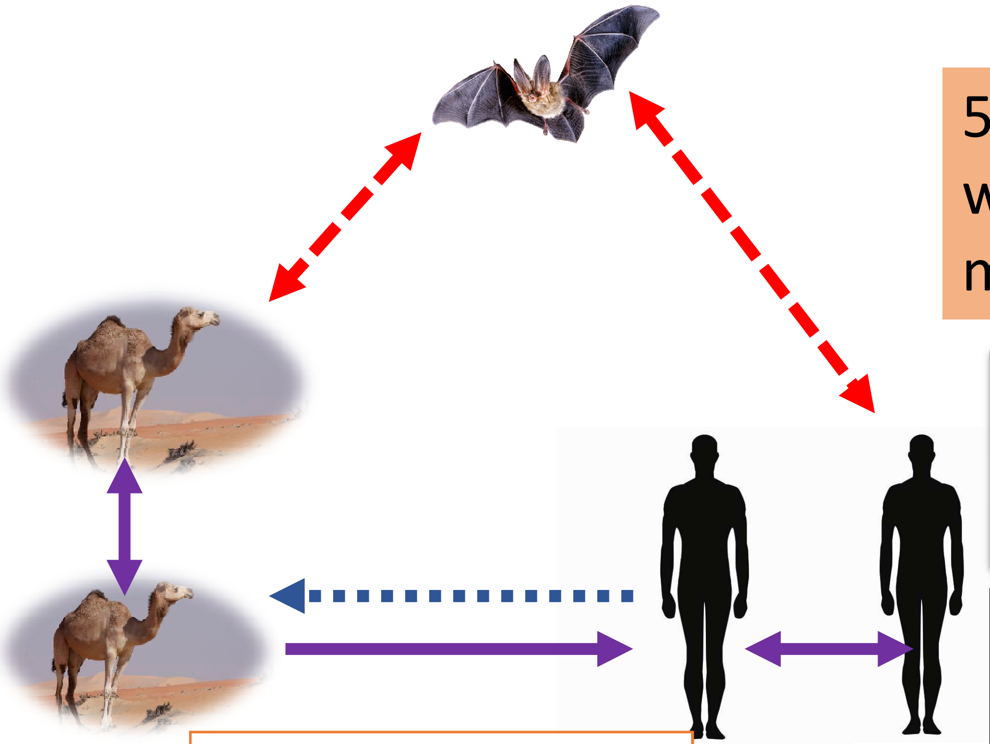
Is it a camel flu ??

Research Article | Open Access

MERS-CoV: An Epidemic Whirlwind

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

5% of MERS patients had contact with camels/consumed raw camel milk



Droplets, aerosol, milk, urine and/or feces ?

Lack of Middle East Respiratory Syndrome Coronavirus Transmission from Infected Camels

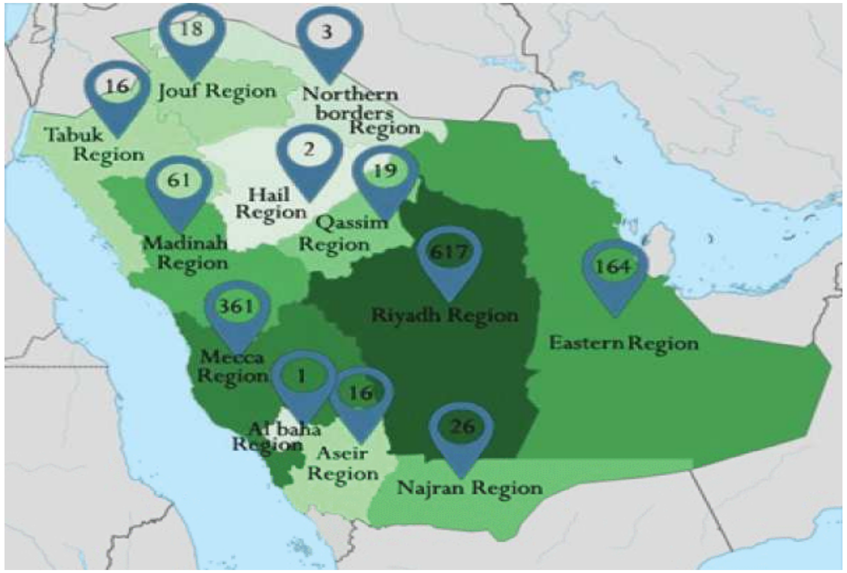
Maged G. Hemida,[1] Abdulmohsen Al-Naeem,[1] Ranawaka A.P.M. Perera,[1] Alex W.H. Chin, Leo L.M. Poon, Malik Peiris

In February 2014, serum samples were obtained from persons with various levels of exposure to camels. Persons were divided into 5 groups.

To determine risk for Middle East respiratory syndrome coronavirus transmission from camels to humans, we tested serum from 191 persons with various levels of exposure to an infected dromedary herd. We found no serologic evidence of human infection, suggesting that zoonotic transmission of this virus from dromedaries is rare.

Camel to human MERS-CoV transmission is well documented but not very efficient.

Hajj and MERS risk



- Annually, hajj brings an estimated 2 million people to Saudi Arabia
- Past 4 annual Hajj pilgrimages passed by without increase in travel-related MERS-CoV cases
- Risk of returning pilgrims infected with MERS-CoV to their home countries remains
- Early identification of MERS-CoV and rapid implementation of appropriate infection control measures for suspected cases is crucial to avoid outbreaks

MOH MERS surveillance

Numbers of notifications

2013 - 125

2014 - 354

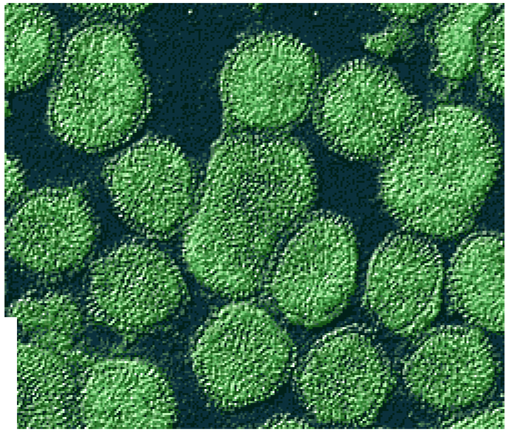
2015 - 726

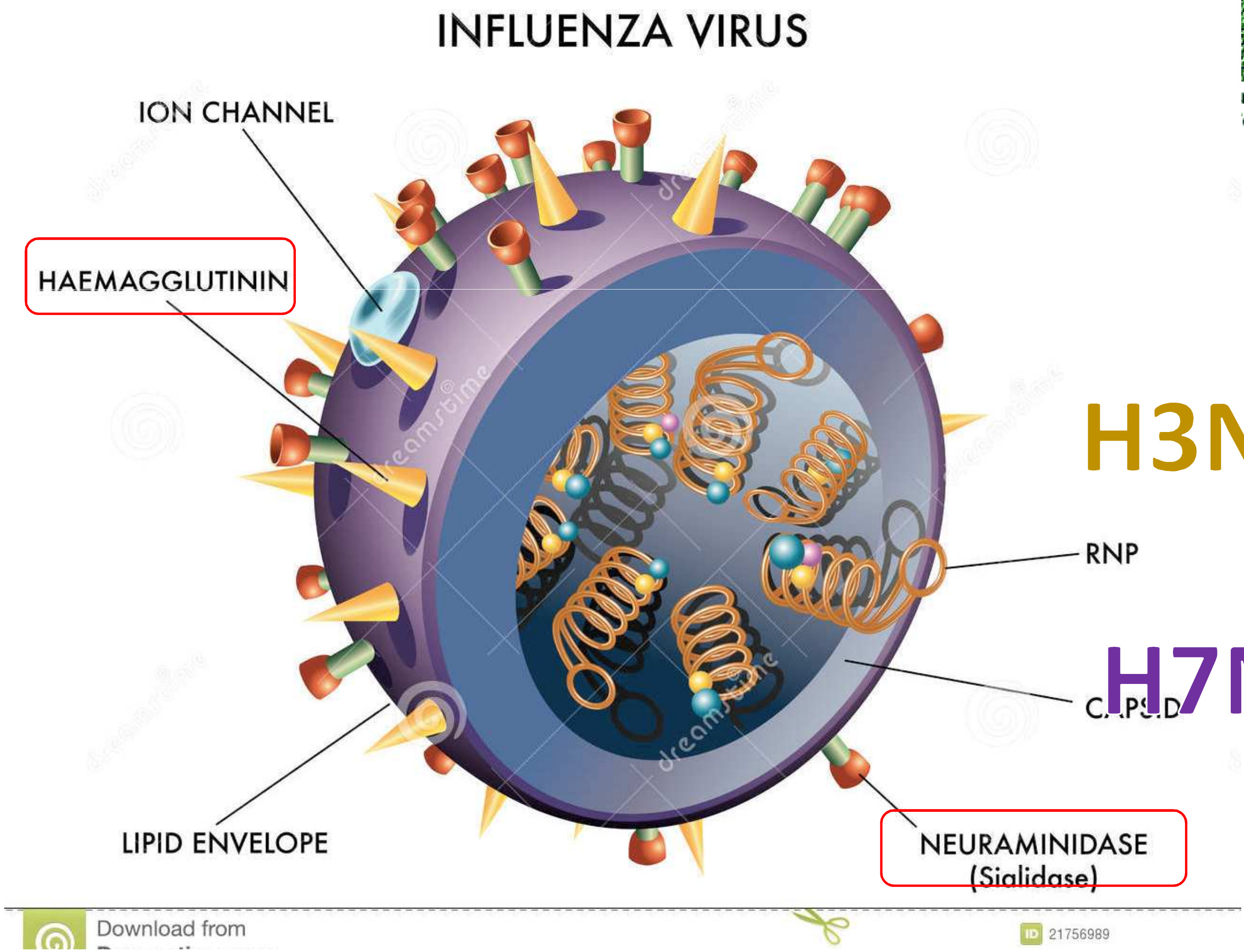
2016 - 850

MINISTRY OF HEALTH MALAYSIA

www.timeasia.com
SEPTEMBER 26, 2005
TIME
IRAQ: IS IT TOO
LATE TO WIN THIS WAR?
AVIAN FLU
DEATH THREAT
SPECIAL REPORT: Inside the global
race to avert a pandemic

The Influenza A virus





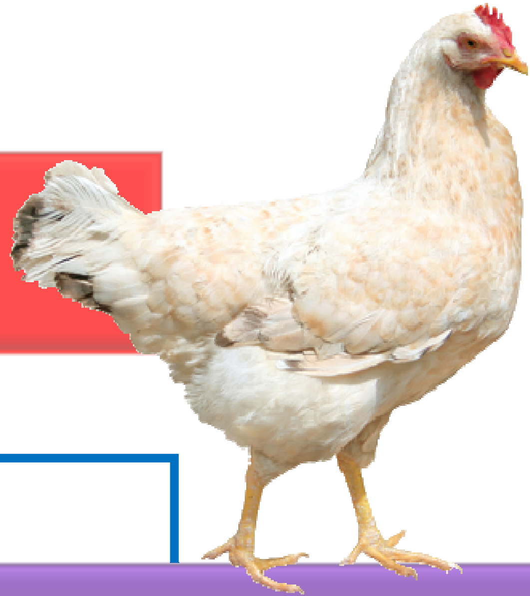
H3N2

H5N1

H7N9

H1N1

Avian Influenza



Low pathogenic avian influenza (LPAI)

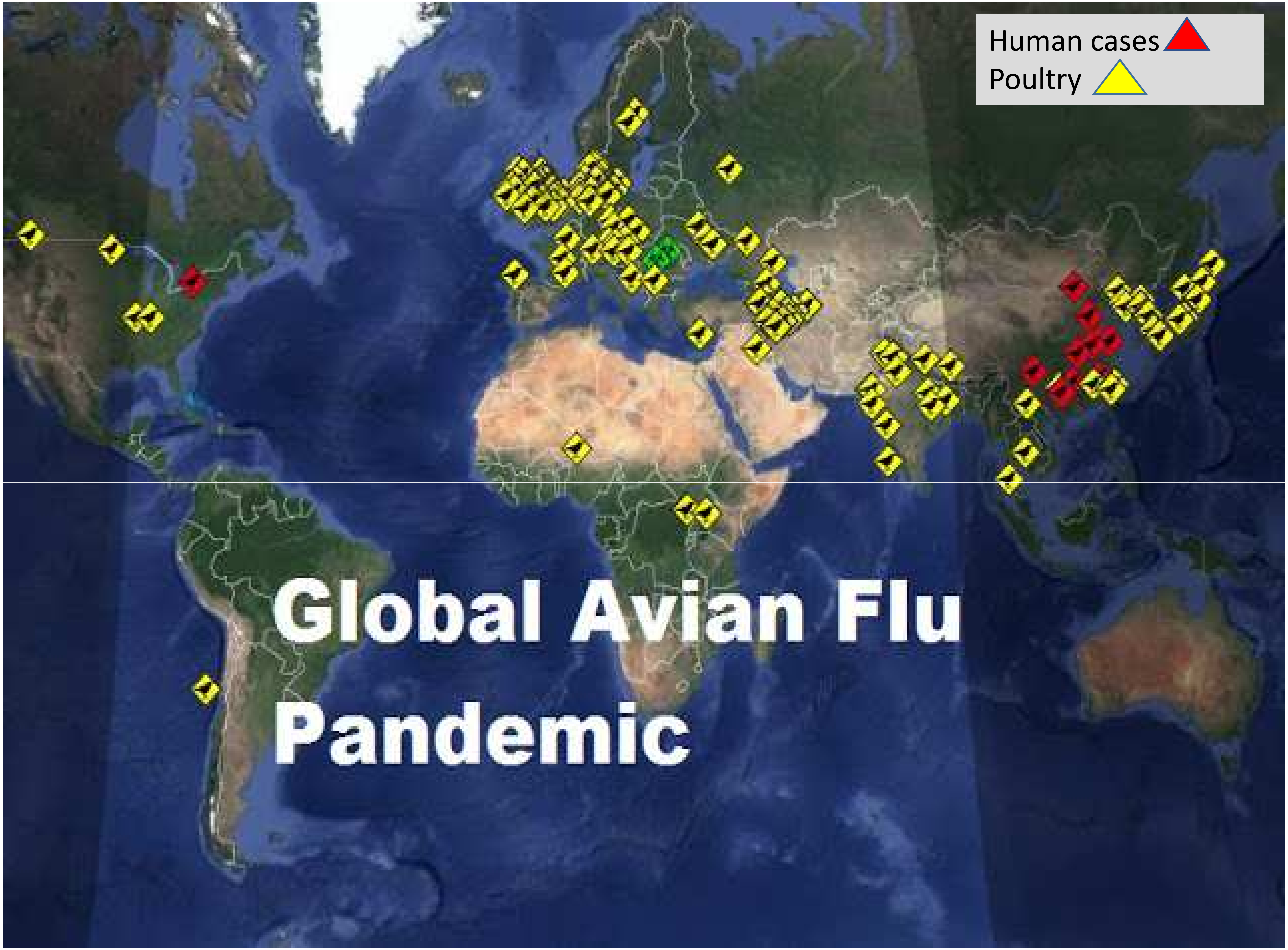
- mild or no clinical signs
- low to moderate mortality
- capable of mutating into highly pathogenic strains

Highly pathogenic avian influenza (HPAI)

- sudden onset
- severe clinical signs
- high mortality

Avian Influenza "at a glance"

- Highly contagious - affecting poultry, pet and wild birds
- Acute clinical disease in poultry associated only with H5 & H7 AI subtypes.
- Potentially causing pandemics
- Most AI viruses do not infect humans
- H5N1 and H7N9 may cause fatal infections in human
- **H5N1**
  - enzootic in Asia and Africa
  - High case fatality rate (60%)
- **H7N9**
  - novel reassortant influenza A discovered in 2013
  - remained low pathogenic in poultry , fatal human infection
  - Feb and March 2017 - LP H7N9 has mutated to HPAI


Human cases
Poultry
Global Avian Flu Pandemic

Avian Influenza in Human

1997

- Bird flu virus H5N1 is isolated for the first time from a human patient in Hong Kong

2003

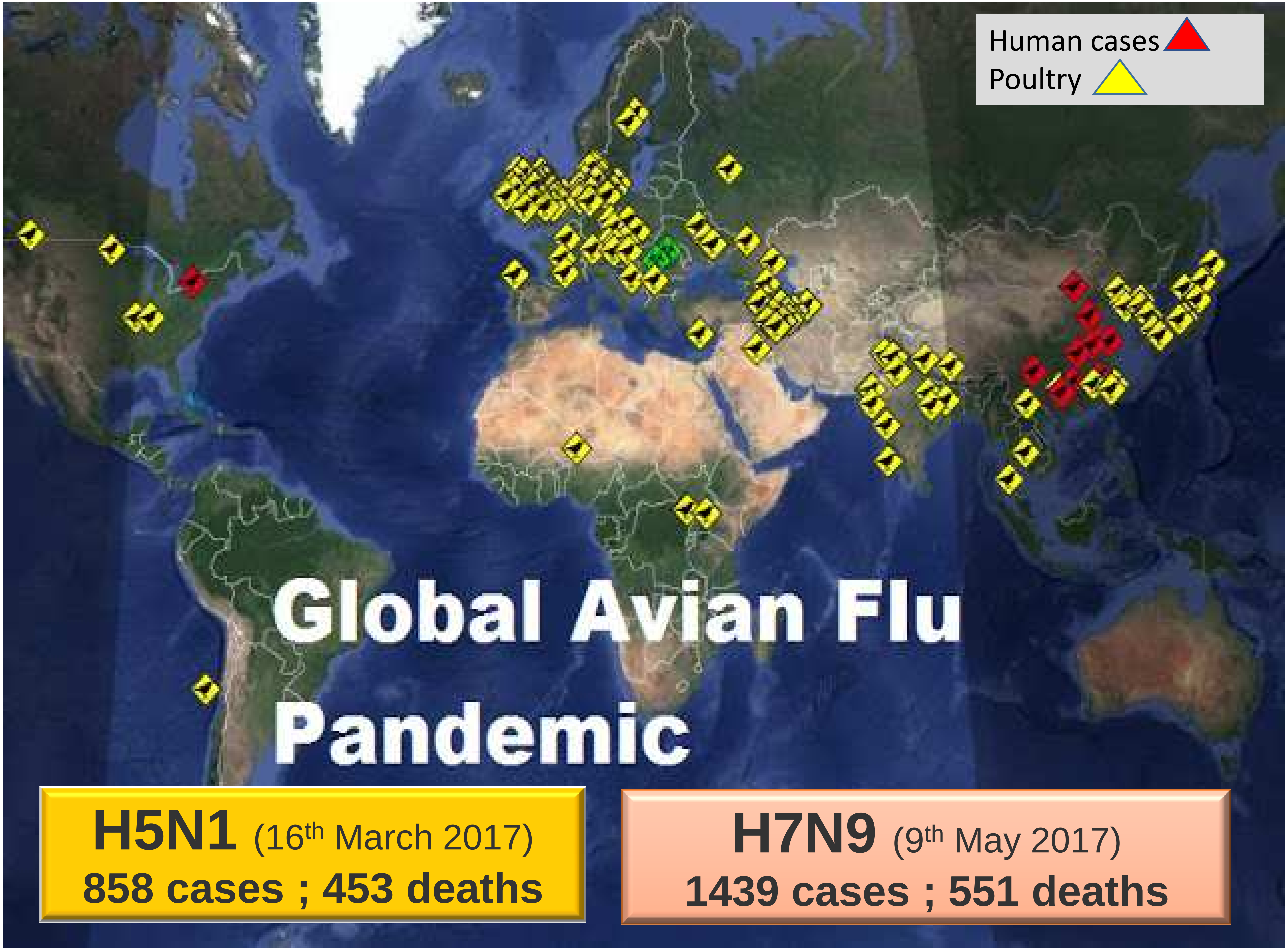
- Netherlands – H7N7 outbreak in poultry
- 83 affected; conjunctivitis, flu-like sx, 1 veterinarian died from acute respiratory infection

2003

- Reappearance of H5N1 , rising no of cases in Vietnam, Thailand, Cambodia, Indonesia

2013

- H7N9 – 1st reported in China in March 2013



Human cases
Poultry
Global Avian Flu Pandemic
H5N1 (16th March 2017)
858 cases ; 453 deaths
H7N9 (9th May 2017)
1439 cases ; 551 deaths

Current situation : **H7N9**

- Triple reassortant novel virus
- Human infections AI H7N9 remain unusual

since 2013

- Pandemic potential - no evidence of sustained person-to-person spread
- Main affected country – China
- Epidemics 1 → 4 : 40% died
- 3 imported cases from China→ M'sia (1) and Canada (2).
- Currently China in 5th epidemic (onset since 1 October 2016) with 641 cumulative cases - largest annual epidemic to date

Avian Influenza outbreak among birds : Malaysia

- **August 2004- first reports H5N1 outbreak in poultry**
  - 22km from Thai border, Thailand had 65 outbreaks during same period
  - virus discovered in fighting cocks smuggled from south Thailand
  - transmitted among local village chickens
  - strain highly homologous to Thailand and Vietnam isolates
- **February 2006 - fresh outbreaks of HPAI H5N1**
  - West coast - Kuala Lumpur, Perak & Pulau Pinang
  - strain similar to Indonesia and China isolates
  - Introduced by poultry trade

Current AI outbreak : Malaysia

Up to 24th March 2017

- Kelantan – 6 districts involved
- 37,741 birds culled and 15,419 eggs destroyed
- Believed to be started from cockfighting activities

ASIA PACIFIC

Kelantan declares 'disaster' over bird flu spread; no human infections so far

By Melissa Goh Posted 15 Mar 2017 16:48 Updated 15 Mar 2017 17:29

Kelantan expects to be declared free of H5N1 by mid-May

Transmission

- globalisation and international trade;
- farming and sale
- Migratory birds
- Chicken/birds related local activities eg cockfighting etc

Disease in birds - HPAI


- Incubation period
  - 1-7 days
  - Disease control purposes - 21 days
- Sudden death- most birds in an affected flock di

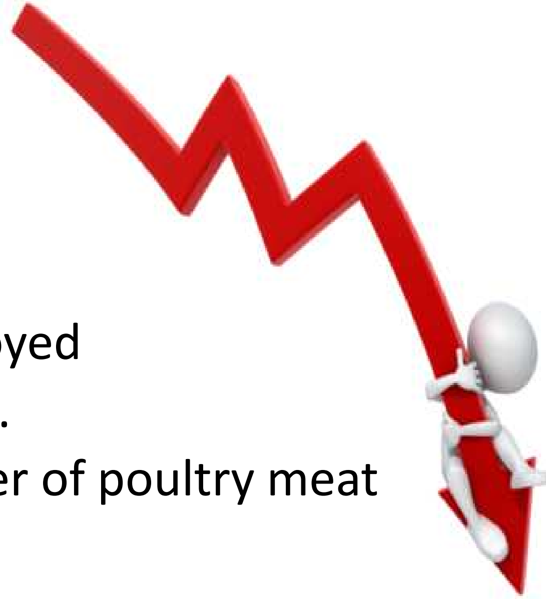
  - Drops in egg production.
  - Depression
  - Reduced feed consumption.
  - Resp signs - coughing , nasal and ocular dc
  - Swollen face.
  - Cyanosis of comb/wattles.
  - Diarrhoea (often green).
  - Nervous signs such as paralysis

Disease control in poultry

- Stamping out (depopulation or culling)
  -identify infected flocks and destroy them to prevent spread (1km radius from infection zone)




Avian Influenza : Economic Impact



- Severe localised effect of AI outbreak
  - 2003-2005
    - >220 million domestic poultry either died or destroyed
    - Economic losses estimated at around US$10 billion.
    - Thailand lost position as world's 5th largest exporter of poultry meat
  - Malaysia 2017 outbreak
    - Saudi, Hong Kong bannned poultry import from Malaysia
    - Ban of Malaysia bird nest import by China (2016 - Msia exported 20.15 metric tonnes of bird's nest, worth RM134.13 million to China.
- Cost of human disease

AI infections in **Human** Transmission

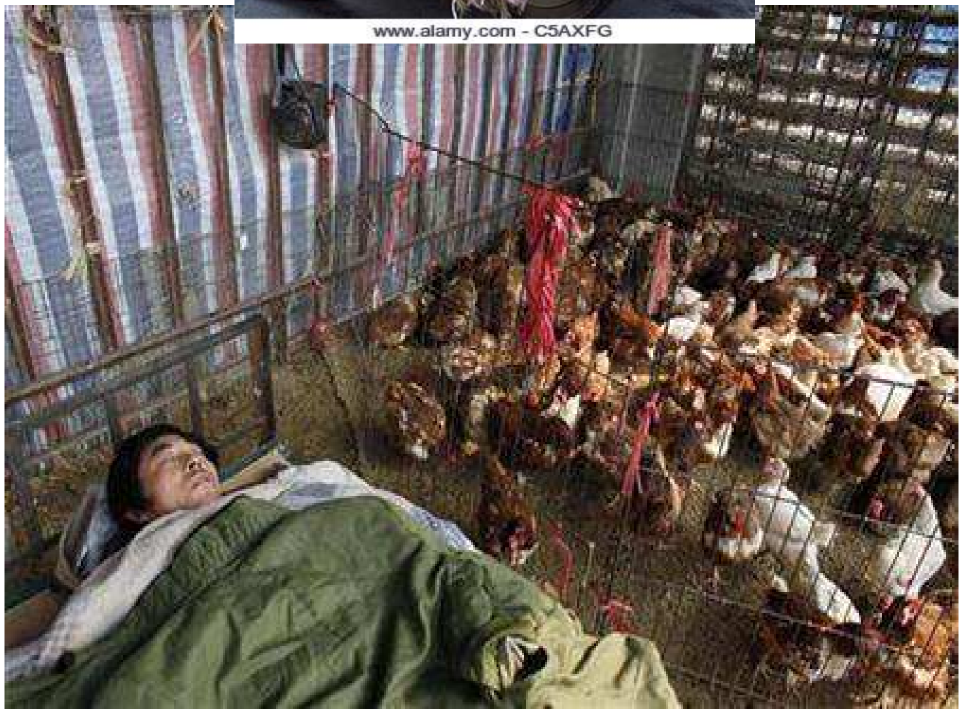
- **<u>Direct contact</u>** with infected animals or contaminated environments
  - Properly cooked poultry/eggs wont transmit AI virus
- Human to human contact is rare, limited, inefficient and not sustained.
  - Case reports of limited human-to-human H5N1 transmission observed after long period (hours) of unprotected close contact with a very ill family member[1,2,3,4]

1.Ungchusak K, Auewarakul P, Dowell SF, et al. Probable person-to-person transmission of avian influenza A (H5N1). N Engl J Med. 2005:352(4):333-40.
2.Wang H, Feng Z, Shu Y, et al. Probable limited person-to-person transmission of highly pathogenic avian influenza A (H5N1) virus in China. Lancet. 2008: 371(9622):1427-34.
3.World Health Organization. Avian influenza situation in Indonesia update 16. 31 May 2006.
4.World Health Organization. Weekly Epidemiological Recor


www.alamy.com - A4DK1A


www.alamy.com - C5AXFG


AP Photo



AI infections in **Human** Clinical features and management

- Disease features & clinical outcome depends on subtype
- Incubation period
  - Average 3-7 days
  - H5N1 : 2-5 days , up to 17 days[1] ; H7N9 : 1 to 10 days[2]
- Mild conjunctivitis→severe pneumonia → death
- Sore throat/coryza - less common
- Diarrhoea, vomiting, abdominal pain, bleeding from the nose or gums, and chest pain have been reported
- Case fatality rate higher than seasonal influenza
- Neuraminidase inhibitors - mainstay of treatment
  - Late initiation of therapy is a major factor for mortality

1. Control of Communicable Diseases Manual 20th Edition. American Public Health Association (2015). APHA Press, Washington DC. ISBN: 978-0-87553-018-5
2. Epidemiology of Human Infections with Avian Influenza A(H7N9) Virus in China Li, Q et al (2014). New England Journal of Medicine, 370:520-532
3. Update on Avian Influenza A (H5N1) Virus Infection in Humans. NEJM 2008

AI infections in **Human** Clinical presentation : H5N1

CURRENT CONCEPTS

Update on Avian Influenza A (H5N1) Virus Infection in Humans

N ENGL J MED 358;3 WWW.NEJM.ORG JANUARY 17, 2008

- Median age of patients 18 years
- 90% of patients ≤ 40 years
- Overall CFR 61%
  - highest among pts 10 - 19 years and lowest among > 50 years
- Most patient were previously healthy
- No cases identified among short-term travellers visiting countries affected by outbreaks
- Asymptomatic or mild case is rare
- Commonest risk factor –handling of sick or dead poultry during the week before the onset of illness

Variable	Vietnam, Thailand, Cambodia, 2004–2005, Clade 1†	Indonesia, 2005–2006, Clade 2.1‡	China, 2005–2006, Clade 2.3§	Egypt, 2006–2007, Clade 2.2¶	Turkey, Azerbaijan, 2006, Clade 2.2‖
Age — yr					
Median	14–22	18.5	30	12.5	16.5–10.0
Contact with poultry within previous 2 weeks — no./total no. (%)	31/36 (86)	41/54 (76)	8/8 (100)**	31/38 (82)	8/8 (100)††

AI infections in **Human** Clinical presentation : **H7N9**

- March 25 → Dec 1 2013
- 139 patients
- Majority epidemiologically unrelated
- 99% hospitalized for pneumonia/respiratory failure
- CFR 34%
- limited, non sustained human-to-human transmission could not be ruled out in 4 family clusters

ORIGINAL ARTICLE

Epidemiology of Human Infections with Avian Influenza A(H7N9) Virus in China

N ENGL J MED 370;6 NEJM.ORG FEBRUARY 6, 2014

Epidemiologic Characteristics of 139 Patients with Confirmed H7N9 Virus Infection in China

Median age	61 years
Age ≥65 yr	42%
Age <5 yr	3%
Poultry worker	6%
Underlying medical conditions	73%
History of exposure to chicken	82%
Exposure to symptomatic case within 2 wk before illness onset	4%
Direct contact with poultry	59%
Visit to live poultry market	65%

	H5N1	H7N9
Spatial distribution	17 countries, predominantly Indonesia, Egypt, Vietnam, Cambodia and China	4 countries, predominantly China
Mechanism of spread	Bird migration patterns and poultry trade routes	Less clear
Behaviour in birds	Highly pathogenic	Low pathogenic
Emergence	Emerged in February 1997 in Hong Kong, re-emerged in 2003 in Beijing, China	Emerged in March 2013 in Shanghai, China
Cumulative no of cases	858	1439
Median age	18–26 years	62 years
CFR	60%, higher in younger age	22%, higher in older age
Proportion of cases exposed to poultry	58–84%	56–75%

Bui C, et al. A systematic review of the comparative epidemiology of avian and human influenza A H5N1 and H7N9 - lessons and unanswered questions. Transbound Emerg Dis. 2016

- MERS-CoV and Avian Influenza have pandemic risk potential which remains unpredictable
- Knowledge gaps
  - transmission risk factors of both viruses
  - Treatment/preventive vaccines for MERS CoV
- The way forward is to be prepared :
  - Pandemic preparedness plan
  - Sentinel-based surveillance systems for severe acute respiratory infection (SARI)
  - Infection prevention and control programs
  - Address critical knowledge gaps – research/rapid dissemination of information

World Health Organization