# Of Camels, Bats and Coronaviruses: the (beginning of the) story of MERS-CoV

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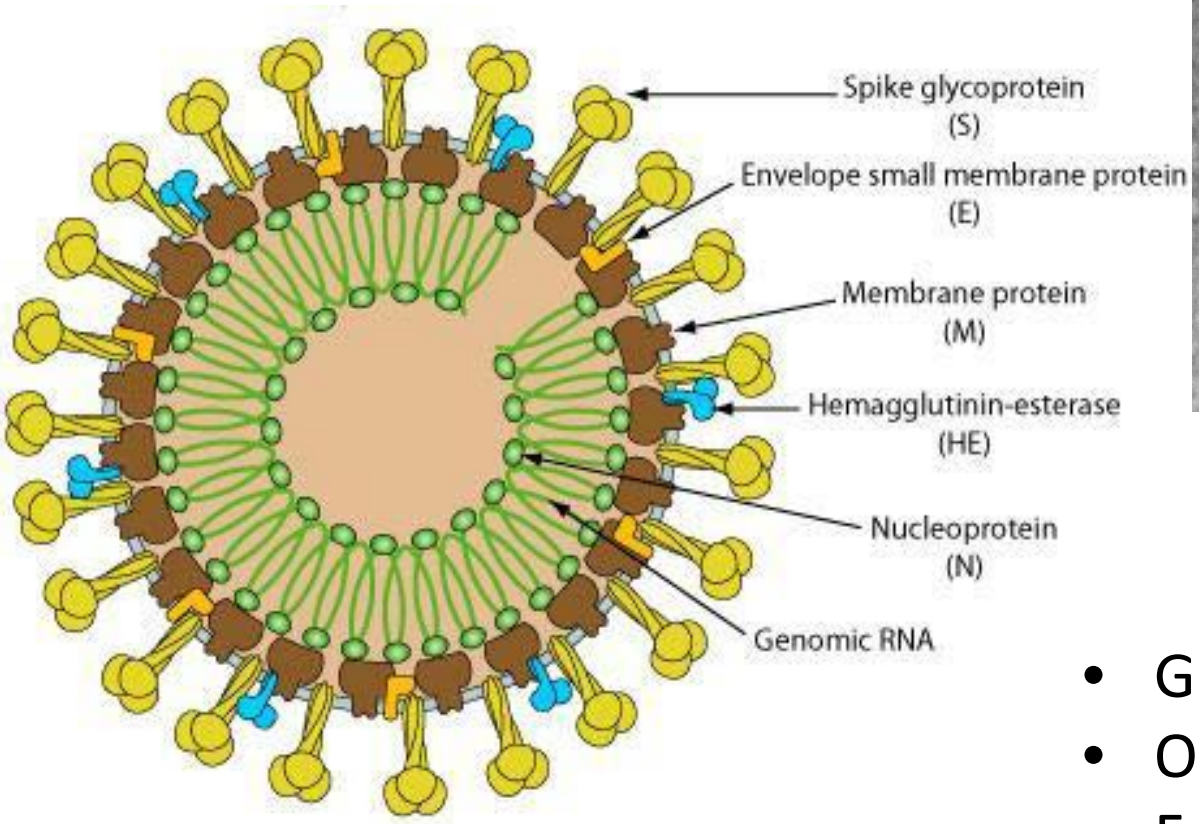
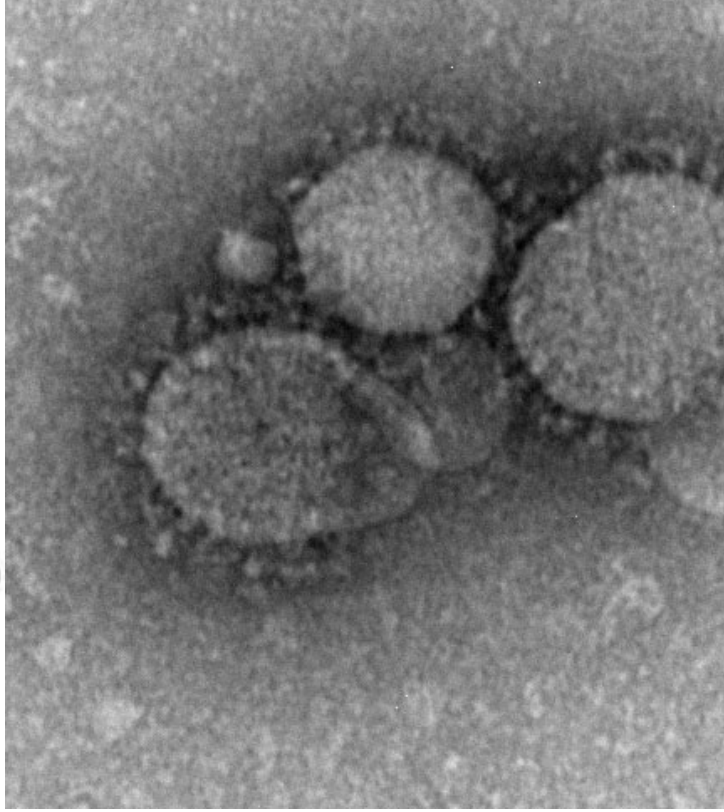
Mount Sinai Hospital
University of Toronto

# Objectives

- Discuss the epidemiology, clinical presentation, diagnosis, and management of MERS
- Review hospital outbreaks of MERS

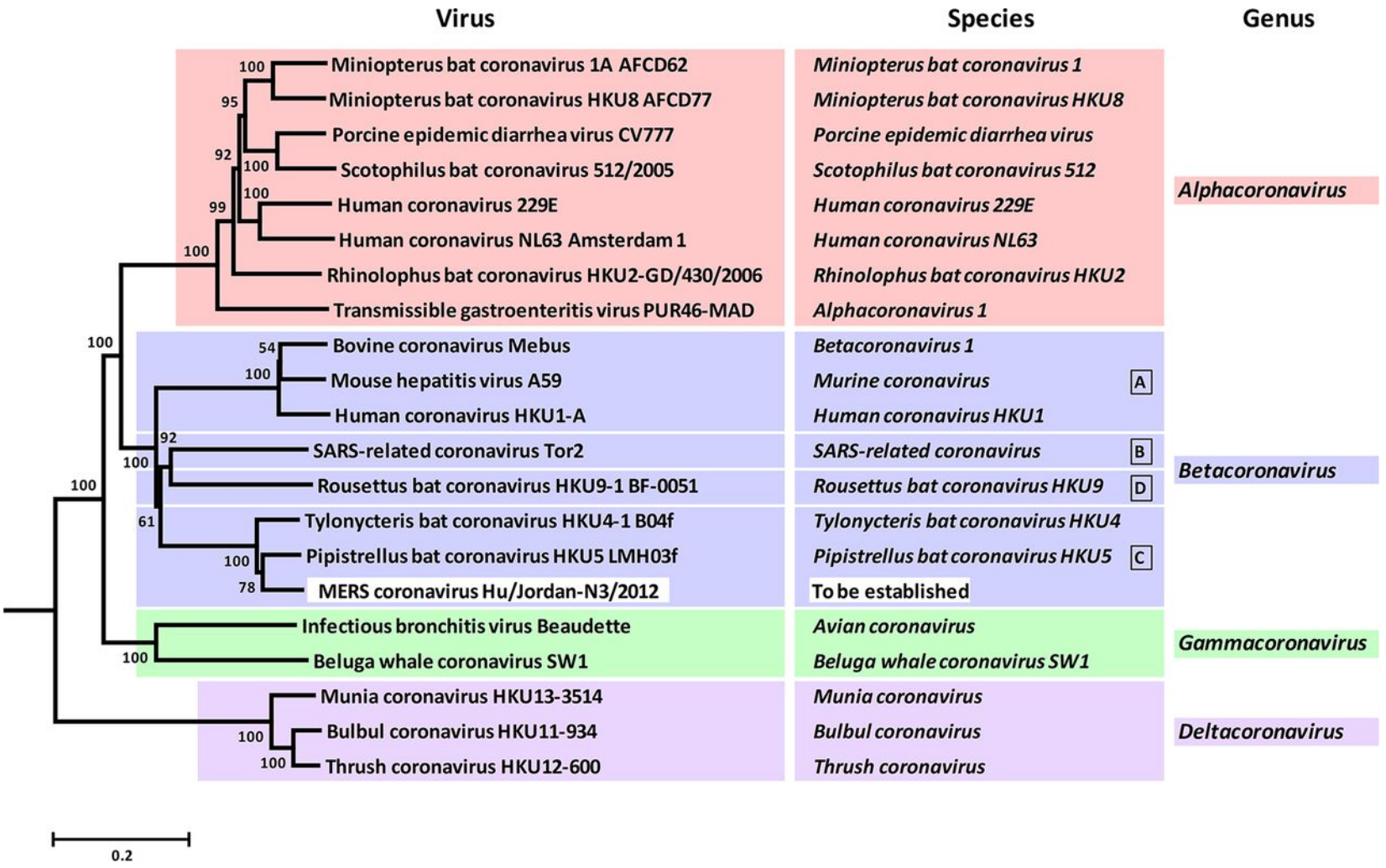
# Coronaviruses



- Group: IV (+)ssRNA
- Order: Nidovirales
- Family: Coronaviridae
- Sub-family: Coronavirinae

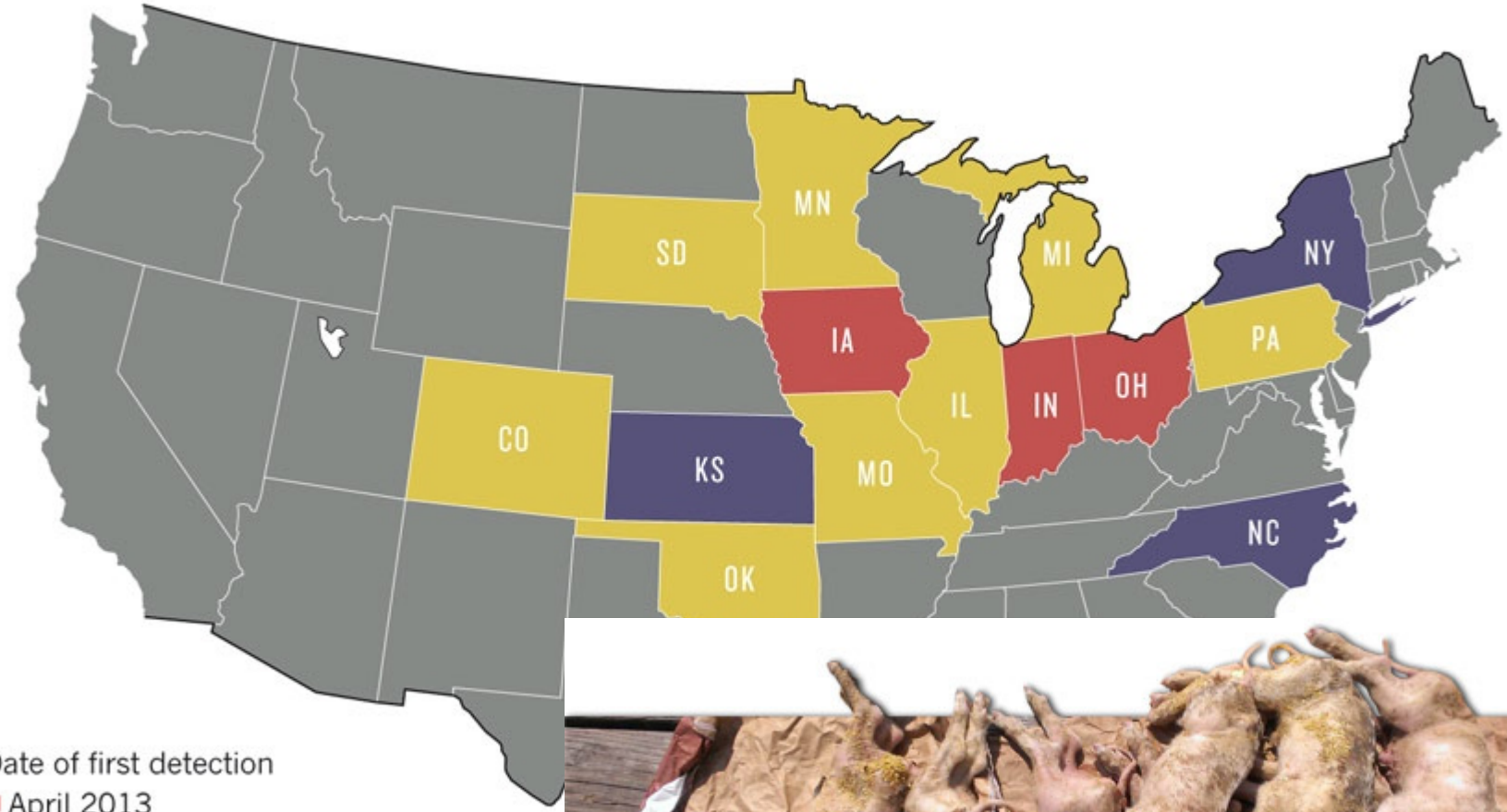
# Phylogenetic relationships among members of the subfamily Coronavirinae and taxonomic position of MERS-CoV.



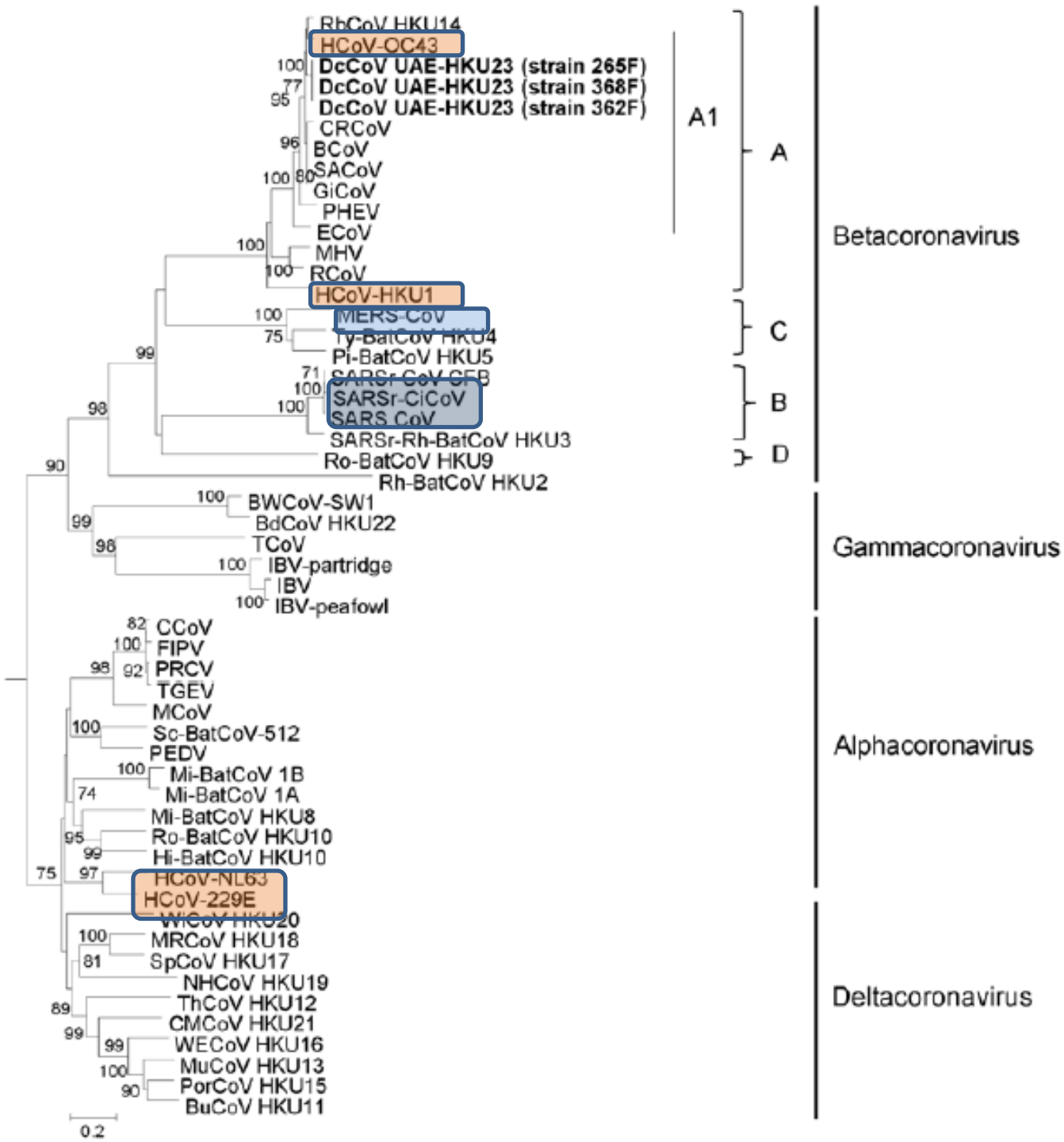

de Groot R J et al. J. Virol. 2013;87:7790-7792

# PIG VIRUS ON THE WING

Porcine epidemic diarrhoea virus, a type of coronavirus that can kill piglets, has been detected in 14 US states.



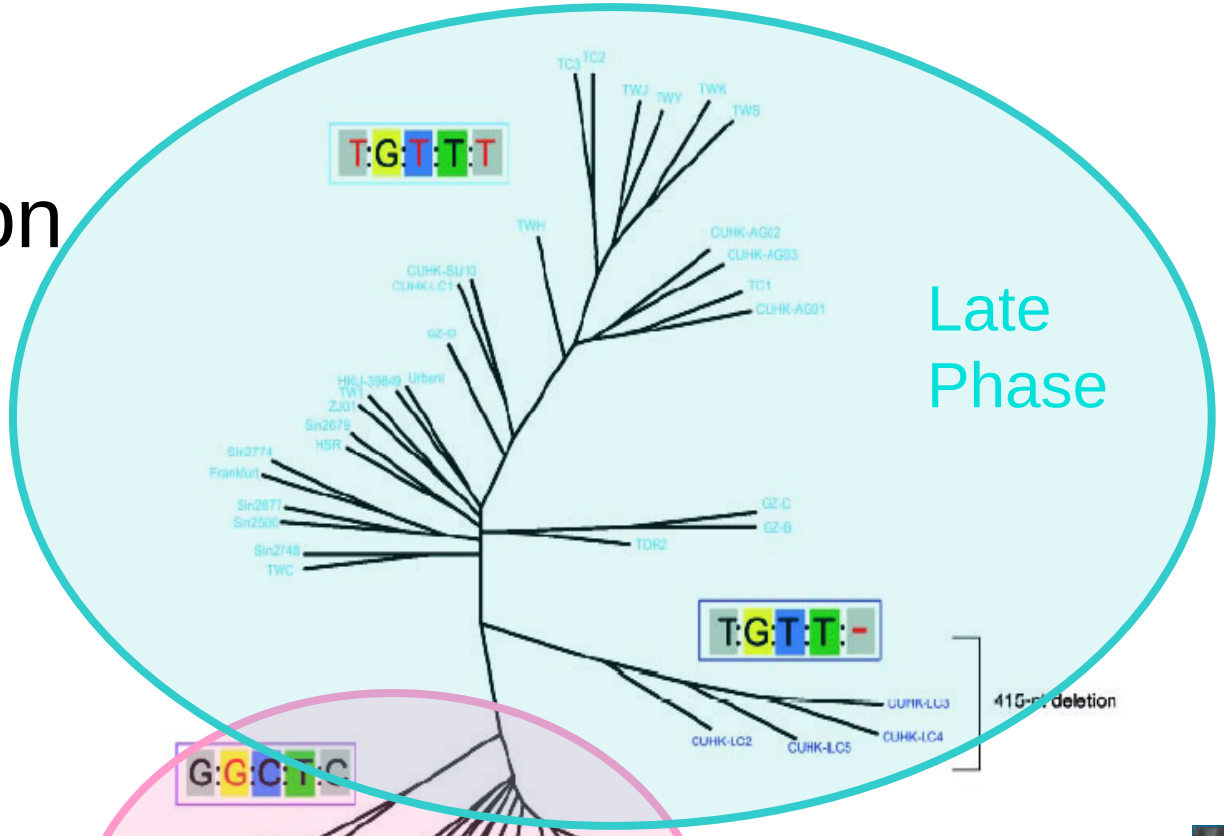

Date of first detection
- April 2013
- May 2013
- June 2013


RbCoV HKU14
HCoV-OC43
DcCoV UAE-HKU23 (strain 265F)
DcCoV UAE-HKU23 (strain 368F)
DcCoV UAE-HKU23 (strain 362F)
CRCoV
BCoV
SACoV
GiCoV
PHEV
ECoV
MHV
RCoV
HCoV-HKU1
MERS-CoV
Ty-BatCoV HKU4
Pi-BatCoV HKU5
SARSr-CoV GZ0
SARSr-CiCoV
SARS-CoV
SARSr-Rh-BatCoV HKU3
Ro-BatCoV HKU9
Rh-BatCoV HKU2
BWCoV-SW1
BdCoV HKU22
TCoV
IBV-partridge
IBV
IBV-peafowl
CCoV
FIPV
PRCV
TGEV
MCoV
Sc-BatCoV-512
PEDV
Mi-BatCoV 1B
Mi-BatCoV 1A
Mi-BatCoV HKU8
Ro-BatCoV HKU10
Hi-BatCoV HKU10
HCoV-NL63
HCoV-229E
WiCoV HKU20
MRCoV HKU18
SpCoV HKU17
NHCoV HKU19
ThCoV HKU12
CMCoV HKU21
WECoV HKU16
MuCoV HKU13
PorCoV HKU15
BuCoV HKU11
0.2
A1
A
C
B
D
Betacoronavirus
Gammacoronavirus
Alphacoronavirus
Deltacoronavirus

# HCoVs: 229E, OC-43, NL-63, HKU1

- Worldwide distribution
- Most often URIs in children
  - LRIs/more severe disease in elderly, immunocompromised
  - Mixed infections; exacerbations chronic illness
- Seasonal in temperate climates
- Transmission likely droplet/contact
- Incubation period ~2 days (1.5-5)
- Viral loads highest early in illness

# SARS evolution




The Chinese SAR
Mol. Epi Consortiu
Science
2004:303;1666-16

# SARS-CoV

- Clinical illness: non-specific fever and cough, followed by progressive pneumonia
  - CRF 3-20% overall, 50-60% in older adults and hospitalized patients
- Incubation period: 5 days (2-12 days)
- Viral load low early in illness – peaks at day 7-9
  - Much less infectious early in illness

# Dr. Ali Zaki
# Dr. Solomon Fakeeh Hospital
# Jeddah, Saudi Arabia

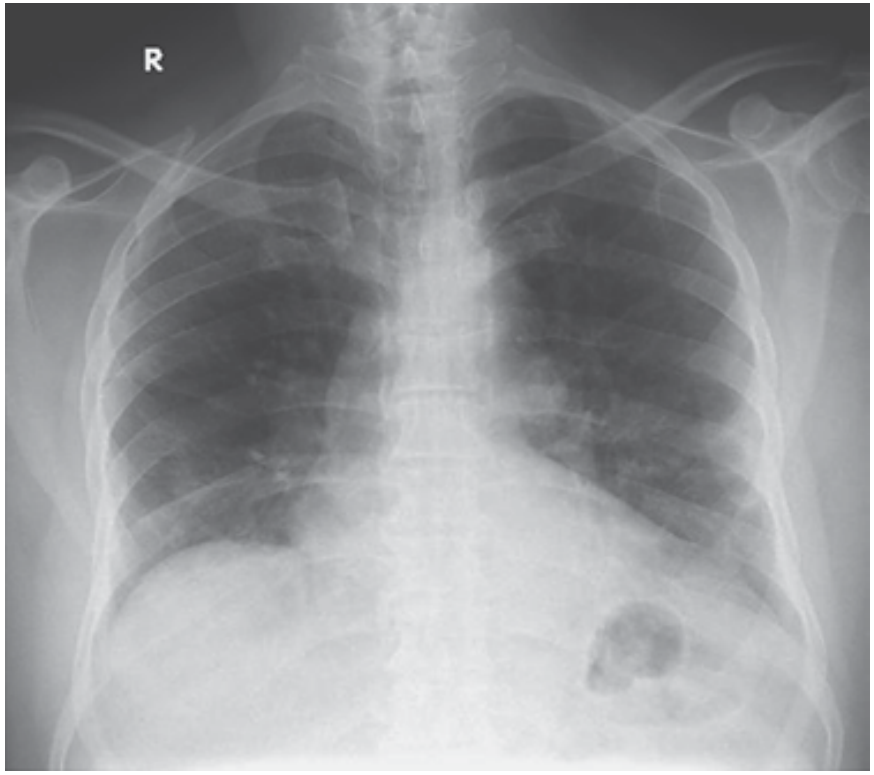
# The First Report

- A 60-year-old Saudi man was admitted to Dr. Solomon Fakeeh Hospital in Jeddah on June 13, 2012
- 7-day history of fever, productive cough, and shortness of breath.
- Admitted with progressive, multifocal pneumonia
  - BAL grew *S. aureus* and *K. pneumoniae*
  - Renal failure developed on day 3
  - Died on day 11 of respiratory and renal failure

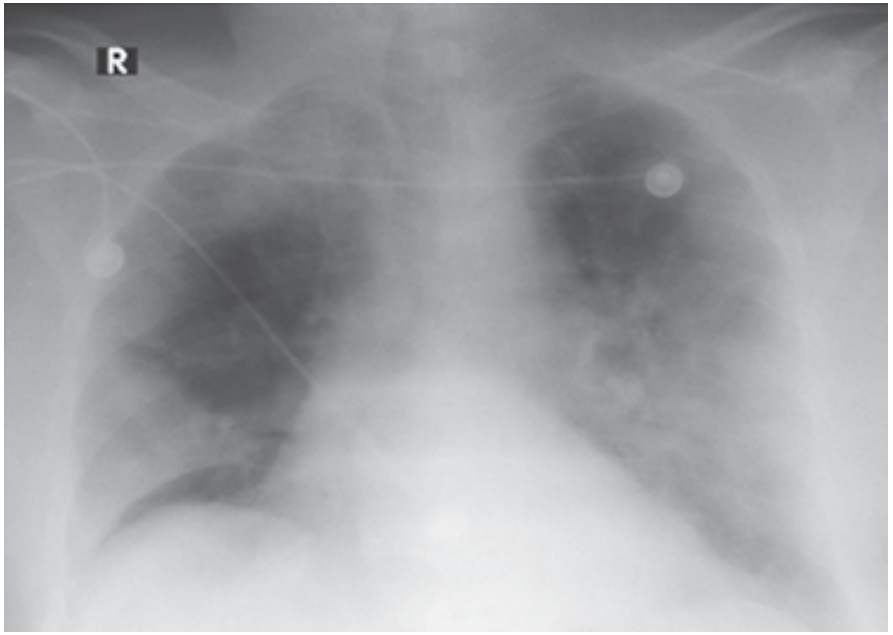
Zaki et al. N Engl J Med 2012 367:1814-20

# Chest Radiography

**Admission**

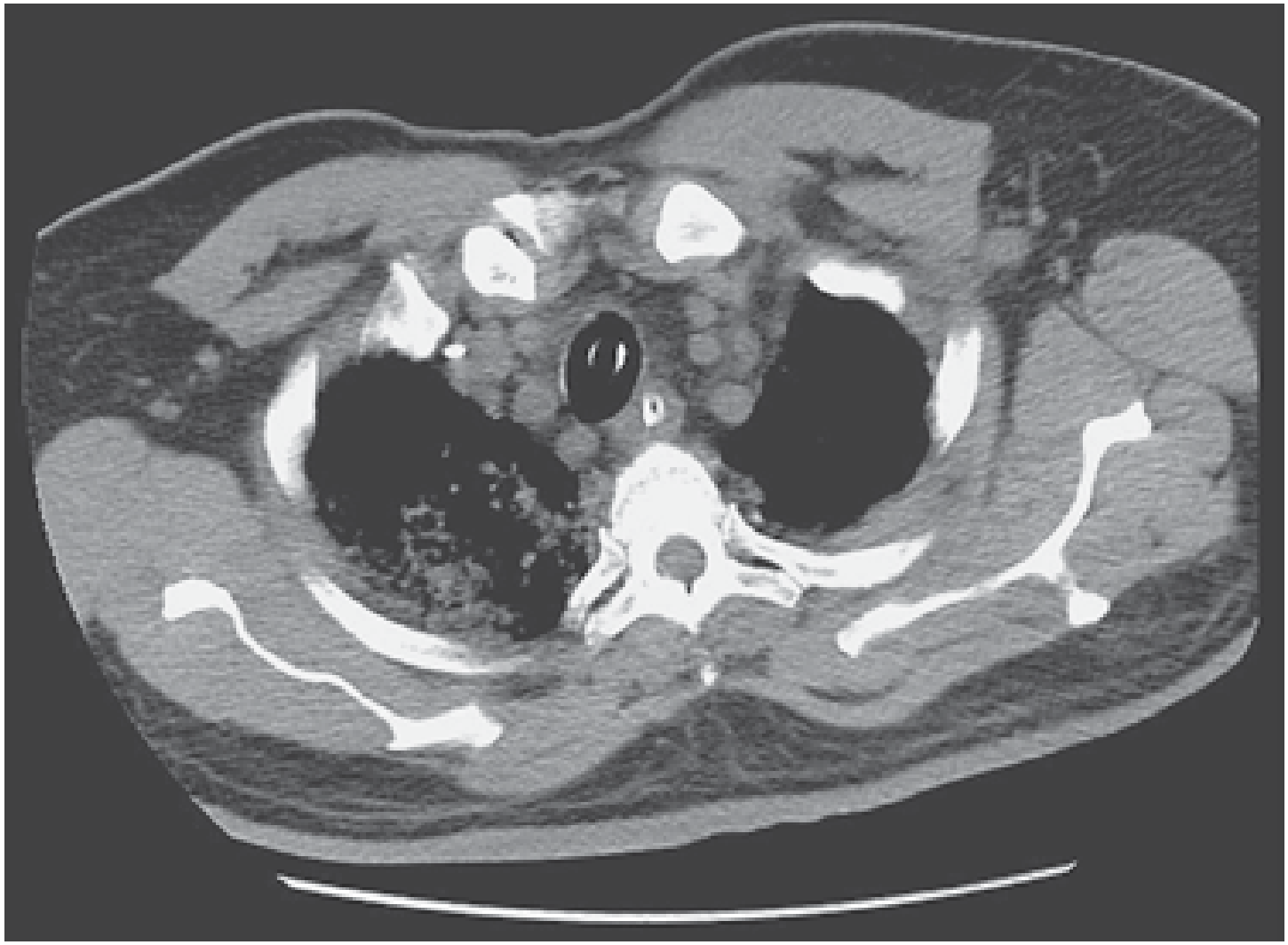



**HD#2**



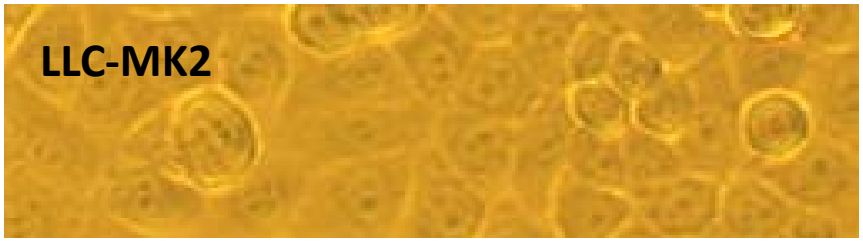

Zaki et al. N Engl J Med 2012 367:1814-20

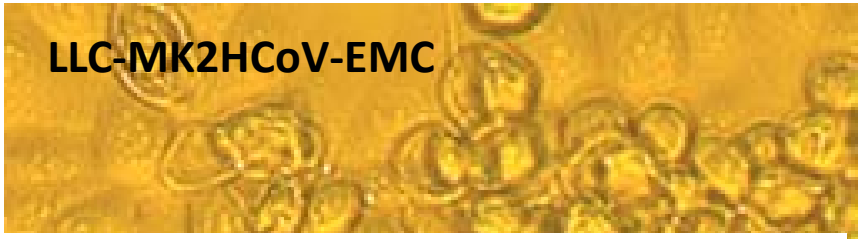
# Computed Tomography



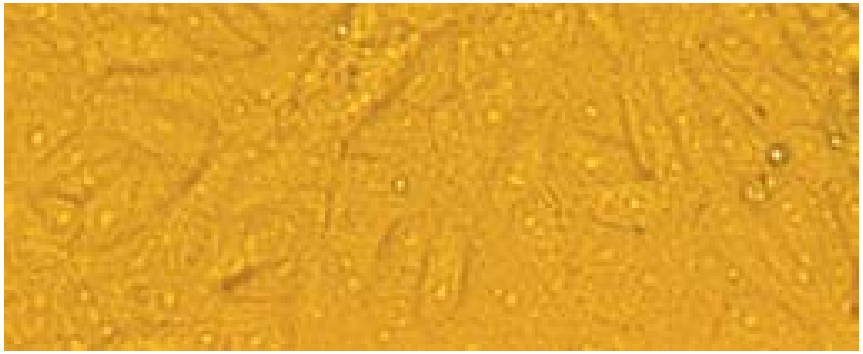
Zaki et al. N Engl J Med 2012 367:1814-20

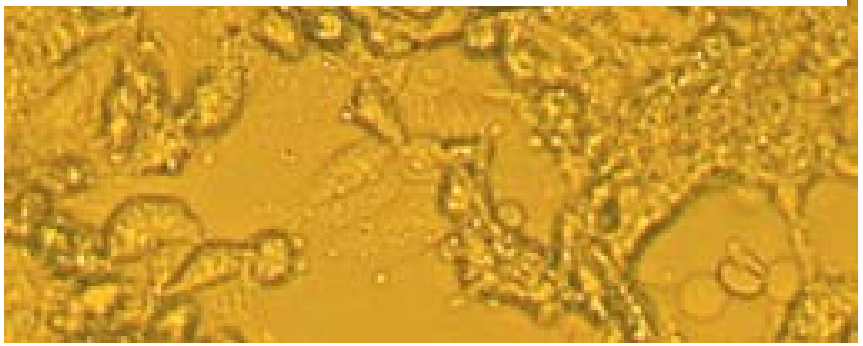
# From an Admission Sputum




- *Familywide PCR assays for coronaviruses yielded fragments of expected sizes*
- *Strong positive IF for IgG antibodies with patient serum at 1:20 (HD #10)*
  - *2400 control samples from 2010-2012 were negative*





Zaki et al. N Engl J Med 2012 367:1814-20

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 Moha

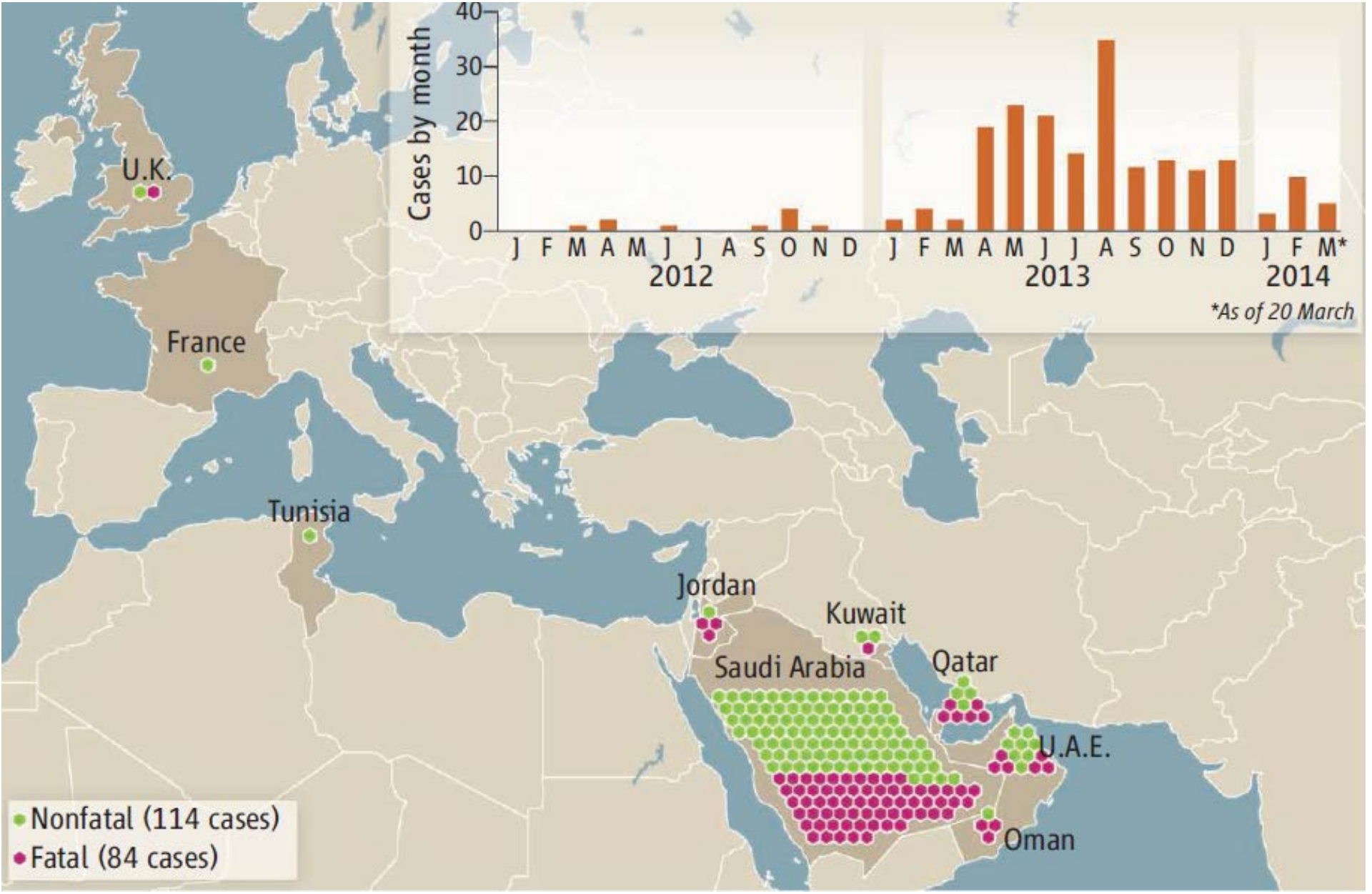
The virus was isolated from sputum of a male patient aged 60 years old presenting w
form of rounding and syncetia formation.

[The clinical isolate] was initially tested for influenza virus A, influenza virus B, parainf
molecular weight appropriate for a coronavirus. The virus RNA was tested also in Dr. R
related to bat coronaviruses. Further analysis is being carried out in the Netherlands.

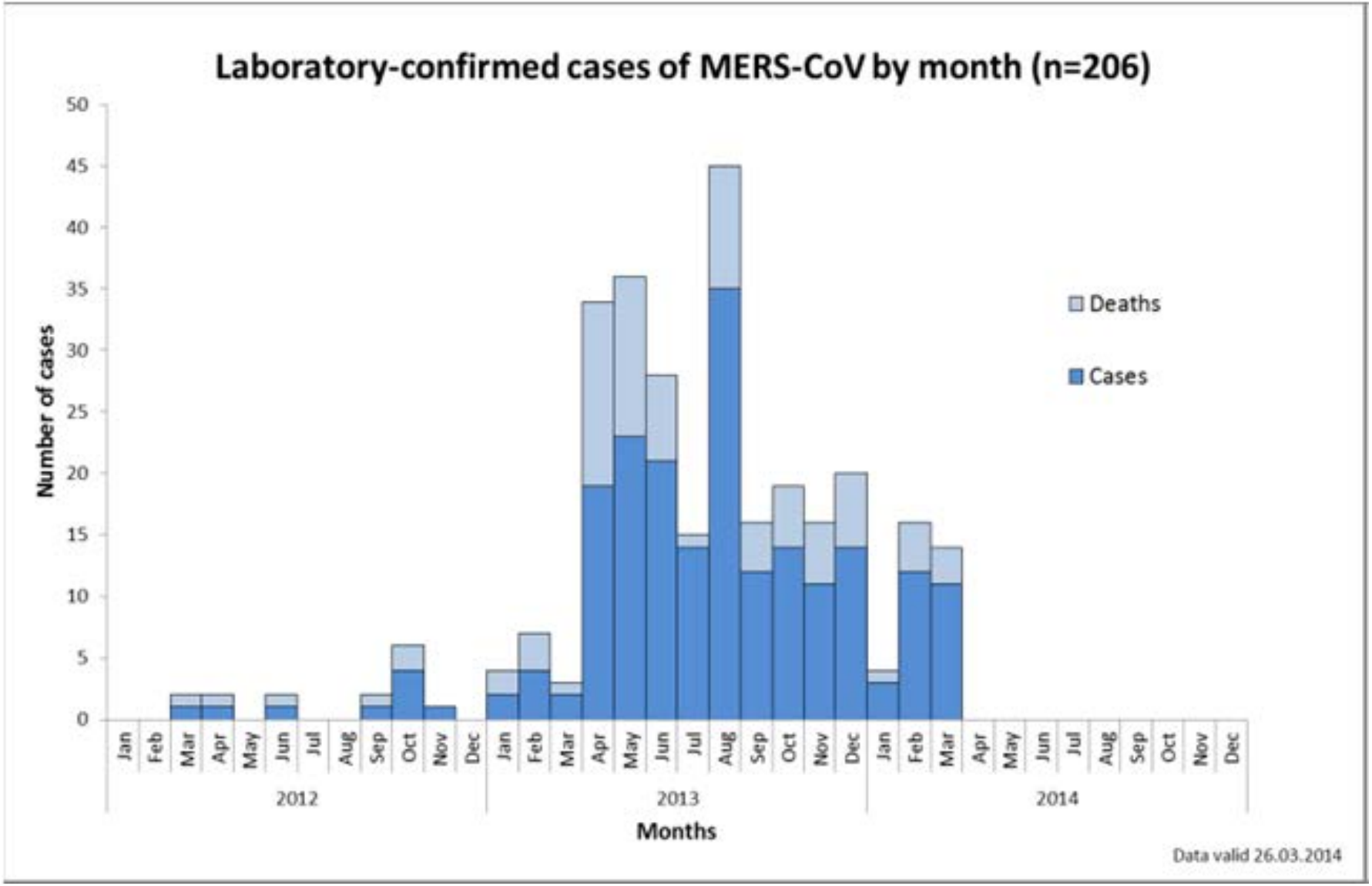
The Virology Laboratory at the Dr Fakeeh Hospital will be happy to collaborate with ot

--
Ali Mohamed Zaki
Professor of Microbiology
Dr Fakeeh hospital Jeddah Saudi Arabia
<azaki53@hotmail.com>

[ProMED-mail welcomes the opportunity to communicate Dr Ali Mohamed Zaki's invitat


Cases by month
40
30
20
10
0
J F M A M J J A S O N D J F M A M J J A S O N D J F M*
2012
2013
2014
*As of 20 March
U.K.
France
Tunisia
Jordan
Kuwait
Saudi Arabia
Qatar
U.A.E.
Oman
Nonfatal (114 cases)
Fatal (84 cases)

# WHO reports to March 27, 2014



# What do we know about MERS clinical infection?

- Median incubation period 5 days (95% by 12 days)
- Causes severe, multifocal pneumonia

# Symptoms at Presentation

| | Patients (n=47) |
|---|---|
| Fever | 46 (98%) |
| Fever with chills or rigors | 41 (87%) |
| Cough | 39 (83%) |
| Dry | 22 (47%) |
| Productive (sputum) | 17 (36%) |
| Haemoptysis | 8 (17%) |
| Shortness of breath | 34 (72%) |
| Chest pain | 7 (15%) |
| Sore throat | 10 (21%) |
| Runny nose | 2 (4%) |
| Abdominal pain | 8 (17%) |
| Nausea | 10 (21%) |
| Vomiting | 10 (21%) |
| Diarrhoea | 12 (26%) |
| Myalgia | 15 (32%) |
| Headache | 6 (13%) |

Assiri et al Lancet Infect Dis 2013; 13: 752–61

# Progression of pulmonary disease

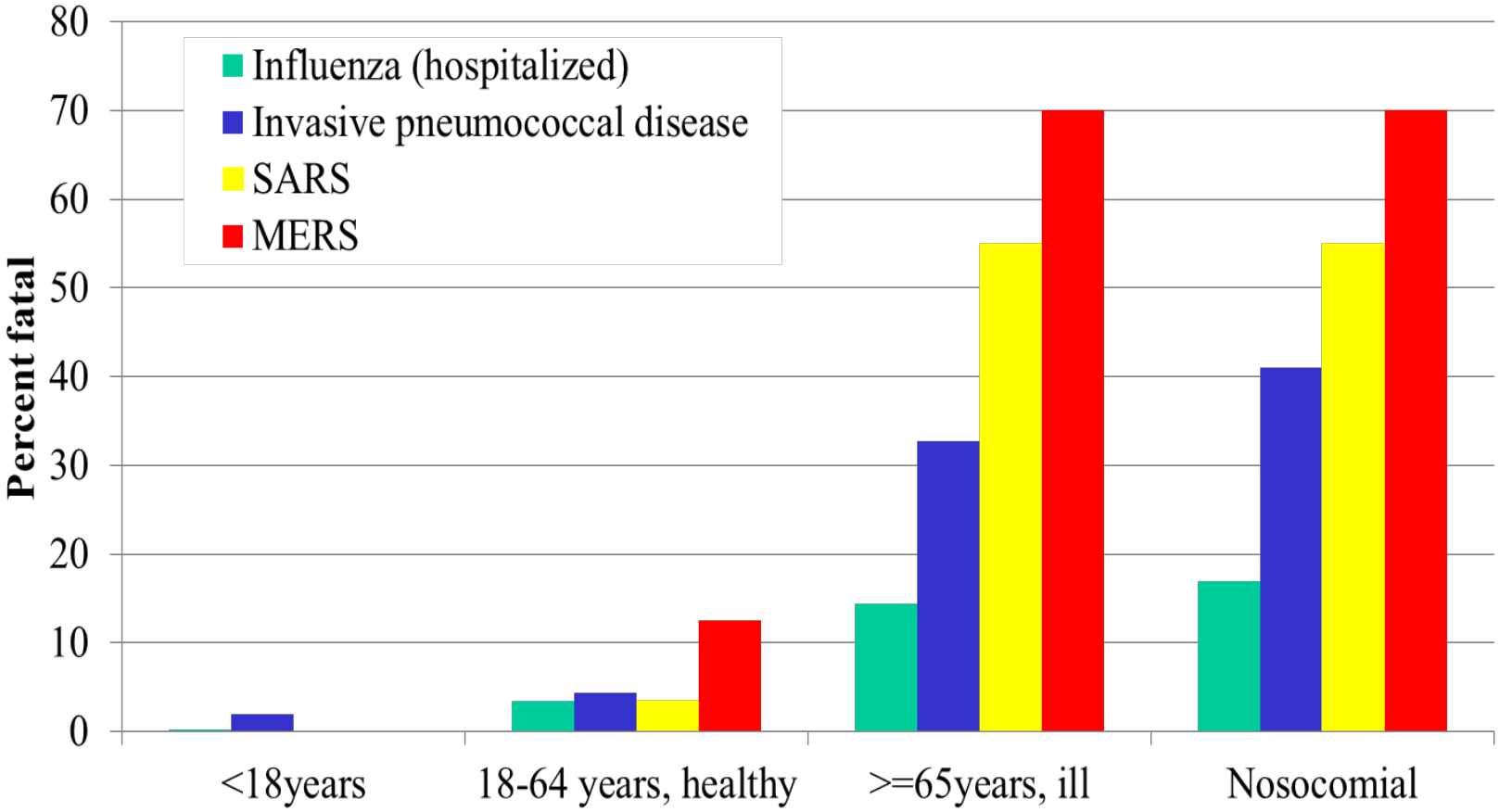
| | Median | Range |
|---|---|---|
| Time from onset of symptoms to: | | |
| Hospitalization | 4 days | 0-16 days |
| ICU admission | 5 days | 1-15 days |
| Mechanical ventilation | 7 days | 3-11 days |
| Death | 11.5 days | 4-298 days |

Assiri et al. NEJM 2013;369:407
WHO MERS-CoV Research group PLOS Currents Outbreaks. 2013 Nov 12.

# What do we know about MERS clinical infection?

- Median incubation period 5 days (95% by 12 days)
- Causes severe, multifocal pneumonia
  - Case fatality rate ~40%
  - ?may be some component of renal disease
- Some mild/asymptomatic cases in younger healthy adults and children
- Very few infections in children
  - most in hospitalized children with severe underlying conditions

# Comparison of case fatality rates



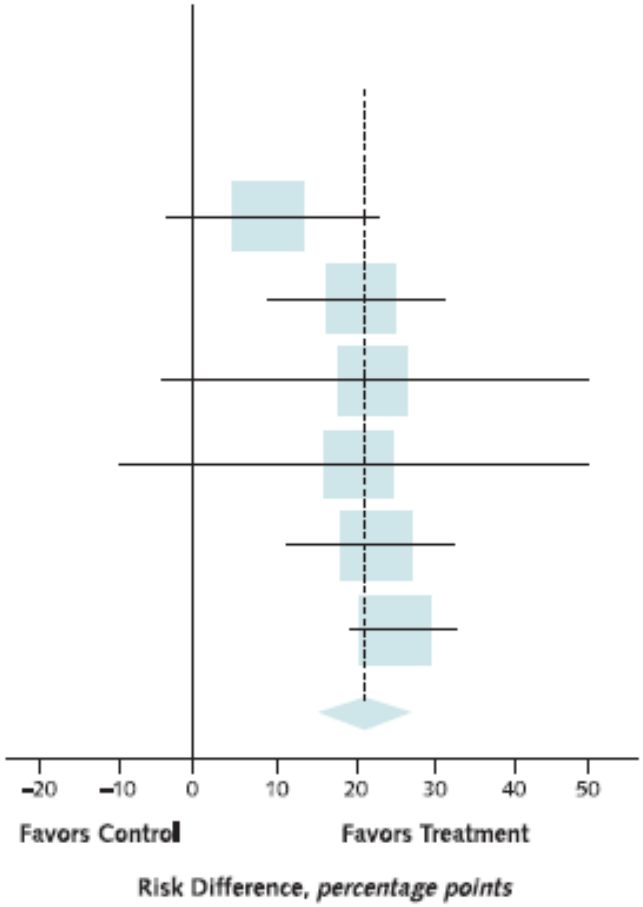
# What do we know about MERS pathogenesis/treatment?

- Presumptive binding domains/proteins identified (lower respiratory tract)
- 3 animal models: mice, rhesus macaques, marmosets
  - In rhesus macaques, ribavirin + interferon seems to have some effect

- Lesson learned:
  - Developing treatments for new infections takes time
  - Convalescent serum may be the most effective initial option

# Convalescent plasma therapy 1918 H1N1 pandemic

| Study (Reference) | Mortality Rate, *n/n (%)* | | Risk Difference (95% CI), *percentage points* |
|---|---|---|---|
| | Treatment Group | Control Group | |
| Stoll (17) | 25/56 (45) | 201/379 (53) | 8 (–6 to 22) |
| O'Malley and Hartman (18)* | 3/46 (7) | 28/111 (25) | 19 (8 to 29) |
| Ross and Hund (19, 20) | 6/28 (21) | 9/21 (43) | 21 (–5 to 47) |
| Kahn (21) | 12/25 (48) | 12/18 (67) | 19 (–11 to 48) |
| Gould (22) | 2/30 (7) | 82/290 (28) | 22 (11 to 32) |
| McGuire and Redden (23, 24)* | 6/151 (4) | 120/400 (30) | 26 (21 to 31) |
| Overall | 54/336 (16) | 452/1219 (37) | 21 (15 to 27) |




Luke AIM 2006

# Hung et al.
# RCT IVIG v. H-IVIG

Chest 2013;144:464

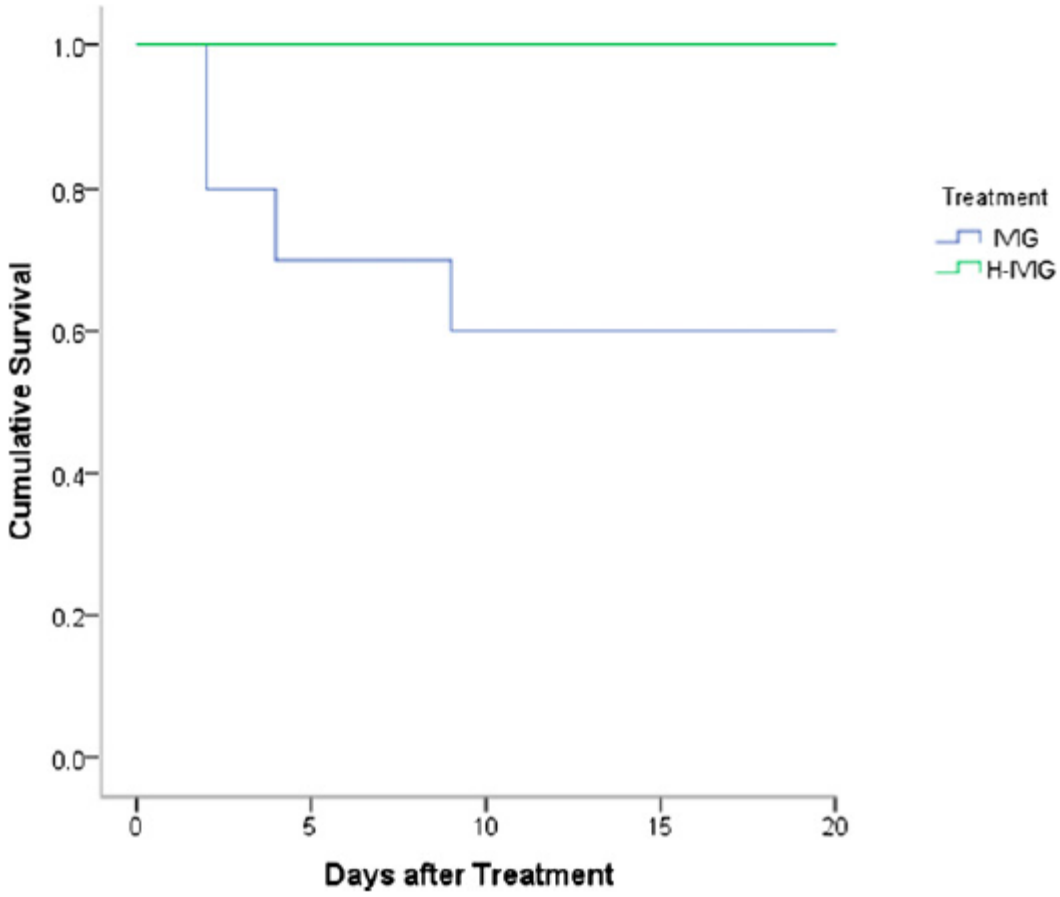
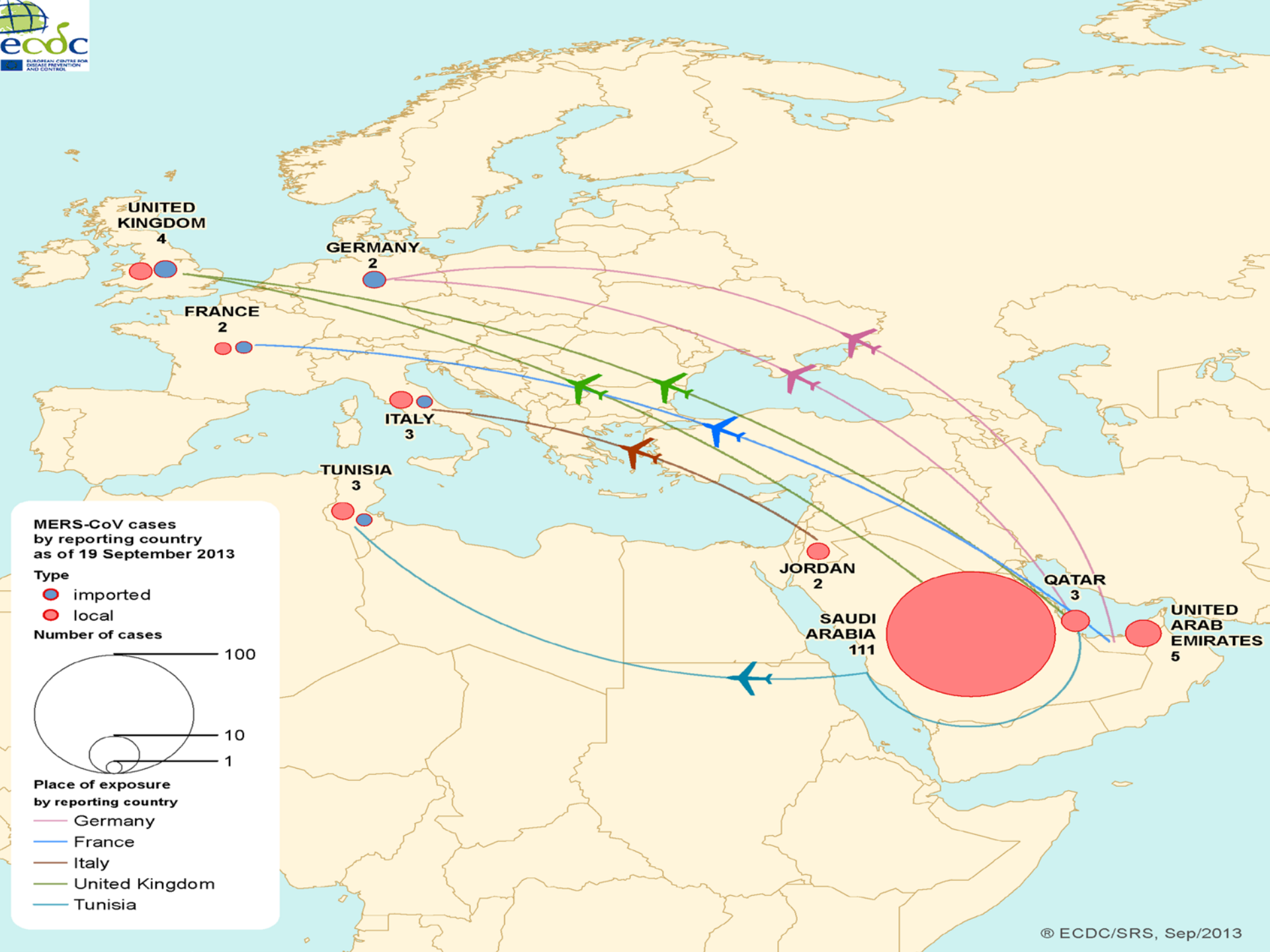


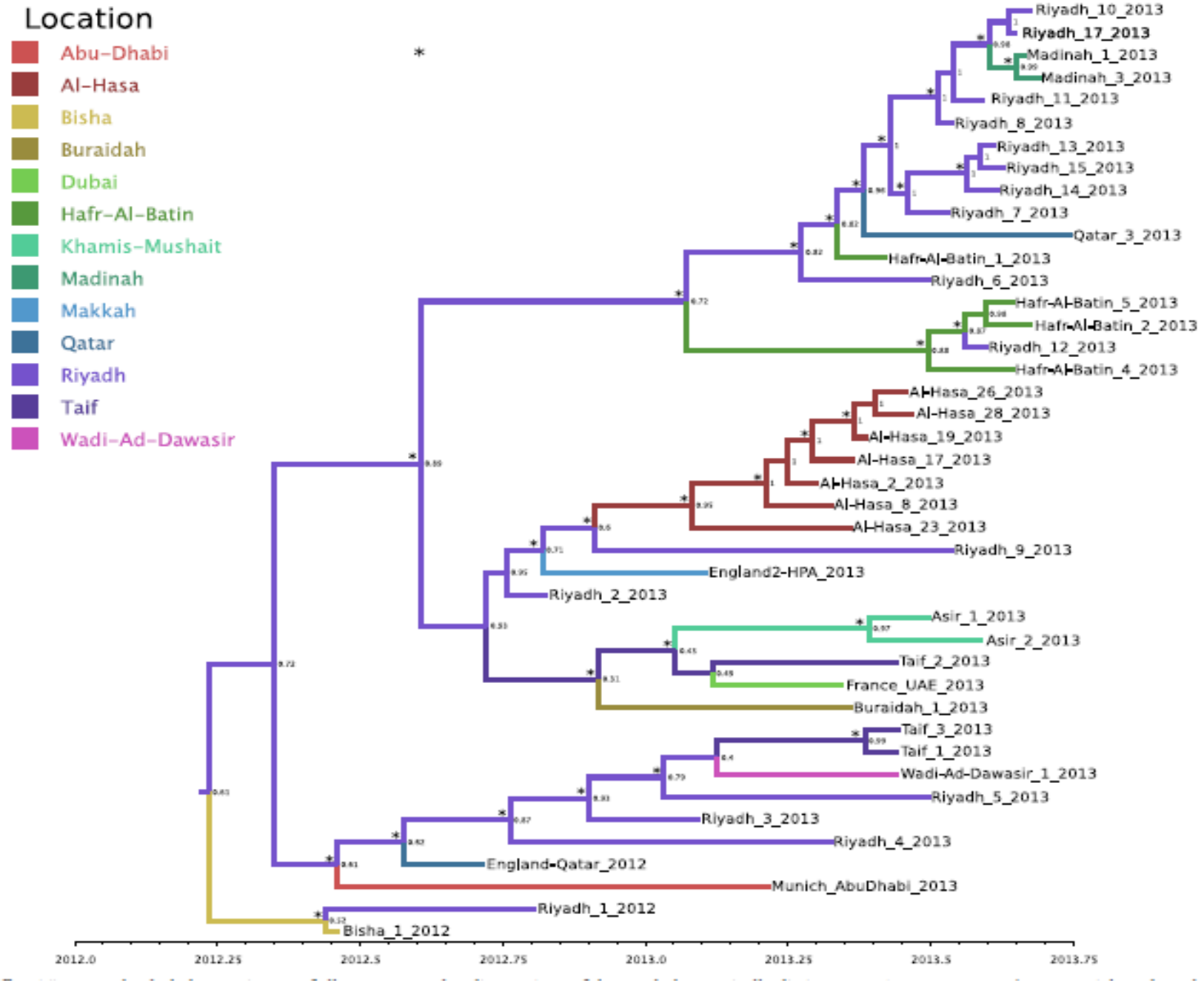

**Table 3—*Multivariate Analysis of Clinical Factors Independently Associated With Death***

| Variable | OR | 95% CI | *P* Value |
|---|---|---|---|
| H-IVIG treatment within 5 d of symptom onset | 0.14 | 0.02-0.92 | .04 |

# SARS vs. MERS

| | SARS-CoV | | | | | MERS-CoV | |
|---|---|---|---|---|---|---|---|
| | Hong Kong | Toronto | Beijing | Taiwan | Singapore | KSA | Elsewhere |
| **Incubation period** | 4.6 days (95% with onset by 12.9 days) | | | | | 5.2 days (12.4 days) | NA |
| **Serial interval** | 8.4 days | | | | | 7.6 days | NA |
| **Household attack rate** | Toronto: 10.2% (95%CI 6.7-23.5%)<br>Vietnam: 4.2% (95% CI 1.5-7%)<br>Singapore: 6.2% (95% CI 3.9-8.5%)<br>Hong Kong: 8% (12% early - 6% late)<br>Beijing: 4.6% | | | | | 11% (4/36) | 5% (1/20) |


UNITED KINGDOM 4
GERMANY 2
FRANCE 2
ITALY 3
TUNISIA 3
JORDAN 2
SAUDI ARABIA 111
QATAR 3
UNITED ARAB EMIRATES 5
MERS-CoV cases by reporting country as of 19 September 2013
Type
imported
local
Number of cases
100
10
1
Place of exposure by reporting country
Germany
France
Italy
United Kingdom
Tunisia
® ECDC/SRS, Sep/2013


Location
Abu-Dhabi
Al-Hasa
Bisha
Buraidah
Dubai
Hafr-Al-Batin
Khamis-Mushait
Madinah
Makkah
Qatar
Riyadh
Taif
Wadi-Ad-Dawasir
Riyadh_10_2013
Riyadh_17_2013
Madinah_1_2013
Madinah_3_2013
Riyadh_11_2013
Riyadh_8_2013
Riyadh_13_2013
Riyadh_15_2013
Riyadh_14_2013
Riyadh_7_2013
Qatar_3_2013
Hafr-Al-Batin_1_2013
Riyadh_6_2013
Hafr-Al-Batin_5_2013
Hafr-Al-Batin_2_2013
Riyadh_12_2013
Hafr-Al-Batin_4_2013
Al-Hasa_26_2013
Al-Hasa_28_2013
Al-Hasa_19_2013
Al-Hasa_17_2013
Al-Hasa_2_2013
Al-Hasa_8_2013
Al-Hasa_23_2013
Riyadh_9_2013
England2-HPA_2013
Riyadh_2_2013
Asir_1_2013
Asir_2_2013
Taif_2_2013
France_UAE_2013
Buraidah_1_2013
Taif_3_2013
Taif_1_2013
Wadi-Ad-Dawasir_1_2013
Riyadh_5_2013
Riyadh_3_2013
Riyadh_4_2013
England-Qatar_2012
Munich_AbuDhabi_2013
Riyadh_1_2012
Bisha_1_2012
2012.0
2012.25
2012.5
2012.75
2013.0
2013.25
2013.5
2013.75

# First 179 cases MERS-CoV
## *primary and secondary cases*

| Characteristic | Primary (N=74) | Secondary (N=105) |
|---|---|---|
| Median age | 58 years | 48 years |
| Gender | 80% male | 58% male |
| Healthcare worker | 3% | 35% (80% female) |
| Hospitalized patient | - | ~35% |

WHO MERS CoV Update 27 March 2014

**Dialysis patient**
**Hospitalized for CHF**
**Infected on Ward A**
**(April 5-8)**


**6 dialysis patients infected**
**April 11-13 (shared shifts)**

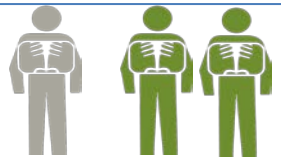
**3 other dialysis patients and one**
**Family member infected secondarily**

Dialysis unit 2: 2 patients infected
(adjacent chair, and shared transport

**Dialysis patient from *different* unit hospitalized for pulmonary edema; infected in ICU (April 20-22)**


Hospital 2: 18 infections
(one MD died)

Ward B – 2 patients and 1 visitor infected



# What is important about hospitals?

1. On-going clusters
    - Due to difficulty in recognizing and diagnosing disease

2. Proportion of cases in hospital clusters
    - 60 /146 (41%) initial cases attributed to transmission in healthcare settings
    - 30 healthcare workers; 19 patients; 6 visitors

3. Case fatality rate
    - Among patients with hospital-acquired disease: >70%
    - Among HCWs: 4/32 (12.5%)

WHO MERS-CoV Research group PLOS Currents Outbreaks. 2013 Nov 12.

# SARS versus MERS

| | Hong Kong | Toronto | Beijing | Taiwan | MERS |
|---|---|---|---|---|---|
| **Percent of healthcare-acquired cases:** | | | | | |
| **Healthcare workers** | 23% | 39% | 16% | 18% | 20% |
| **Hospital patients** | - | 22% | 6% | - | 13% |
| **Visitors** | - | 16% | - | - | 4% |
| **Patients and visitors** | 53% | | | | |

# Disease distribution in healthcare workers

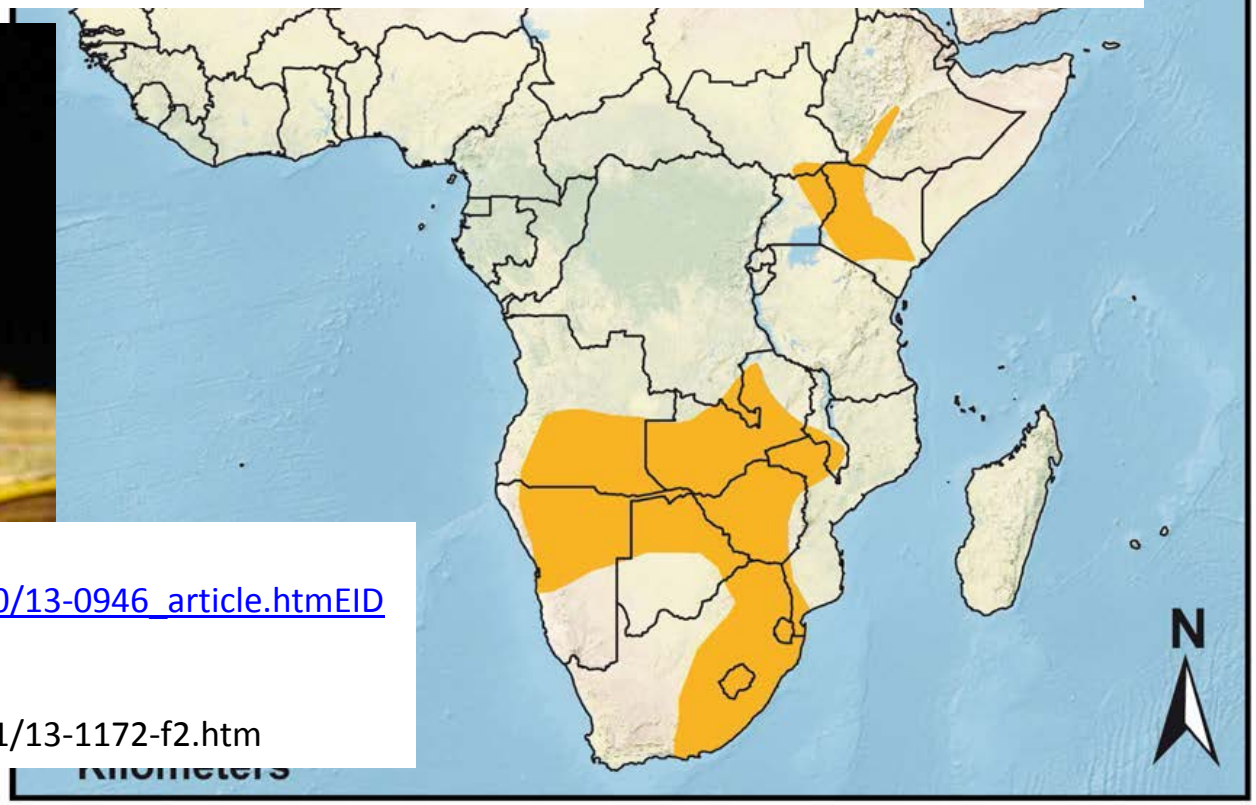
- Al-Musa outbreak
  - 100 exposed HCWs, including 18 full-time staff of dialysis unit – 1 case; one ARI (untested)
- Reported from KSA
  - 12 HCWs; 3 asymptomatic, 4 ILI, 3 severe disease, 2 deaths
- WHO update Jan 2014
  - 32 HCWs: 7 severe disease, 4 died

http://www.who.int/csr/disease/coronavirus_infections/archive_updates/en/index.html


# *Taphozous perforatus*

Memish et al. EID Nov 2013
http://wwwnc.cdc.gov/eid/article/19/11/13-1172-f2.htm

*Neoromicia* cf. *zuluensis*

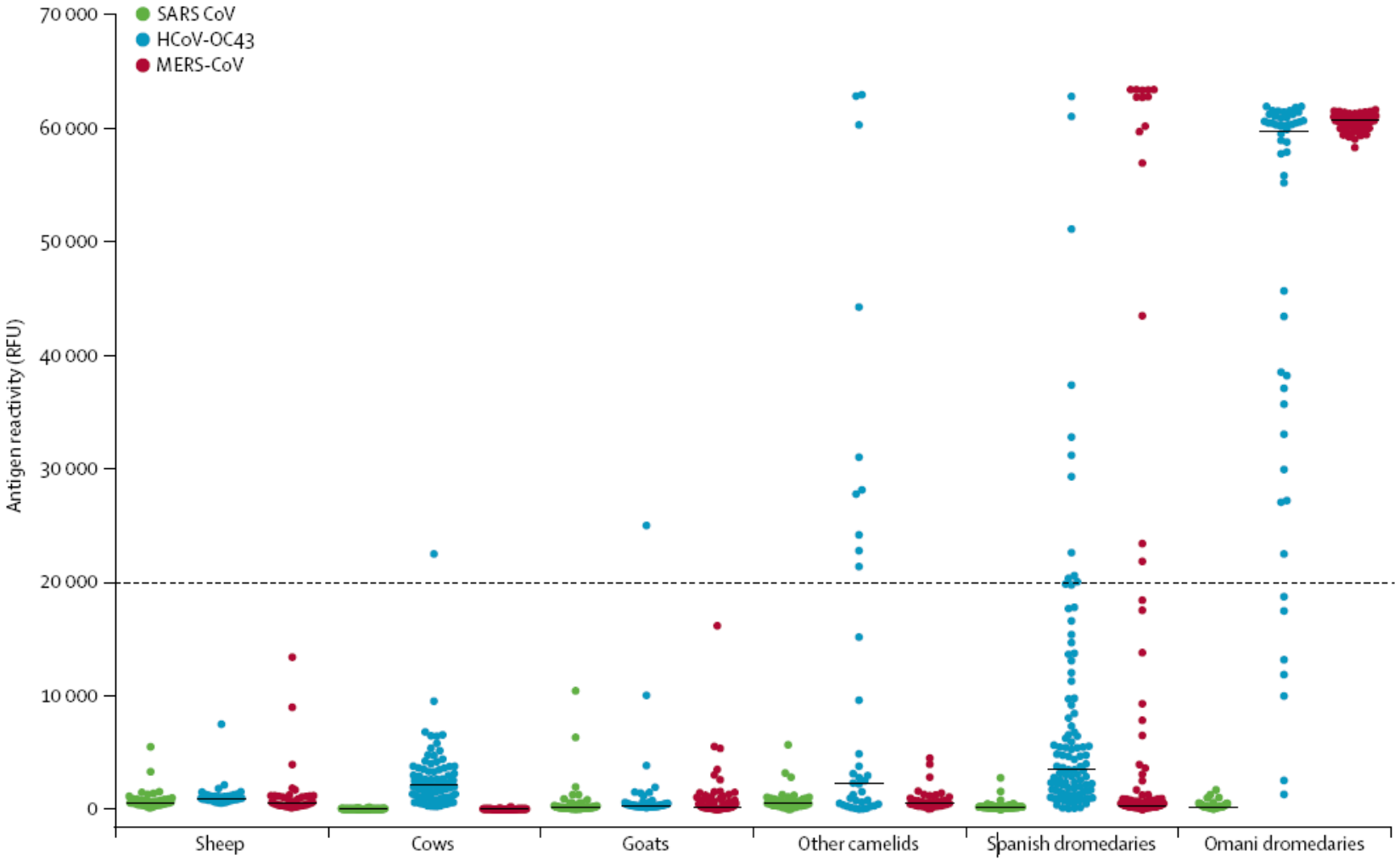




Ithete et al. EID Oct 2013
http://wwwnc.cdc.gov/eid/article/19/10/13-0946_article.htmEID

Memish et al. EID Nov 2013
http://wwwnc.cdc.gov/eid/article/19/11/13-1172-f2.htm

# Intermediary Host:  Camels?

# Reactivity of livestock sera with three coronavirus S1 antigens




*Chantal B E M Reusken et al,* The Lancet 2013

# What do we know about MERS-CoV in camels?

- Present (same or highly related virus) since at least 1990s

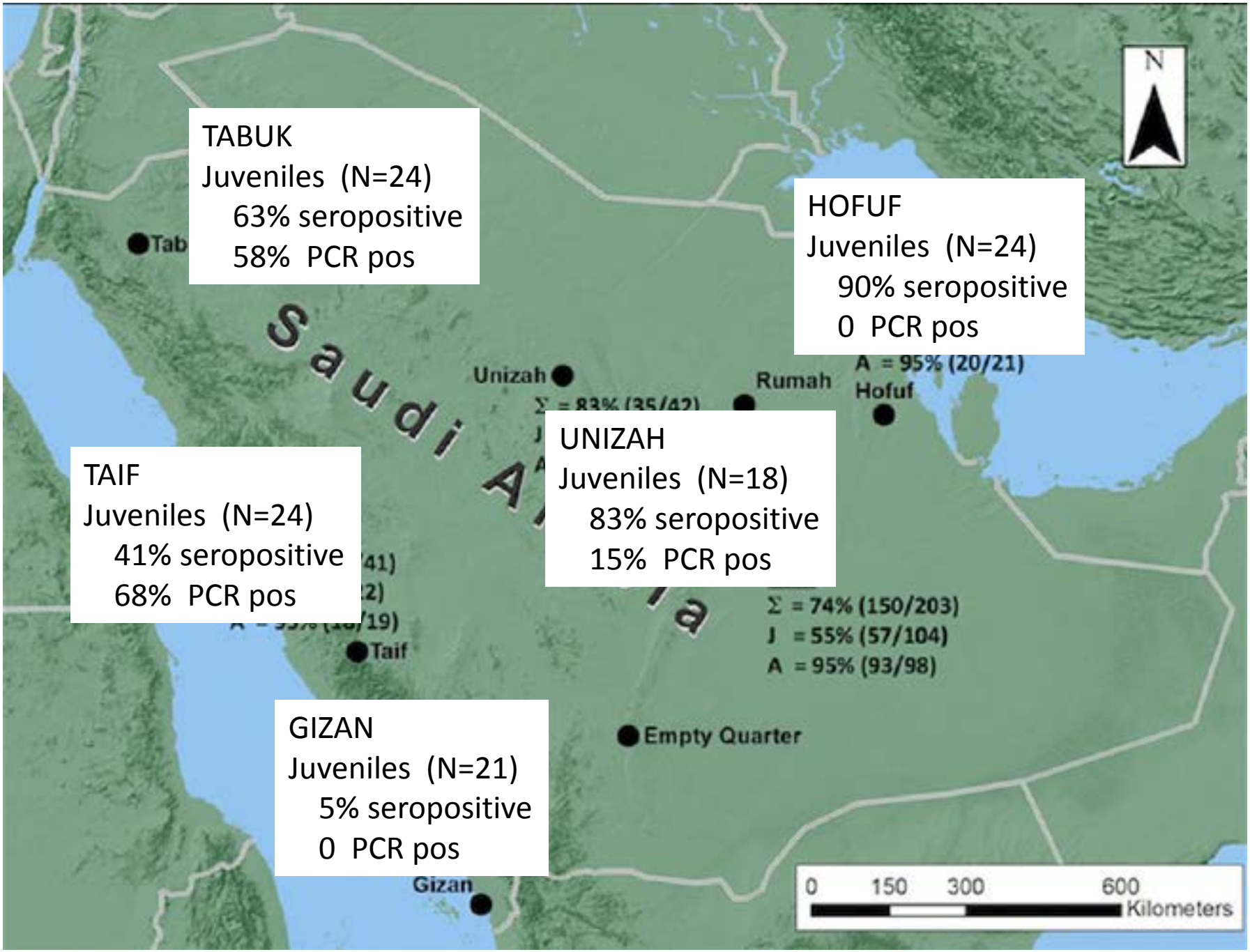
TABLE 2 Analysis of archived DC sera from the KSA from 1992 to 2010

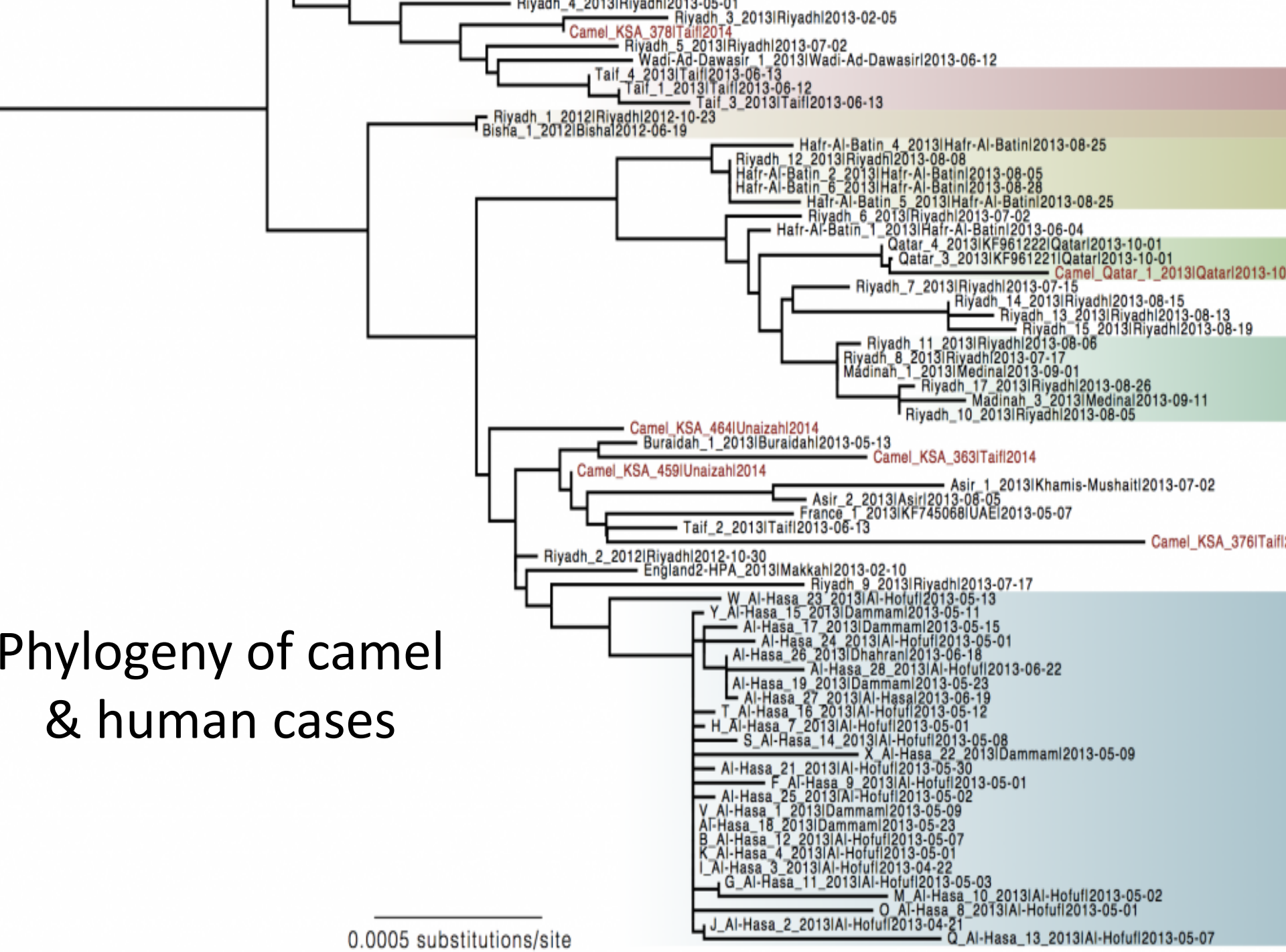
| Yr | Location | Age group | No. | % Seropositive (no. positive/total) |
|---|---|---|---|---|
| 1992 | Riyadh | Adult | 1 | 100 (1/1) |
| 1993 | Riyadh | Adult | 2 | 100 (2/2) |
| 1994 | Empty quarter | Adult | 123 | 93 (114/123) |
| 1996 | Riyadh | Adult | 6 | 100 (6/6) |
| 2004 | Riyadh | Adult | 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) |

# What do we know about MERS-CoV in camels?

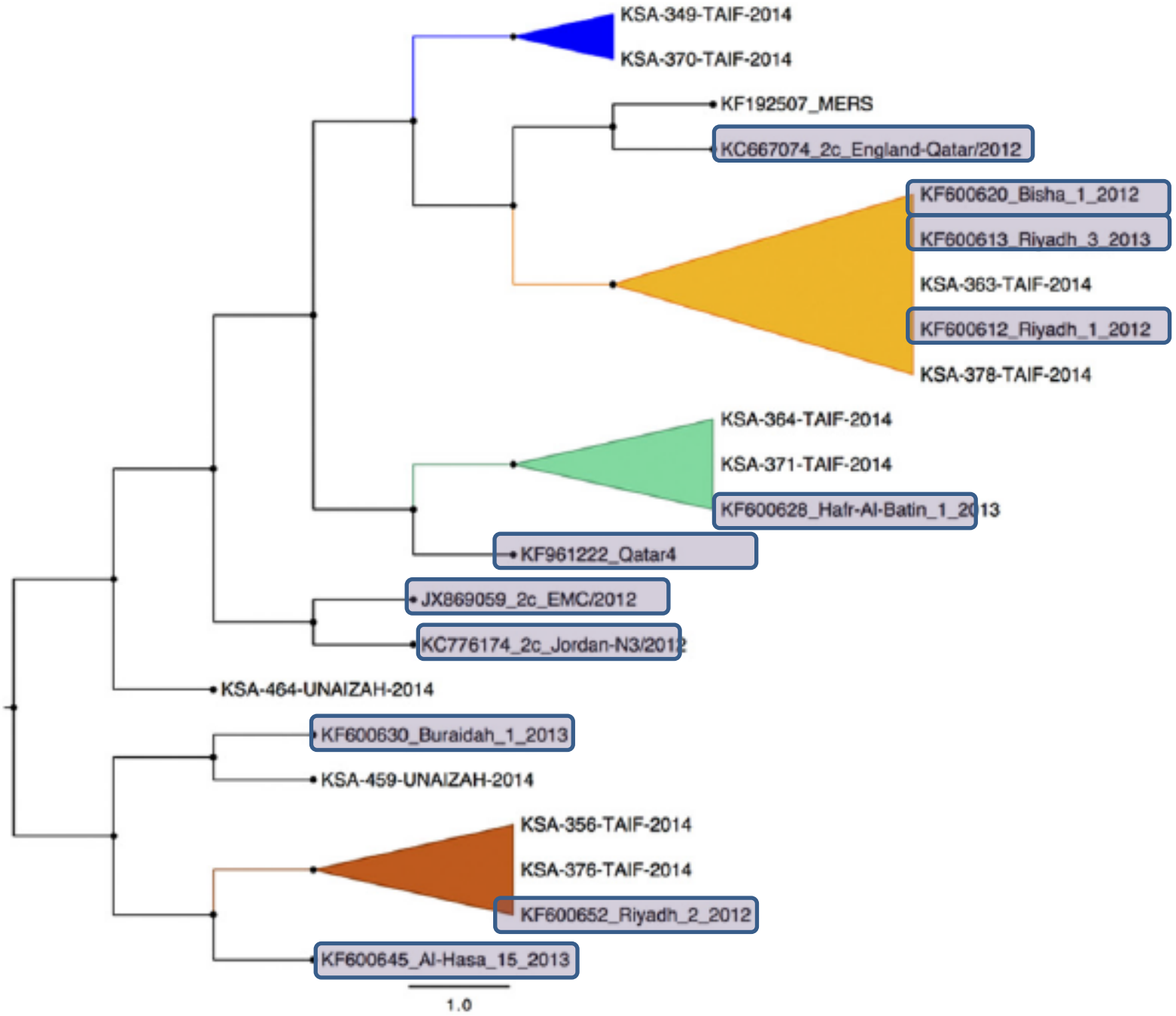
- Present (same or highly related virus) since at least 1990s
- Some camels seropositive in all countries tested
- Seropositivity higher in adult (≥2yrs) than juvenile camels (93% vs. 55%)
- Appears to be associated with (mild) respiratory illness in some cases
- Infection rates variable geographically

Chu EID 2014:20 June; Memish EID 2014:20 June; Aligaili mBio 2014:5:2


TABUK
Juveniles (N=24)
63% seropositive
58% PCR pos
HOFUF
Juveniles (N=24)
90% seropositive
0 PCR pos
UNIZAH
Juveniles (N=18)
83% seropositive
15% PCR pos
TAIF
Juveniles (N=24)
41% seropositive
68% PCR pos
GIZAN
Juveniles (N=21)
5% seropositive
0 PCR pos
N
Tab
Unizah
Rumah
Hofuf
A = 95% (20/21)
Σ = 74% (150/203)
J = 55% (57/104)
A = 95% (93/98)
Taif
Empty Quarter
Gizan
0 150 300 600
Kilometers




# Phylogeny of camel & human cases


KSA-349-TAIF-2014
KSA-370-TAIF-2014
KF192507_MERS
KC667074_2c_England-Qatar/2012
KF600620_Bisha_1_2012
KF600613_Riyadh_3_2013
KSA-363-TAIF-2014
KF600612_Riyadh_1_2012
KSA-378-TAIF-2014
KSA-364-TAIF-2014
KSA-371-TAIF-2014
KF600628_Hafr-Al-Batin_1_2013
KF961222_Qatar4
JX869059_2c_EMC/2012
KC776174_2c_Jordan-N3/2012
KSA-464-UNAIZAH-2014
KF600630_Buraidah_1_2013
KSA-459-UNAIZAH-2014
KSA-356-TAIF-2014
KSA-376-TAIF-2014
KF600652_Riyadh_2_2012
KF600645_Al-Hasa_15_2013
1.0

# So what is the problem with camels?

- Most cases don't have direct exposure

# Comparison of primary and secondary cases of MERS

| Characteristic | Primary (N=74) | Secondary (N=105) |
|---|---|---|
| Median age | 58 years | 48 years |
| Gender | 80% male | 58% male |
| Healthcare worker | 3% | 35% (80% female) |
| Hospitalized patient | - | ~35% |
| Camels | | |
| Contact | 20% | 4% |
| Any association | 55% | 4% |

WHO MERS CoV Update 27 March 2014

# So what is the problem with camels?

- Most cases don't have direct exposure

- People who DO have direct exposure aren't getting sick and aren't seropositive
  - 179 abattoir workers in Egypt

- Disease is limited to the Arabian peninsula and predominantly KSA
  - But only 260,000 of 27,000,000 camels live in KSA

# What next?

# Next steps

- Identify means of transmission from camels to humans
  - Essential to preventing human infections
- Understand what happened that led to camel-human transmission
- Continue to monitor evolution carefully
- Treatment, vaccines, diagnosis, understanding hospital transmission

Questions?