Update on Virology and Clinical Management of MERS-CoV

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PMH/IDC

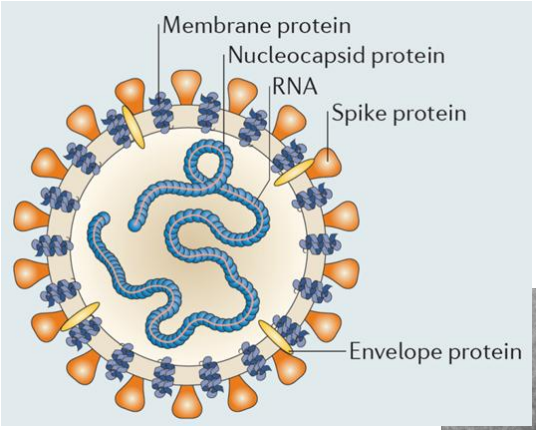
22-6-2-14

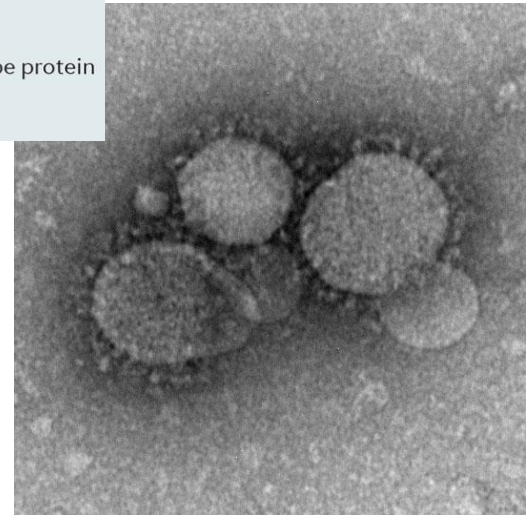
Virology of MERS- CoV

23/9/2012 :
The WHO reported 2 laboratory-confirmed cases of
severe respiratory disease associated with a novel coronavirus - HCoV-EMC
(Erasmus Medical Center in Rotterdam, the Netherlands)

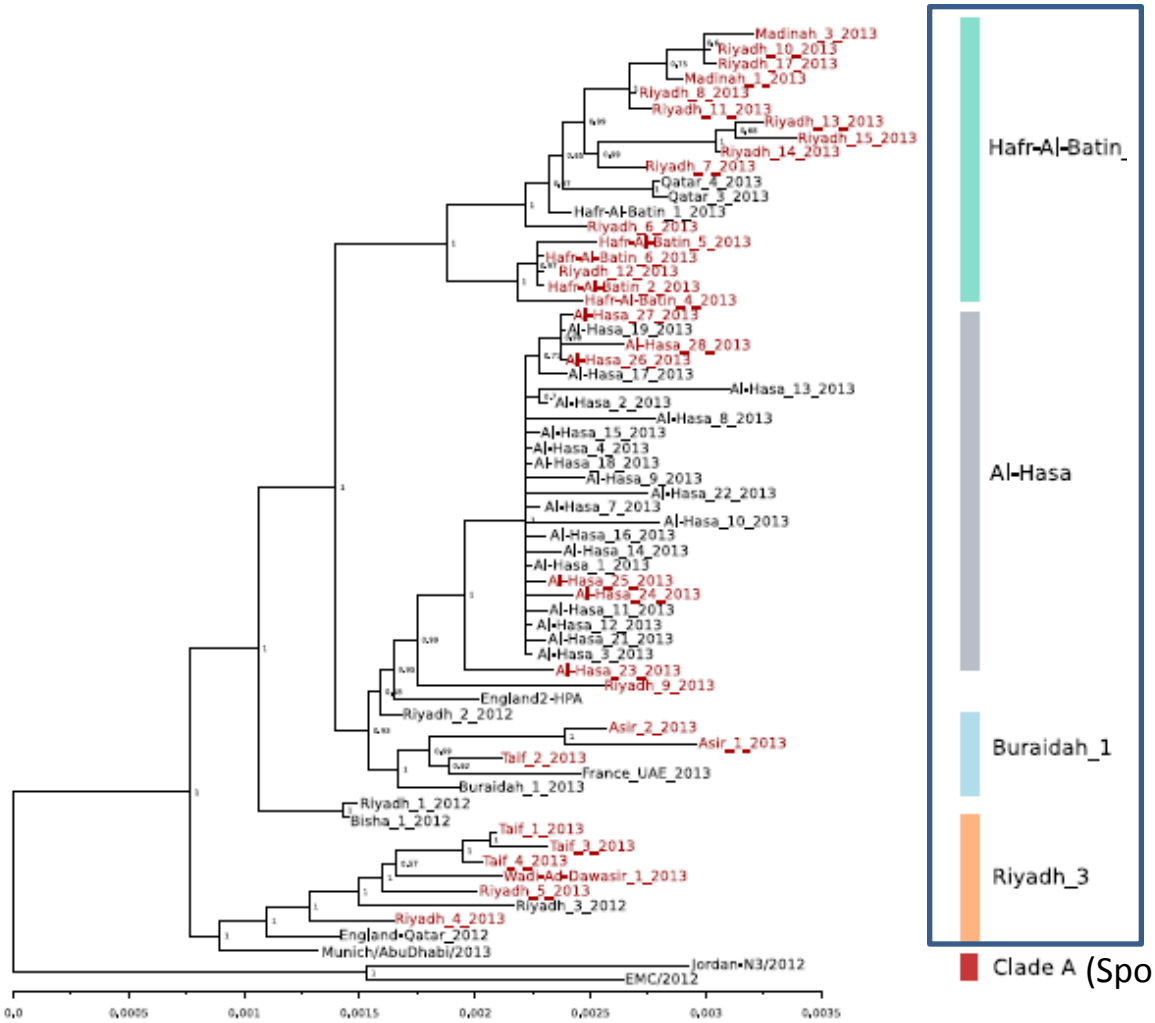
Order : *Nidovirales*
Family : *Coronaviridae*
Genus : betacoronavirus - Group C

Enveloped positive-sense
single stranded
RNA virus
genome size of about 30 kb





Spread, Circulation, and Evolution of the Middle East Respiratory Syndrome Coronavirus



4 major clades

Cotton et al. mBio 2014

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]

Most human coronaviruses cause mild upper respiratory tract disease but may be associated with more severe pulmonary disease in immunocompromised individuals[1]. However, SARS coronavirus caused severe lower respiratory disease with nearly 10% mortality and evidence of systemic spread[2]. Recently, another coronavirus (human coronavirus-Erasmus Medical Center (hCoV-EMC)) was identified in patients with severe and sometimes lethal lower respiratory tract infection[3,4]. Viral genome analysis revealed close relatedness to coronaviruses found in bats[5]. Here we identify dipeptidyl peptidase 4 (DPP4; also known as CD26) as a functional receptor for hCoV-EMC. DPP4 specifically co-purified with the receptor-binding S1 domain of the hCoV-EMC spike protein from lysates of susceptible Huh-7 cells. Antibodies directed against DPP4 inhibited hCoV-EMC infection of primary human bronchial epithelial cells and Huh-7 cells. Expression of human and bat (*Pipistrellus pipistrellus*) DPP4 in non-susceptible COS-7 cells enabled infection by hCoV-EMC. The use of the evolutionarily conserved DPP4 protein from different species as a functional receptor provides clues about the host range potential of hCoV-EMC. In addition, it will contribute critically to our understanding of the pathogenesis and epidemiology of this emerging human coronavirus, and may facilitate the development of intervention strategies.

Nature 2013, 495, 251-156
Cell Research (2013) 23:986-993

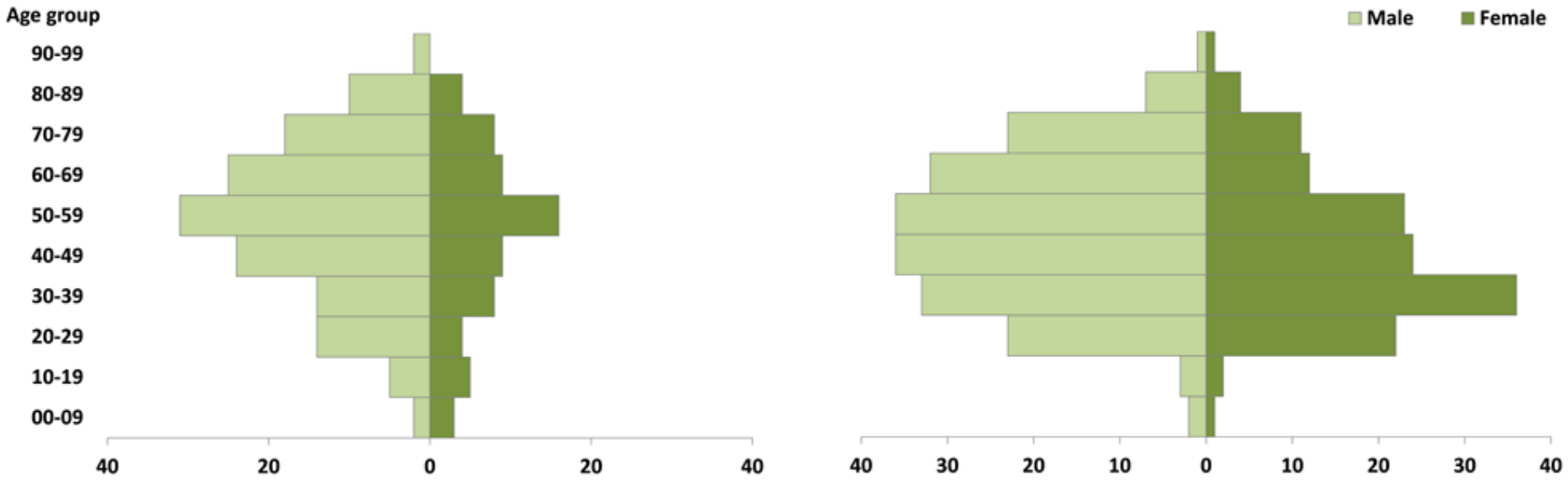
Epidemiology: MERS-CoV vs SARS

	MERS-CoV	SARS, global[27-34]
Demographic factors		
Date of first case report (place)	April, 2012 (Jordan); June, 2012 (first Saudi case)	November, 2002 (China)
Mean (95% CI) incubation period (days)	5·2 (1·9–14·7); range 2–13	4·6 (3·8–5·8); range 2–14
Serial interval (days)	7·6	8·4
Age distribution	98% adults, 2% children	93% adults, 5–7% children
Mean (range) age (years)	56 (14–94)	39·9 (1–91)
Sex distribution	77% male, 23% female	43% male, 57% female
Sex ratio (male:female)	3·3:1	1:1·3
Mortality	55%	0–40%
Case-fatality rate (overall)	Undefined	9·6%
In patients with comorbidities	60%	1–2%
Mean time from onset to death (days)	16·5	23·7

Assiri A, et al. Lancet Infect Dis 2013;13:752-61

Distribution of age and sex

Distribution of confirmed cases of MERS-CoV by age and sex, March 2012 – 31 March 2014 (n=210*) and 1 April – 16 May 2014 (n=332**) by first available date



* 11 cases has been excluded due to missing data on age or sex
** 68 cases have been excluded due to missing data on age or sex

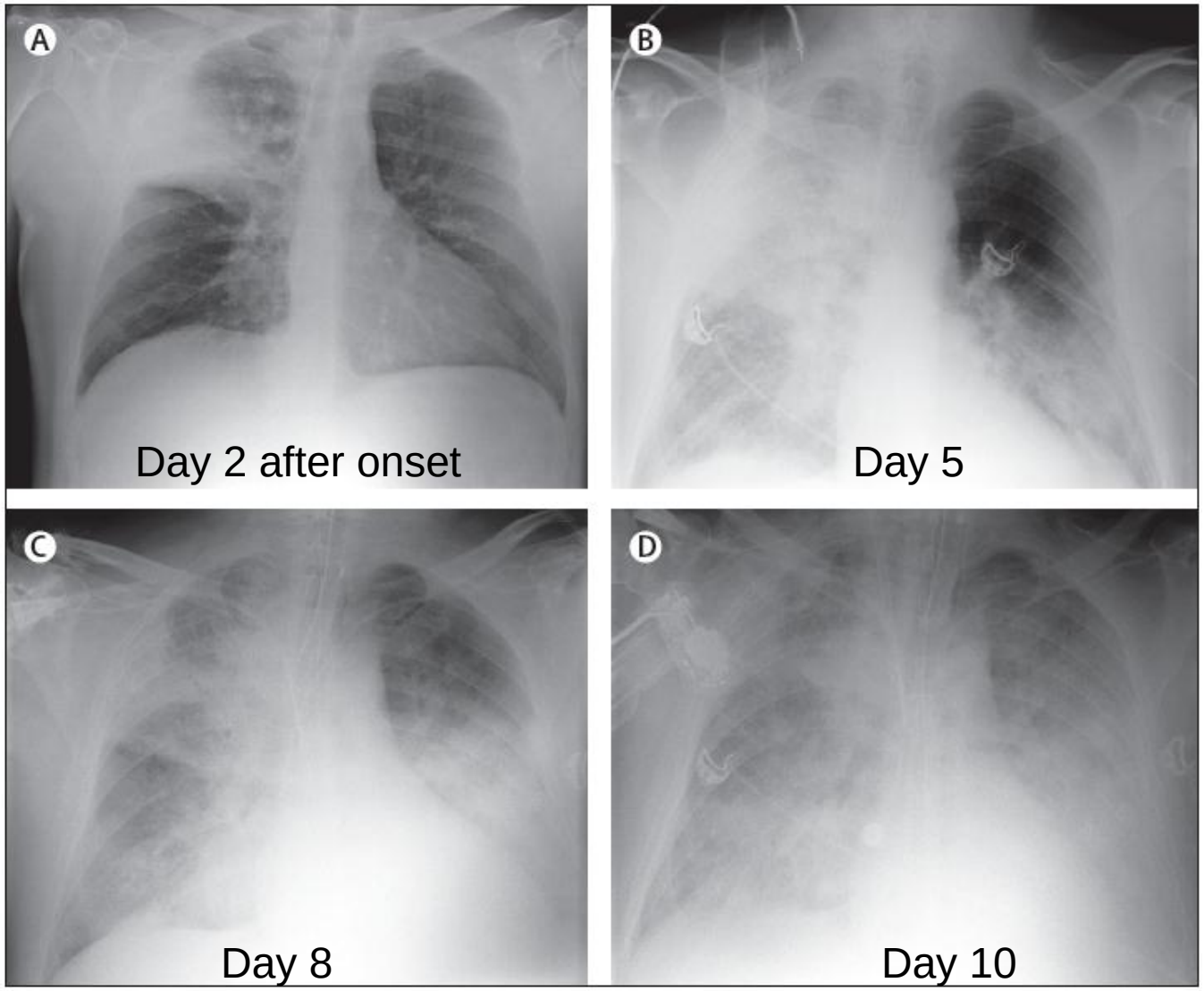
ECDC. Epidemiological update: MERS-CoV 16 May 2014

Symptoms: SARS vs MERS-CoV

Symptoms	SARS (%) (N=752)	MERS-CoV (%) (N= 47)
Fever	***99.9***	***98***
Chill/rigors	***51.5***	***87***
Cough	***65.6***	***83***
Dyspnoea	***45.9***	***72***
Myalgia	67.7	32
Diarrhoea	**20.1**	**26**
Sore throat	16.5	21
Nausea/vomiting	26.6	21
Abdominal pain	/	17
Hemoptysis	/	17
Chest pain	19.5	15
Headache	38.8	13
Running nose	13.8	4

Assiri A, et al. Lancet Infect Dis 2013;13:752-61

Radiological findings of MERS



Guery B, et al. Lancet 2013; 381:2265-72

Laboratory findings: SARS vs MERS-CoV

Variables	SARS (%) (N = 752)	MERS-CoV (%) (N = 47)
Anemia	12.6	/
Leukopenia	24.2	/
Lymphocytopenia	***66.4***	***34***
Lymphocytosis	/	11
Thrombocytopenia	29.7	36
↑ Alanine aminotransferase	44.1	11
↑ Lactate dehydrogenase	45.6	49

Assiri A, et al. Lancet Infect Dis 2013;13:752-61

Other clinical manifestations

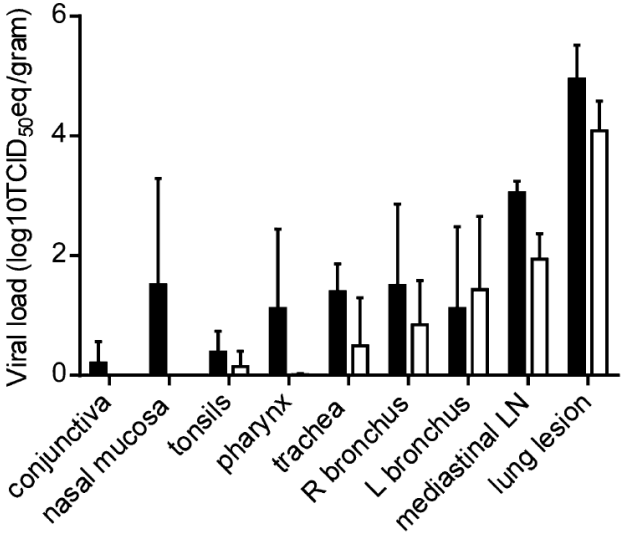
- Case series of 12 ICU patients at 2 tertiary care hospitals in Saudi Arabia, between December 2012 and August 2013

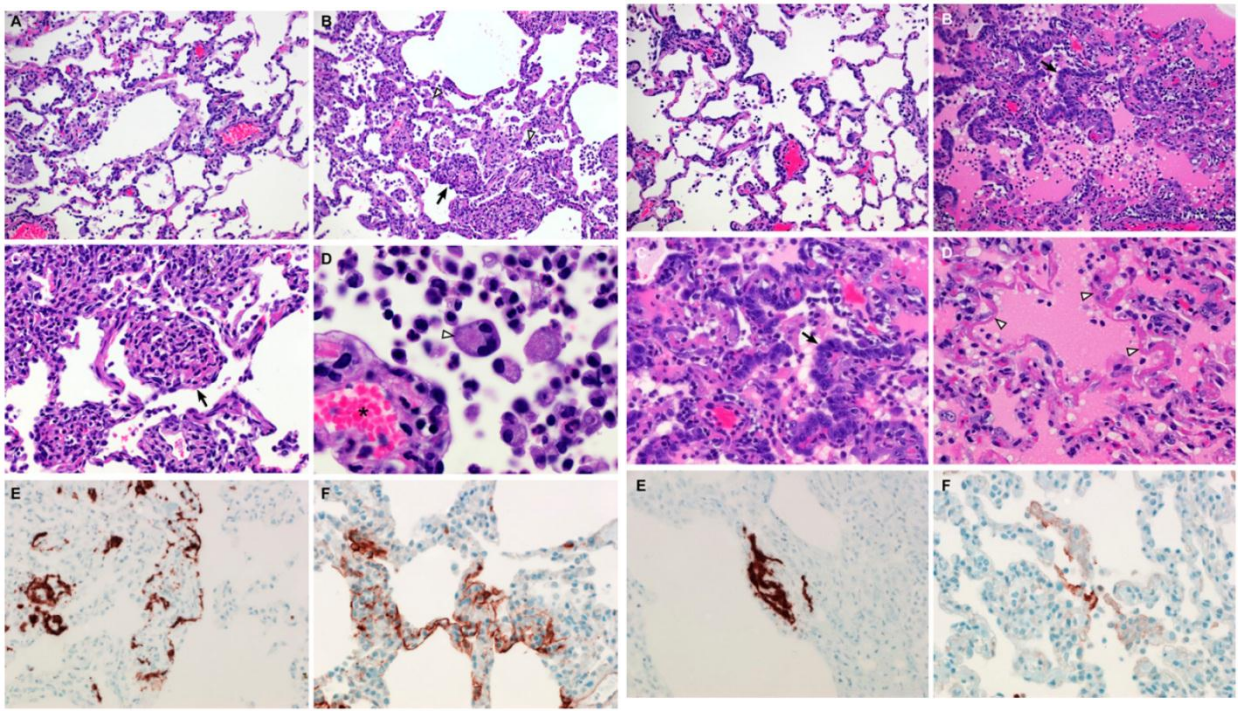
Noninvasive positive-pressure ventilation, *n (%)*	5 (42)
Invasive ventilation, *n (%)*	12 (100)
Neuromuscular blockade, *n (%)*	4 (33)
High-frequency oscillation ventilation, *n (%)*	2 (17)
Nitric oxide, *n (%)*	6 (50)
Prone positioning, *n (%)*	3 (25)
Barotrauma, *n (%)*	2 (17)
Vasopressors, *n (%)*	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)*

Arabi YM et al. Ann Inter Med 2014

Pathogenesis

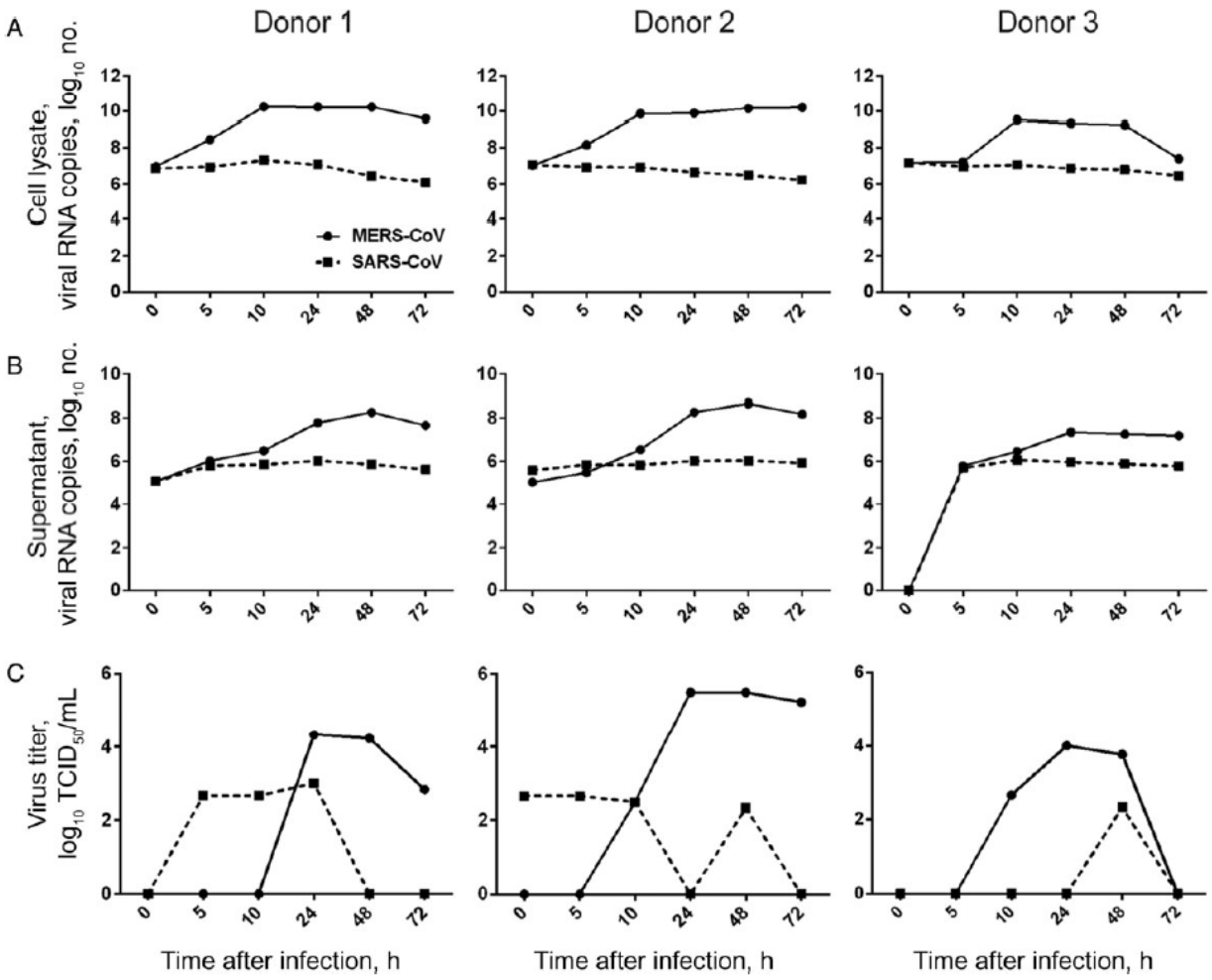
Middle East respiratory syndrome coronavirus (MERS-CoV) causes transient lower respiratory tract infection in rhesus macaques





Wit et al PNAS 2013

Active Replication of Middle East Respiratory Syndrome Coronavirus and Aberrant Induction of Inflammatory Cytokines and Chemokines in Human Macrophages: Implications for Pathogenesis



Zhou et al JID 2014

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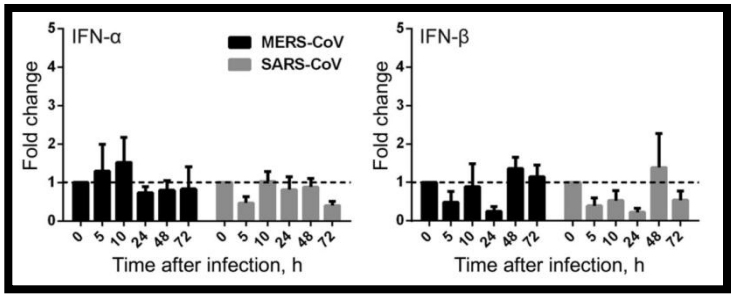
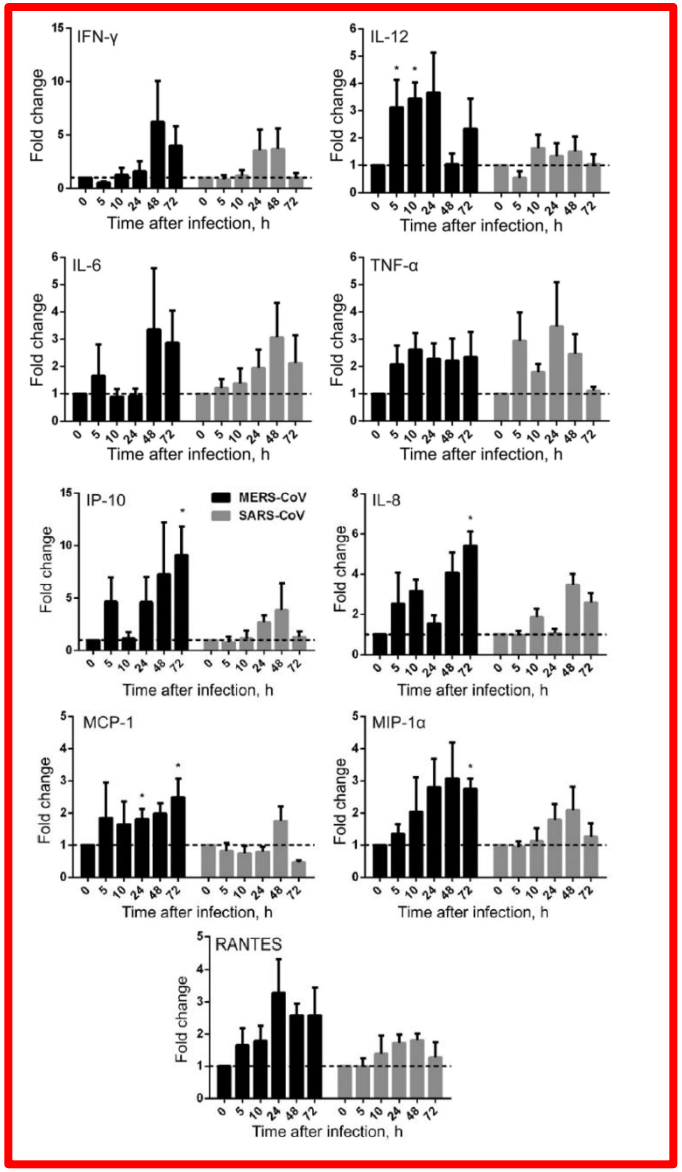




Zhou et al JID 2014

Cell line susceptibility to MERS-CoV

Cell Line	Viral Load, log_{10} copies/mL, mean ± SD[a,b]					
	Day 0	Day 1	*P*	Day 3	*P*	Day 5	*P*
Human							
Respiratory tract							
Hep-2	5.87 ± 0.10	5.84 ± 0.04	.784	5.85 ± 0.02	.823	5.85 ± 0.10	.859
A549	5.90 ± 0.16	6.97 ± 0.11	.025	7.18 ± 0.04	.050	7.45 ± 0.31	.045
Calu-3	5.62 ± 0.04	9.63 ± 0.04	<.001	10.42 ± 0.22	.016	10.25 ± 0.06	.001
HFL	5.72 ± 0.02	9.54 ± 0.35	.041	10.73 ± 0.03	.002	10.45 ± 0.04	.003
Gastrointestinal tract							
Caco-2	5.82 ± 0.04	10.19 ± 0.61	.060	10.49 ± 0.17	.009	10.26 ± 0.16	.018
Liver							
Huh-7	5.87 ± 0.07	10.47 ± 0.22	.011	9.56 ± 0.11	.002	9.63 ± 0.02	.006
Genitourinary tract							
HeLa	5.75 ± 0.06	5.94 ± 0.08	.124	5.86 ± 0.17	.522	5.99 ± 0.08	.079
HEK	5.82 ± 0.05	10.45 ± 0.25	.015	9.97 ± 0.17	.012	9.90 ± 0.03	.001
Neuromuscular cells							
NT2	5.72 ± 0.04	7.83 ± 0.02	.002	8.22 ± 0.04	<.001	8.40 ± 0.14	.015
RD	5.66 ± 0.04	6.68 ± 0.24	.098	6.90 ± 0.02	.003	6.78 ± 0.01	.013
Immune cells							
THP-1	6.75 ± 0.01	7.03 ± 0.02	.020	7.28 ± 0.06	.044	7.40 ± 0.06	.036
U937	6.70 ± 0.06	7.10 ± 0.07	.028	7.19 ± 0.04	.016	7.25 ± 0.07	.015
Raji	6.71 ± 0.05	6.85 ± 0.02	.106	6.76 ± 0.08	.528	7.05 ± 0.04	.019
H9	6.52 ± 0.03	6.55 ± 0.57	.592	6.73 ± 0.04	.038	6.71 ± 0.03	.020
His-1	5.55 ± 0.04	9.44 ± 0.08	.001	9.27 ± 0.05	<.001	9.12 ± 0.01	.004

The Journal of Infectious Diseases 2013

Diagnosis

- **RT-PCR or real time PCR**:
  - Target at upstream of the E protein gene (upE), the open reading frame 1b (ORF 1b) and the open reading frame 1a (ORF 1a)
  - upE: highly sensitive and is recommended for screening,
  - ORF 1a assay considered of equal sensitivity.
  - ORF 1b assay is considered less sensitive
- Serology:
  - Screening: ELISA
  - Confirmation: whole-virus indirect fluorescent antibody (IFA) test or microneutralization test.

Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission

*Benoit Guery, Julien Poissy, Loubna el Mansouf, Caroline Séjourné, Nicolas Ettahar, Xavier Lemaire, Fanny Vuotto, Anne Goffard, Sylvie Behillil, Vincent Enouf, Valérie Caro, Alexandra Mailles, Didier Che, Jean-Claude Manuguerra, Daniel Mathieu, Arnaud Fontanet, Sylvie van der Werf, and the MERS-CoV study group**

Summary

Background Human infection with a novel coronavirus named Middle East Respiratory Syndrome coronavirus (MERS-CoV) was first identified in Saudi Arabia and the Middle East in September, 2012, with 44 laboratory-confirmed cases as of May 23, 2013. We report detailed clinical and virological data for two related cases of MERS-CoV disease, after nosocomial transmission of the virus from one patient to another in a French hospital.

Methods Patient 1 visited Dubai in April, 2013; patient 2 lives in France and did not travel abroad. Both patients had underlying immunosuppressive disorders. We tested specimens from the upper (nasopharyngeal swabs) or the lower (bronchoalveolar lavage, sputum) respiratory tract and whole blood, plasma, and serum specimens for MERS-CoV by real-time RT-PCR targeting the upE and Orf1A genes of MERS-CoV.

Findings Initial clinical presentation included fever, chills, and myalgia in both patients, and for patient 1, diarrhoea. Respiratory symptoms rapidly became predominant with acute respiratory failure leading to mechanical ventilation and extracorporeal membrane oxygenation (ECMO). Both patients developed acute renal failure. MERS-CoV was detected in lower respiratory tract specimens with high viral load (eg, cycle threshold [Ct] values of 22·9 for upE and 24 for Orf1a for a bronchoalveolar lavage sample from patient 1; Ct values of 22·5 for upE and 23·9 for Orf1a for an induced sputum sample from patient 2), whereas nasopharyngeal specimens were weakly positive or inconclusive. The two patients shared the same room for 3 days. The incubation period was estimated at 9–12 days for the second case. No secondary transmission was documented in hospital staff despite the absence of specific protective measures before the diagnosis of MERS-CoV was suspected. Patient 1 died on May 28, due to refractory multiple organ failure.

Interpretation Patients with respiratory symptoms returning from the Middle East or exposed to a confirmed case should be isolated and investigated for MERS-CoV with lower respiratory tract sample analysis and an assumed incubation period of 12 days. Immunosuppression should also be taken into account as a risk factor.

Funding French Institute for Public Health Surveillance, ANR grant Labex Integrative Biology of Emerging Infectious Diseases, and the European Community's Seventh Framework Programme projects EMPERIE and PREDEMICS.

Lancet Published Online May 29, 2013 http://dx.doi.org/10.1016/S0140-6736(13)60982-4

Interim Recommendation on Clinical Management of Cases of Middle East Respiratory Syndrome

5.3 Baseline investigations

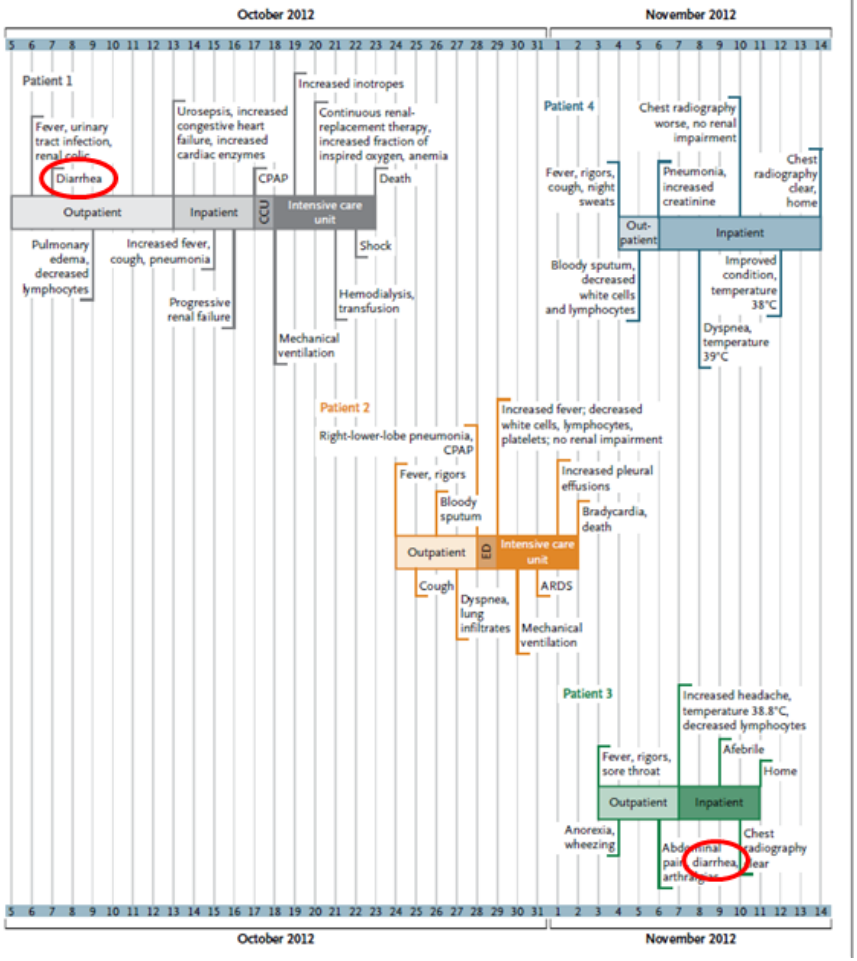
5.3.1 Test of Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

- Upper respiratory tract (NPA, NPS); lower respiratory tract (sputum, tracheal aspirate, BAL) - for patients with pneumonia, lower respiratory tract specimens may have a better diagnostic yield
- Repeated testing may be necessary to exclude the diagnosis. Please consult the clinical microbiologists or infectious disease physicians for advice
- Paired serum (acute and convalescent)
- Stool for MERS-CoV for patient with epidemiological link presenting with diarrhea. Please consult the clinical microbiologists on the testing.

Interim recommendation on clinical management cases of MERS

BRIEF REPORT

Family Cluster of Middle East Respiratory Syndrome Coronavirus Infections



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Memish ZA, et al. N Engl J Med. 2013
Guery B, et at. Lancet 2013

Clinical features and virological analysis of a case of Middle East respiratory syndrome coronavirus infection

Summary

Background The Middle East respiratory syndrome coronavirus (MERS-CoV) is an emerging virus involved in cases and case clusters of severe acute respiratory infection in the Arabian Peninsula, Tunisia, Morocco, France, Italy, Germany, and the UK. We provide a full description of a fatal case of MERS-CoV infection and associated phylogenetic analyses.

Methods We report data for a patient who was admitted to the Klinikum Schwabing (Munich, Germany) for severe acute respiratory infection. We did diagnostic RT-PCR and indirect immunofluorescence. From time of diagnosis, respiratory, faecal, and urine samples were obtained for virus quantification. We constructed a maximum likelihood tree of the five available complete MERS-CoV genomes.

Findings A 73-year-old man from Abu Dhabi, United Arab Emirates, was transferred to Klinikum Schwabing on March 19, 2013, on day 11 of illness. He had been diagnosed with multiple myeloma in 2008, and had received several lines of treatment. The patient died on day 18, due to septic shock. MERS-CoV was detected in two samples of bronchoalveolar fluid. Viral loads were highest in samples from the lower respiratory tract (up to $1{\cdot}2\times10^6$ copies per mL). Maximum virus concentration in urine samples was 2691 RNA copies per mL on day 13; the virus was not present in the urine after renal failure on day 14. Stool samples obtained on days 12 and 16 contained the virus, with up to 1031 RNA copies per g (close to the lowest detection limit of the assay). One of two oronasal swabs obtained on day 16 were positive, but yielded little viral RNA (5370 copies per mL). No virus was detected in blood. The full virus genome was combined with four other available full genome sequences in a maximum likelihood phylogeny, correlating branch lengths with dates of isolation. The time of the common ancestor was halfway through 2011. Addition of novel genome data from an unlinked case treated 6 months previously in Essen, Germany, showed a clustering of viruses derived from Qatar and the United Arab Emirates.

Drosten et al Lancet Infect Dis 2013

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

- **Serum, whole blood, and rectal and nasal swabs** were freshly collected from DC, sheep, and goats in **November and December of 2013** in the southwestern (Gizan), western (Taif), northwestern (Tabuk), eastern (Hofuf), and central (Unizah, Riyadh) regions of the KSA
- **archived serum samples** obtained from DC in **1992 through 2010**

TABLE 1 Samples collected in 2013 by animal species, geographic location, age group, and specimen type

Animal species	Location(s)	Age group[a]	No.	Specimens[b]
DC	Hofuf	Juvenile	19	S, B, N, R
DC	Hofuf	Adult	21	S, B, N, R
DC	Gizan	Juvenile	21	S, B, N, R
DC	Gizan	Adult	19	S, B, N, R
DC	Taif	Juvenile	22	S, B, N, R
DC	Taif	Adult	19	S, B, N, R
DC	Tabuk	Juvenile	24	S, B, N, R
DC	Tabuk	Adult	16	S, B, N, R
DC	Riyadh	Juvenile	12	S, B, N, R
DC	Riyadh	Adult	8	S, B, N, R
DC	Unizah	Juvenile	6	S, B, N, R
DC	Unizah	Adult	16	S, B, N, R
Goat	Unizah	3 mo–2 yr	31	S, B, N, R
Goat	Riyadh	Unknown	5	S, B, N, R
Sheep, Barbari[c]	Unizah	3 mo–2 yr	29	S, B, N, R
Sheep, Harri	Unizah, Riyadh	3 mo–2 yr	10	S, B, N, R
Sheep, Najdi	Unizah	3 mo–2 yr	21	S, B, N, R
Sheep, Naimi	Unizah	3 mo–2 yr	21	S, B, N, R
Sheep, Sawakni	Unizah	3 mo–2 yr	31	S, B, N, R

[a] Juvenile animals were defined as being ≤2 years of age; adults were defined as being >2 years of age.
[b] Specimens collected from each animal: S, serum; B, blood; N, nasal swab; R, rectal swab.
[c] Domestic sheep were separated into the breeds commonly found in the KSA: Barbari, Harri, Najdi, Naimi, and Sawakni.

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)

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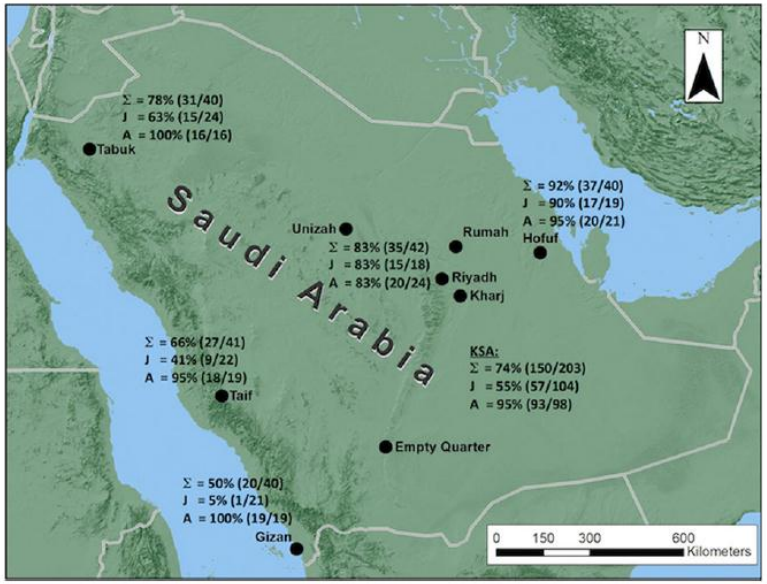
Middle East Respiratory Syndrome Coronavirus Infection in Dromedary Camels in Saudi Arabia

A **Antibody reactivity**



B **Nuclei acid detection**

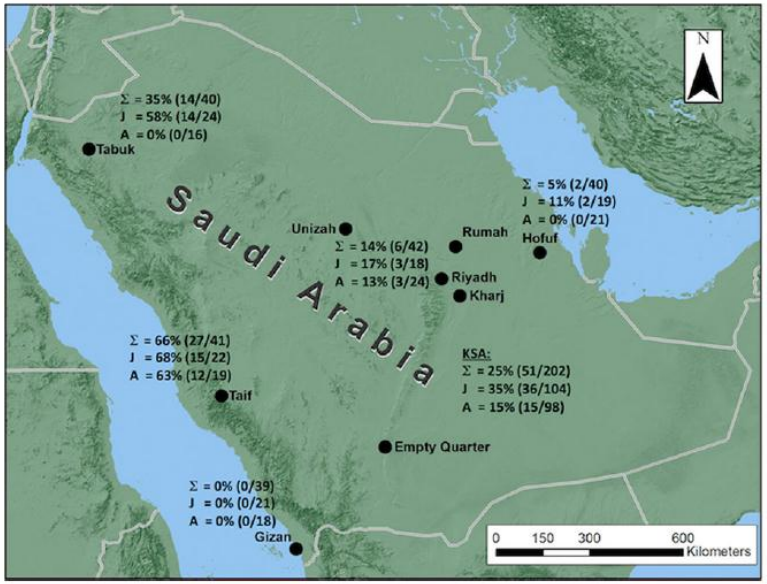


FIG 1 Prevalence of MERS-CoV antibody reactivity in serum (A) and nucleic acid detection in nasal swabs (B) by geographic region in KSA DC. Images were created with software from ESRI maps.

Prevalence lower in southwest of KSA due to

- Restriction of live stock movement in and out of Gizan Province
- Lower DC population in the region

No evidence of infection in domestic sheep or domestic goats

Alagaili AN et al. mBio 2014

Middle East respiratory syndrome coronavirus in dromedary camels: an outbreak investigation

- presence of MERS-CoV in dromedary camels from a farm in **Qatar** linked to two human cases of the infection in October, 2013
- Case 1: 61-year-old man who was the **owner of a farm**; substantial contact with animals including camels, sheep, pigeons, and hens; no recent travel history
- Case 2: 23-year-old male **employee of the farm** owned by case 1; regular contact with the animals on the farm; no recent travel history

	MERS-CoV detection					MERS-CoV serology		
	upE	ORF1a	Nucleocapsid	Spike*	Virus isolation	IFA	VNT†	Array‡
Camel 1	Negative	37·77	38·16	Negative	Negative	Positive	640	25 978
Camel 2	38·73	37·01	37·11	Negative	Negative	Positive	5120	63 645
Camel 3	Negative	Negative	36·53	Negative	Negative	Positive	640	14 684
Camel 4	Negative	Negative	Negative	Negative	Negative	Positive	2560	53746
Camel 5	32·52	33·05	30·64	Positive	Negative	Positive	640	12 007
Camel 6	Negative	37·16	Negative	Negative	Negative	Positive	2560	57 667
Camel 7	33·97	34·43	32·72	Positive	37·71	Positive	640	10740
Camel 8	Negative	Negative	37·38	Negative	Negative	Positive	5120	63775
Camel 9	38·04	38·35	36·63	Negative	Negative	Positive	2560	63 465
Camel 10	Negative	Negative	38·22	Negative	Negative	Positive	160	8002
Camel 11	37·09	34·99	34·90	Positive	Negative	Positive	2560	37 612
Camel 12	Negative	Negative	36·94	Negative	Negative	Positive	640	12 396
Camel 13	Negative	Negative	Negative	Negative	Negative	Positive	2560	63 521
Camel 14	Negative	Negative	Negative	Negative	Negative	Positive	1280	27 527

Presence of MERS-CoV *E* gene (upE), ORF1a, and nucleocapsid was assessed with a specific TaqMan assay. Virus isolation was done in Vero cells; values shown are cycle threshold values by upE test on day 4 after inoculation. IFA was done with fixed MERS-CoV infected Huh-7 cells tested at a 1/200 dilution. MERS-CoV=Middle East respiratory syndrome coronavirus. IFA=immunofluorescence assay. VNT=virus neutralisation titre. *PCR by MERS-CoV spike specific primers and subsequent sequence confirmation. †Lower detection limit of 20. ‡Relative fluorescence units are shown of 1/2560 dilution of sera when tested in a microarray format.

Table: Detection of genomes and antibodies specific for MERS-CoV in 14 dromedary camels

- **All** serology +ve

Nose swabs

- **8**/14 : one or more RT-PCRs +ve, but could not be confirmed by sequencing
- **3**/14 : independent PCR +ve, confirmed by sequencing

Haagmans et al Lancet Infect Dis 2014

上月騎駱駝 返港婦疑染「新沙士」

香港文匯報訊（記者 文森）衛生署衛生防護中心昨日宣布，正調查一宗中東呼吸綜合症懷疑個案。有關病人為一名曾去過突尼斯並曾經騎駱駝的59歲女子，本身有長期病患，自4月29日起視覺出現重影，昨日入住那打素醫院，目前情況穩定。

中心初步調查顯示，病人曾於4月26日至5月5日與丈夫到訪突尼斯，往返途中曾於迪拜轉機。她曾於4月28日騎駱駝，而其丈夫至今沒有出現病徵。院方將為病人採集呼吸道樣本作化驗。

衛生署發言人強烈建議營辦中東團的旅行社，不應安排旅客騎駱駝，或參與接觸駱駝的活動，以免增加感染風險。他又提醒長期病患者在旅程中較易出現健康問題，包括中東呼吸綜合症，因應近期的朝覲活動，信徒應於出發前徵詢醫護人員的意見，評估是否適宜前往。

三宗港人新沙士驚魂

本港衛生防護中心接獲三宗懷疑新沙士個案，其中一對夫婦在中東新沙士疫情嚴峻下，仍在當地騎駱駝，返港後不適。幸而最終證實三名病人均無受感染，虛驚一場。本港專家表示，在中東騎駱駝是高感染風險的活動，市民實在不宜進行，「下次未必咁好彩」。

夫婦曾騎駱駝

本港衛生防護中心表示，該對夫婦本月十八日至二十五日到訪突尼斯，並於杜拜轉機。他們於本月十九日到過當地動物園，期間沒有接觸動物，但於二十日騎駱駝。五十三歲丈夫和五十二歲太太先後於本月十九日及二十七日出現呼吸道感染徵狀，昨日留醫瑪嘉烈醫院隔離治療，情況穩定。

至於另一名五十六歲的男子，本月十八日經多哈到訪威尼斯，再乘搭郵輪到訪巴里、希臘、土耳其和克羅地亞，期間沒有接觸過動物。他本月二十二日出現病徵，前日返港，並入住伊利沙伯醫院，情況穩定。

中東呼吸綜合症（新沙士）的疫情愈趨嚴重，其中，沙特阿拉伯新增十六宗確診個案，另有八人死亡，包括一名九個月大嬰兒，令到當地確診病人增至三百三十九人，死亡人數多達一百零二人，單是本月的確診個案有一百四十三宗，三十九人死亡。

綜合外電報道

高永文籲中東旅團停騎駱駝

【明報專訊】中東呼吸綜合症（MERS）至今已在全球累積逾300宗病例，駱駝被指是病毒的宿主，本港食物及衛生局長高永文昨稱，中東呼吸綜合症可人傳人，呼籲本港旅行社停辦當地的騎駱駝活動，免遊客受感染。旅遊業議會表示，大部分本港旅行社中東團已取消騎駱駝活動，部分改爲騎馬。

駱駝或為MERS病毒宿主

衛生防護中心近日呼籲本港旅行業停辦中東團的騎駱駝活動，旅遊業議會總幹事董耀中昨說，騎駱駝活動向來受旅客歡迎，不少中東旅行團都有舉辦，多屬自費活動，大部分旅行團因應呼籲現已取消騎駱駝，部分改爲騎馬。至於若旅客騎駱駝後受感染責任誰屬，董耀中則說因目前難以確認感染源頭，若有團友騎駱駝後感不適，應向當局報告。

高永文昨出席護士協會活動後表示，中東呼吸綜合症在過去一兩個月，病例大爲增加，並已由中東地區傳播至東南亞，本港人流不會少於這些地方，有必要提高防禦。他提醒市民到受影響地區時避免接觸駱駝等野生動物，本港醫護人員亦會爲有呼吸系統病徵、而不能在短時間內對抗菌素藥物治療有合理反應的人，檢查有否染中東呼吸綜合症。

港男女染中東呼吸症

一曾遊地中海 一在多哈工作

香港衛生署衛生防護中心昨晚公布兩宗「中東呼吸綜合症」懷疑個案，兩名患者互不相識，他們曾分別到卡塔爾多哈工作，以及乘郵輪到歐洲和地中海旅遊，途中兩度乘機經多哈，二人在外遊期間皆沒有接觸動物或相關病人，二人病情穩定。衛生署發言人強烈建議營辦中東團的旅行社不應安排旅客騎駱駝，或參與接觸駱駝的活動，以免增加感染風險。另一方面，由於美國近日亦出現首宗中東呼吸綜合症個案，香港衛生署正密切監察美國的情況。 本報港聞部報道

目前，香港至今沒有發現人類感染「中東呼吸綜合症」，但該病已列為香港法定須呈報傳染病。

期間無接觸動物

衛生防護中心昨日分別接獲聖保祿醫院及東區尤德夫人那打素醫院呈報各一宗中東呼吸綜合症懷疑個案，涉及一名35歲男子及一名32歲女子。

該名男病人過往健康良好，自前天起出現發燒、咳嗽、流鼻水、喉嚨痛及肌肉疼痛等病徵，昨日前往聖保祿醫院門診求醫，其後入住東區尤德夫人那打素醫院接受隔離治療，目前情況穩定。衛生防護中心初步調查顯示，病人曾於4月23日至25日到卡塔爾多哈工作，期間沒有接觸動物或病人，亦沒有到過醫療機構。他的家居接觸者沒有出現病徵。

另一宗個案的女病人自4月27日起出現發燒、咳嗽和呼吸困難，她昨日入住東區尤德夫人那打素醫院接受隔離治療，目前情況穩定。衛生防護中心初步調查顯示，病人曾於4月18日至27日與家人乘郵輪到歐洲和地中海旅遊，途中兩度乘機經多哈，期間沒有接觸動物或病人。她的母親和丈夫近日出現流感病徵，並已向私家醫生求診，兩人情況穩定。其餘同遊人士至今沒有出現病徵。院方已為兩名病人採集呼吸道樣本，並將送交衛生防護中心公共衛生化驗服務處作初步化驗。

美出現首宗個案

全球新增愈來愈多「中東呼吸綜合症」個案，在美國亦出現首宗個案。根據美國疾病控制及預防中心及英格蘭衛生部門的資料，這名病人於4月24日從沙特阿拉伯王國利雅得乘英國航空262號班機到英國倫敦，再轉乘美國航空99號班機由倫敦到美國芝加哥，其後再乘巴士到印第安那州。病人於4月27日出現呼吸困難、咳嗽和發燒；4月28日入住當地一醫院接受治療，病人情況穩定，並於5月2日確診中東呼吸綜合症。英國和美國的衛生當局正追蹤上述兩航班的接觸者。

香港衛生防護中心正向世界衛生組織及相關衛生當局跟進個案資料，並會保持警覺，與世衛、海外及鄰近地區的衛生部門緊密合作，監察最新發展。

■「中東呼吸綜合症」病毒。

■衛署強烈建議旅行中東不應參與接觸駱駝的活動，以免增加感染「中東呼吸綜合症」的風險。

Source of MERS-CoV

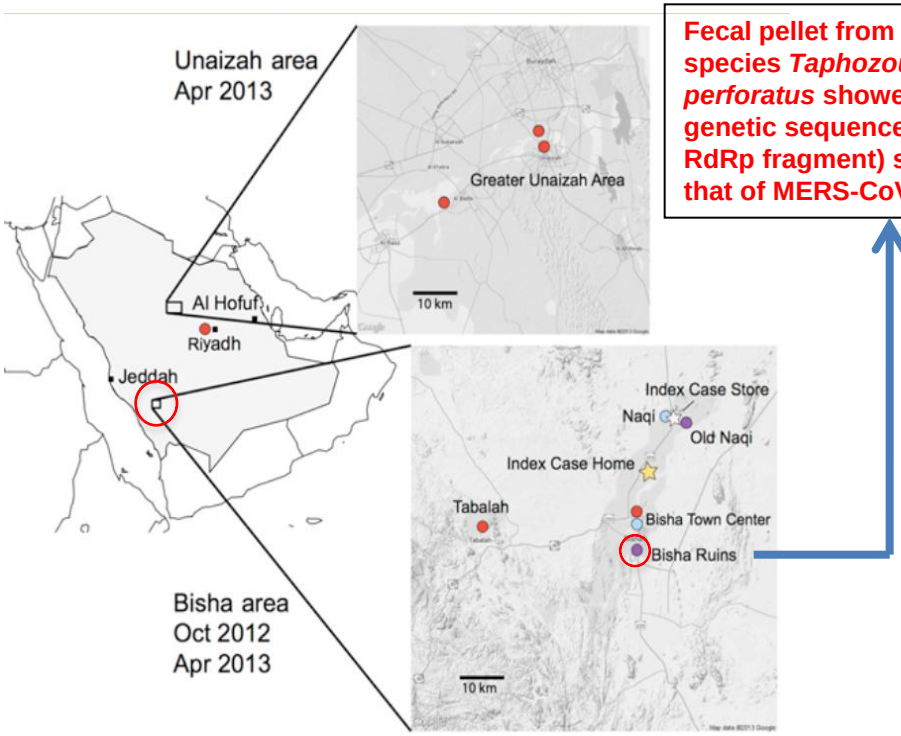
Middle East Respiratory Syndrome Coronavirus in Bats, Saudi Arabia

埃及墓蝠 - ***Taphozous perforatus***
(Egyptian tomb bat)

Roosting bats and guano in abandoned wells and ruins < 12 km of the home of a index case and **insectivorous bats at dusk in the garden** behind his place of employment

→

Collected samples from bats < 12 km, in an **abandoned date palm orchard (棗樹)** and < 1 km from his place of employment (a hardware store fronted a garden and date palm orchard)



Fecal pellet from a Bat species *Taphozous perforatus* showed 100% genetic sequence (190-nt RdRp fragment) similar to that of MERS-CoV

Memish ZA, et al. Emerg Infect Dis 2013

Interim Recommendation on Clinical Management of Cases of Severe Respiratory Disease Associated with Novel Coronavirus

Isolation and notification

- Isolate the patient(s) in single room with Standard, Contact and Airborne precautions
- Notify via NDORS

Baseline investigations

- Test of Novel Coronavirus
  - Upper respiratory tract (NPA, NPS); lower respiratory tract (sputum, tracheal aspirate, BAL) - for patients with pneumonia, lower respiratory tract specimens may have a better diagnostic yield
    - Repeated testing may be necessary to exclude the diagnosis. Please consult the clinical microbiologists or infectious disease physicians for advice
  - Paired serum (acute and convalescent)
- Other microbiological workup
  - Sputum, urine and blood culture
  - NPA for flu A/B and other respiratory viruses
  - NPA for atypical pneumonia PCR
  - Urine for Legionella antigen
  - Other microbiological tests as appropriate
- Other investigations e.g. CBP with D/C, L/RFT, CaPO4, glucose, ESR, CRP, CXR and ECG etc

Interim Recommendation on Clinical Management of Cases of Severe Respiratory Disease Associated with Novel Coronavirus

Empirical antimicrobial agents

- β-lactam/β-lactamase inhibitor combination OR 3rd generation cephalosporin + macrolide
- Respiratory fluoroquinolones for patient with β-lactam allergy

Supportive treatment

- Monitor vital signs and organ functions, and recognize complication(s) early
- Liaise with lCU early for intensive care if anticipate clinical deterioration
- Provide supportive treatments
  - Oxygen
  - IV fluid
  - Inotropic support +/- steroid* (septic shock)
  - Mechanical ventilation +/- ECMO (respiratory failure)
  - Renal dialysis (renal failure)

Specific treatment

- Based on the current scientific evidence, no specific anti-viral treatment can be recommended at the moment (to be updated in accordance to the latest research results and international recommendations)

* Avoid high-dose systemic corticosteroids for viral pneumonitis; consider 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

Public Health England

Treatment of MERS-CoV: Decision Support Tool

ISARIC

Treatment cornerstone

The most important recommendation remains that general supportive care continues to be the keystone of management, as similarly expressed in the Surviving Sepsis Campaign guidelines for the care of the critically ill, and that any additional benefit of novel pharmacological agents remains uncertain, through lack of evidence, rather than lack of plausibility. Treatment with other therapeutic agents should ideally occur in the context of systematic data collection (patient characteristics, severity of illness, other treatments and outcomes), formal observational studies or in controlled trials.

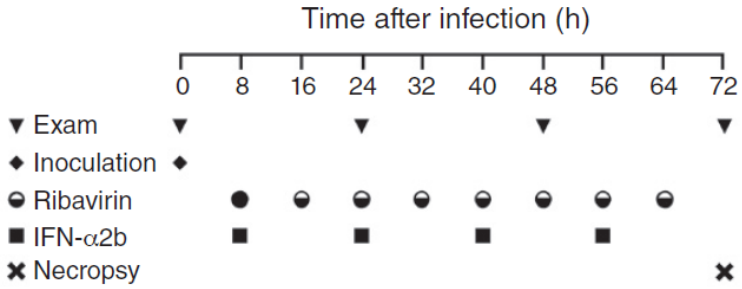
Literature

A list of references is given at the end of this document. This document takes much of the SARS information from the systematic review of SARS treatment performed by Lauren Stockman, Richard Bellamy and Paul Garner published in PLoS Medicine in 2006:

- Stockman LJ, Bellamy R, Garner P (2006) SARS: Systematic review of treatment effects. PLoS Med 3(9): e343. DOI: 10.1371/journal.pmed.0030343

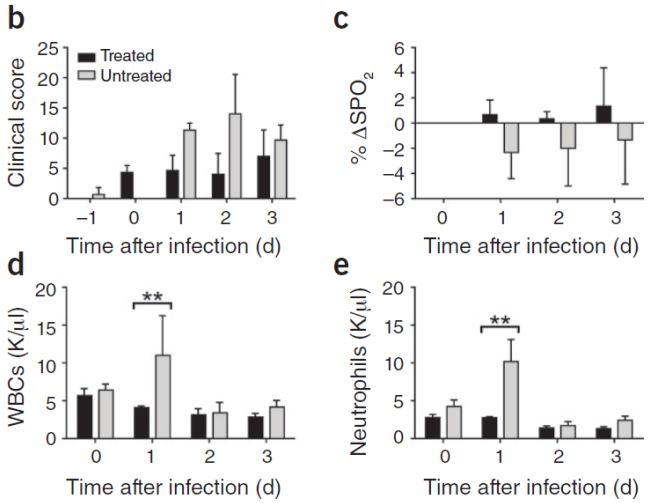
Some information contained herein is unpublished *in vitro* and animal investigatory work on MERS-CoV from several international groups to whom we are indebted. Experts consulted are listed at the end.

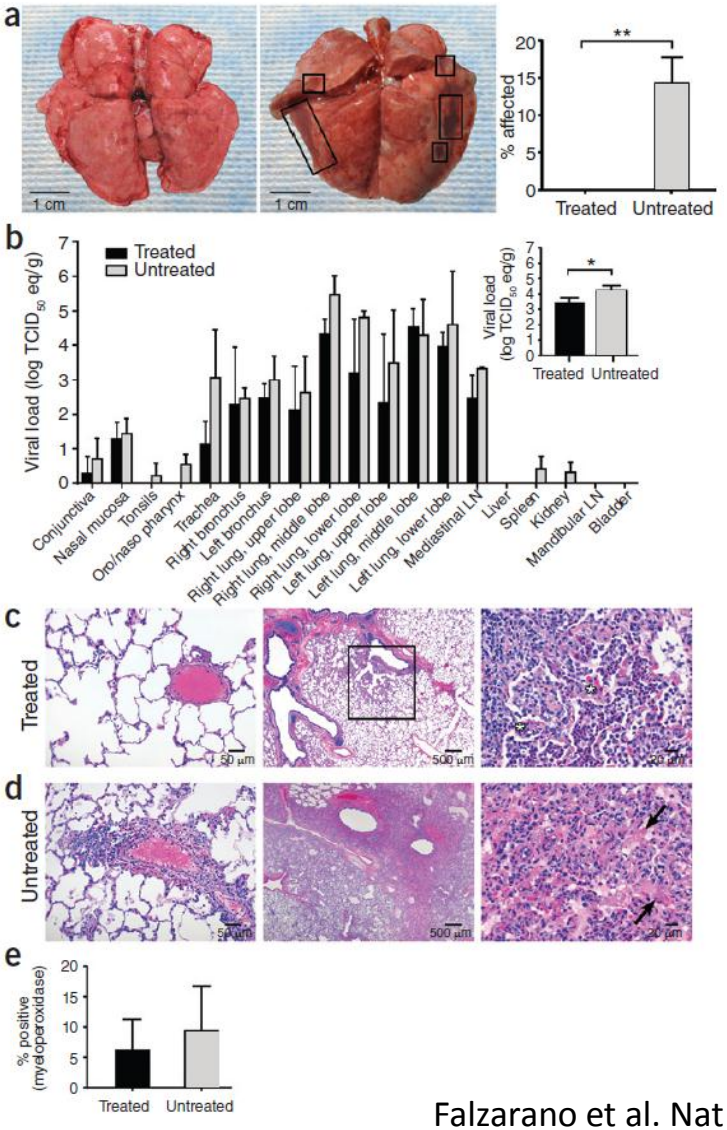
Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV–infected rhesus macaques



Treated animals showed

- lower levels of systemic (serum) and local (lung) proinflammatory markers
- fewer viral genome copies and distinct gene expression
- Less severe histopathological changes in the lungs





Falzarano et al. Nat Med 2013

Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study☆

- All (5) patients were critically ill with acute respiratory distress syndrome treated with adjunctive corticosteroids and were on mechanical ventilation at the time of initiation of therapy

Table 1
Patient demographics and underlying conditions

Case No.	Age, years	Gender	Body weight, kg	Hypertension	Diabetes mellitus	Chronic renal disease	ClCr, ml/min	Dialysis	Other chronic conditions
1	62	F	78	Yes	Yes	Yes	8.5	HD	No
2	58	M	52	Yes	Yes	Yes	15.8	HD	No
3	63	F	96	Yes	Yes	Yes	15.7	No	Asthma, obstructive sleep apnea, coronary artery disease
4	81	M	71	Yes	Yes	Yes	40.7	HD	Atrial fibrillation
5	24	M	58	No	No	Yes	12.8	HD	End-stage renal disease

ClCr, creatinine clearance; F, female; M, male; HD, hemodialysis.

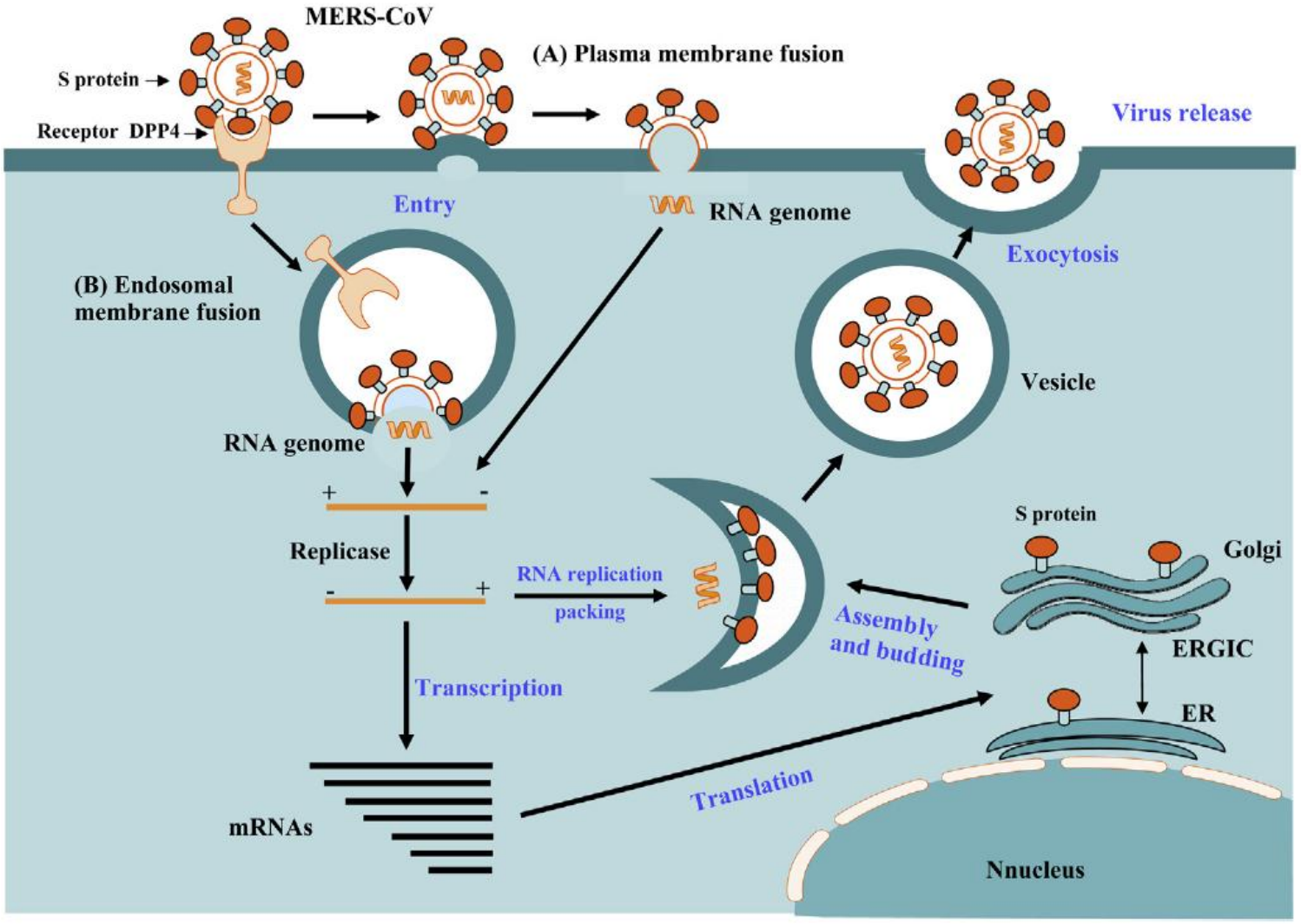
Table 4
Days from admission to initiation of therapy or death

Patient	Days to antiviral therapy	Days to steroid therapy	Days to death
1	21	21	34
2	22	6	35
3	10	0	15
4	19	19	53
5	18	18	33

Median time from admission to therapy with ribavirin and interferon was 19 (range 10–22) days

Al-Tawfiq et al. Int J Inf Dis 2014

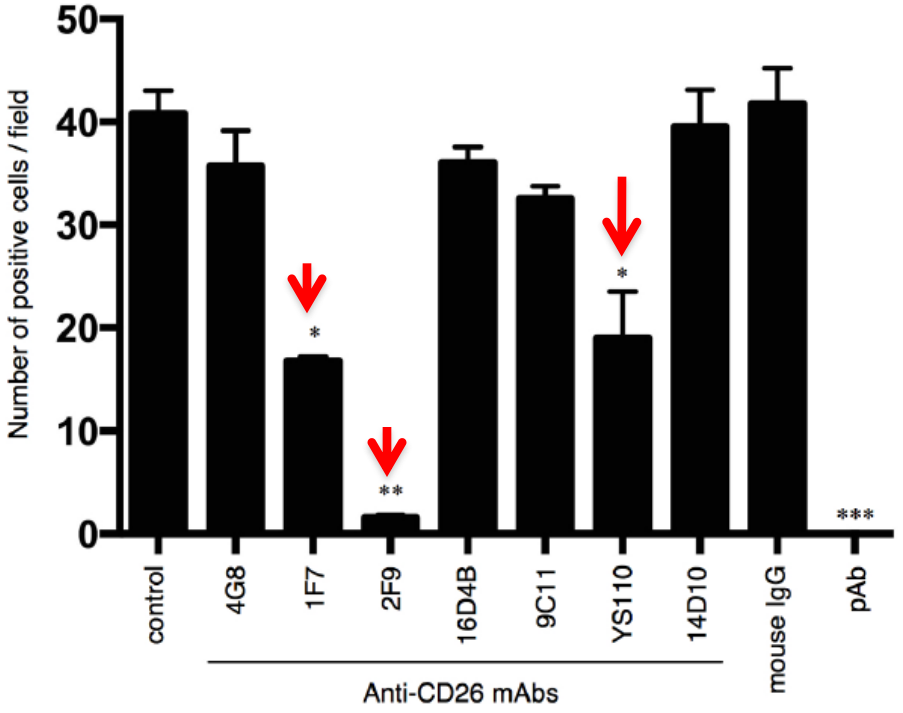
life cycle of MERS-CoV



L. Lu et al. Microbes and Infection 15 (2013) 625-629

Potential treatment options – Anti-CD26 Monoclonal antibodies

- Receptor for entry: DPP4, also call CD26
- Anti-CD26 has been undergoing clinical trial
- Especially one clone, named **2F9**, almost **completely inhibited** viral entry.
- Clone **YS110** also significantly inhibited infection.
- **YS110** is a good candidate for immediate testing as a therapeutic modality for MERS since it has been undergoing phase I trial for CD26 expressing colon cancer
- Preliminary trial showed no major side effect for **Anti-CD26 YS110** clone



Ohnuma K, et al. J Virol 2013 Sep 25. ePub ahead of print

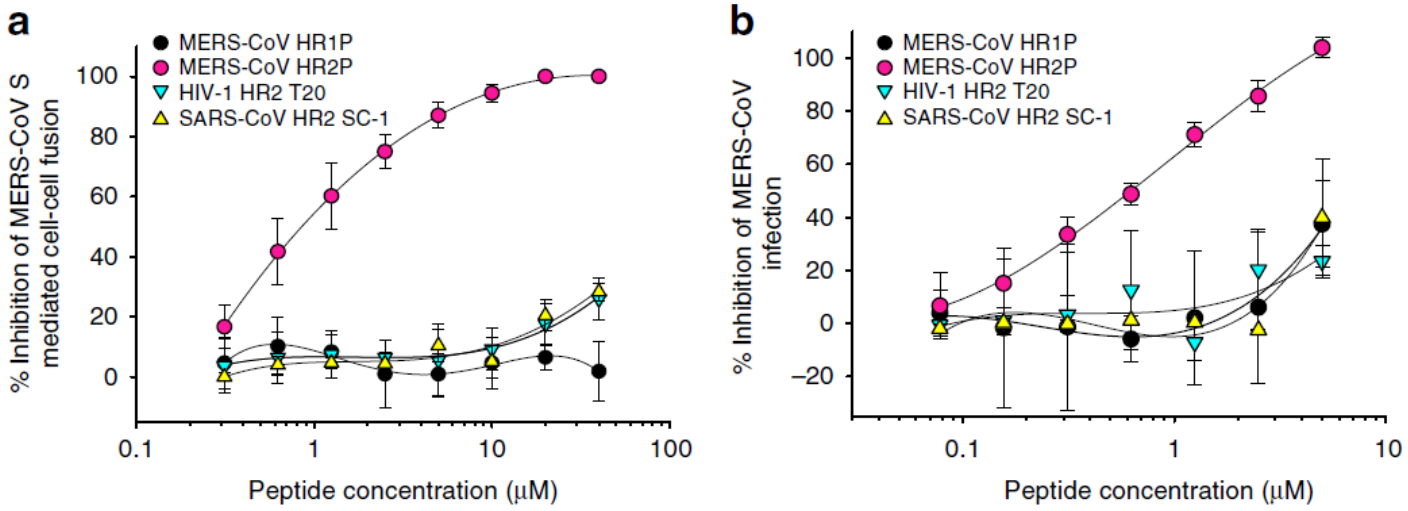
Potential treatment option – fusion inhibitor

ARTICLE

Received 25 Jun 2013 | Accepted 4 Dec 2013 | Published 28 Jan 2014

DOI: 10.1038/ncomms4067

Structure-based discovery of Middle East respiratory syndrome coronavirus fusion inhibitor



Jing Gao J. Virology 2013

Strength of evidence

	Study Focus: *	Quality of Best Available Evidence®	Order of Recommendation¥
Convalescent plasma ≠	SIV; SA; SC; MIV	SC (Moderate)	1
Interferon	SIV; SA; SC; MIV	MIV (Low)	2
Protease Inhibitors	SIV; SA; SC	SIV (Very Low)	2
Intravenous Immunoglobulin	SIV; SA; SC; MIV	Nil	3
Nitazoxanide	Nil	Nil	3
Others e.g. Cyclosporin A	SIV; MIV	MIV (Very Low)	3
Ribavirin	SIV; SA; SC	SIV (Very Low)	4
Corticosteroids	SIV; SA; SC	SA (Low)	4
Interferon plus ribavirin	SIV; SC; MIV; MA	MA (Very Low)	4

≠ Hyperimmune globulin or human neutralising monoclonals when available. The latter were shown active in SARS animal models.

* SARS *in vitro* (SIV); SARS animal (SA); SARS clinical (SC); MERS-CoV *in vitro* (MIV); MERS animal (MA)

¥ Recommendations

1 (Consider for use) = Probable Clinical Effect

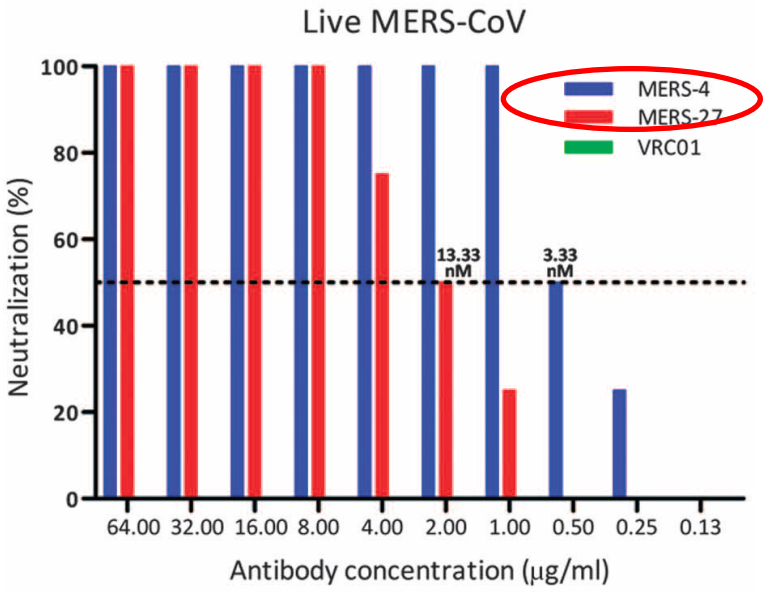
2 (Do Not Consider for use outside of an appropriately planned evaluation of effectiveness) = Potential Clinical Effect or Proven *In Vitro* Effects with Some Potential Side Effects

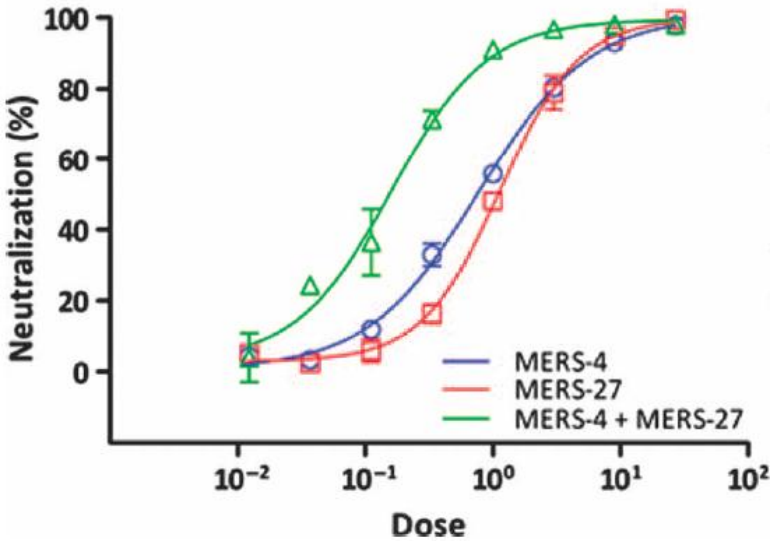
3 (Do Not Consider for use at this time outside of an RCT) = Little or No Evidence of Either *In Vitro* or Clinical Effect

4 (Do Not Consider for use at this time outside of an RCT) = Suggested Clinical Effect or Proven *In Vitro* Effect with Potential Serious Side Effects

Potential treatment option – monoclonal antibodies to spike protein

Potent Neutralization of MERS-CoV by Human Neutralizing Monoclonal Antibodies to the Viral Spike Glycoprotein





Jiang LW et al Science Trans Med 2014

Conclusion

- MERS-CoV is a novel coronavirus causing high mortality in Middle East
- Spreading to the other countries in other continents
- Limited human to human transmission
- Treatment are largely supportive at the moment, although specific treatment and vaccine are under investigation