Middle East Respiratory Syndrome (MERS) – situation update & review on current literature

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What is MERS?

- An acute respiratory illness caused by MERS coronavirus (MERS-CoV)
- First identified in Saudi Arabia in June, 2012
- Formerly known as HCoV-EMC (Erasmus Medical Centre)
- Classification of coronaviruses known to be causing human infections:
  - Alpha coronavirus: NL63, HCoV-229E
  - Beta coronavirus: HCoV-OC43, HCoV-HKU1, MERS-CoV (lineage c), and SARS-CoV (lineage b)
- Manifestation range from asymptomatic or mild to severe and life-threatening

Receptor:
Dipeptidyl peptidase 4 (DPP4; also known as CD26)
Epidemiology

- Between 2012 and 7 July 2015, **1368 laboratory-confirmed cases** reported to WHO
- 65% are male and the median age is 50 years (9 months–99 years)

26 Countries with Lab-Confirmed MERS Cases:

- **Countries in or near the Arabian Peninsula with MERS cases**: Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, **Saudi Arabia**, **United Arab Emirates (UAE)**, and Yemen.
- **Countries with travel-associated MERS cases**: Algeria, Austria, China, Egypt, France, Germany, Greece, Italy, Malaysia, Netherlands, Philippines, Republic of Korea, Thailand, Tunisia, Turkey, United Kingdom (UK), and United States of America (USA).

**Majority of the cases including clusters**

**Limited human to human transmission among close contacts of index cases**

CDC (accessed on 12 July 2015)
Number of cases of Middle East Respiratory Syndrome in affected areas (Middle East and Korea) since 2012 (as of July 6, 2015)

(For unaffected areas with imported or import-related cases, please refer to the World Health Organization’s website http://www.who.int/csr/disease/coronavirus_infections/mers-cov-global-situation-map-2015-07-03.png?ua=1)
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<th>Country</th>
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<tr>
<td><strong>Total</strong></td>
<td>9</td>
<td>168</td>
<td>768</td>
<td>423</td>
<td>1368</td>
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</table>
Figure 1. Epidemic curve of MERS-CoV cases (n=1368) (as of 7 July 2015)
Figure: The epidemiology of Middle East respiratory syndrome coronavirus

Black arrows represent unconfirmed routes of transmission. Red arrows represent plausible routes of transmission. Red human figures represent people infected with Middle East respiratory syndrome.
Role of camels in transmission

- Current belief is that dromedary camels are the intermediate hosts and an important source of human infection
  - Positive RT-PCR from nasal swab of camels
  - Viral sequence identical to infected human case
  - Serological evidence in camels of Saudi Arabia dating back to 1993
  - Significantly higher seroprevalence among camel-exposed individuals than the general population in Saudi Arabia
  - Juvenile camels have higher viral load indicating higher risk of transmission
  - However only about 13% of the cases have reported recent direct contact with camels
  - Potential route of acquiring the infection is respiratory, fecal oral, or direct contact but the exact mechanism is still under investigation

ECDC updated rapid risk assessment on MERS
WHO MERS CoV summary and literature update
Lancet Infectious Diseases. 2015 May;15(5):559-64.
Evidence suggesting bats as reservoirs

- Related coronaviruses can be easily found in several bat species
- Part of the sequence in fecal pellet of *Taphozous perforatus* bat in Saudi Arabia was identical to index case
- MERS-CoV grows easily in bat cell lines

*Emerging Infectious Diseases* Vol. 19, No. 11, November 2013
*MBio.* 2012;3(6)
Sac-winged bat

Sac-winged bats

Scientific classification

These bats prefer to roost in areas generally lighter than other species of bats. Their dwellings can often be found in hollow trees and entryways to caves or other structures. Some, such as the tomb bats, live in large roosts, but others are solitary. Species living away from the tropics may become torpid, or even hibernate in winter.

Sac-winged bats feed mainly on insects, and occasionally on fruit. Most of these bats, such as ghost bats, catch their meals while flying; the proboscis bat, on the other hand, catches its prey above water surfaces.

List of species

Family Emballonuridae

Genus Balantiopteryx
- Ecuadorian sac-winged bat, *Balantiopteryx nubicalo*
- Thomas's sac-winged bat, *Balantiopteryx thomasi*
- Grey sac-winged bat, *Balantiopteryx pliacta*

Genus Cornyctertis
- Thomas's shaggy bat, *Cornyctertis centralis*
- Shaggy bat, *Cornyctertis maculiformis*

Genus Colobus
- African sheath-tailed bat, *Cololobus afer*
- Seychelles sheath-tailed bat, *Cololobus seychellensis*
- Greater sac-winged bat, *Corniglans brevirostris*
- Corniglans

See text

- Short-eared bat, *Cynopterus alberto*
- Genus Dicliduris - ghost bats
  - Northern ghost bat, *Dicliduris albus*
  - Greater ghost bat, *Dicliduris ingens*
  - Isabelle's ghost bat, *Dicliduris tuberculosis*
  - Lesser ghost bat, *Dicliduris scutata*

Genus Emballonura
- Small Asian sheath-tailed bat, *Emballonura alecto*
- Peter's sheath-tailed bat, *Emballonura atrata*
- Beccari's sheath-tailed bat, *Emballonura beccarii*
- Large-sheathed bat, *Emballonura dives*
- Greater sheathed bat, *Emballonura furax*
- Lesser sheathed bat, *Emballonura monticola*
- Kaffray's sheathed bat, *Emballonura rafflesii*
- Pacific sheathed bat, *Emballonura semicandens*
- Sen's sheath-tailed bat, *Emballonura senni*
- Western sheathed bat, *Emballonura thoraci*

Genus Mensa
- Dark sheathed bat, *Menega cristata*

Genus Peropygus
- Greater dog-like bat, *Peropygus hypolagi*
- White-winged dog-like bat, *Peropygus leucopoma*
- Lesser dog-like bat, *Peropygus micropterus*
- Pale-winged dog-like bat, *Peropygus pallipumma*
- Trinidad dog-like bat, *Peropygus trinidadensis*

Genus Rhyynchocitrus
- Proboscis bat, *Rhyynchocitrus musum*

Genus Saccoleucus
- Yellow-billed toucan bat, *Saccoleucus flavicollis*
- Trougthou's pouched bat, *Saccoleucus mixtus*
- Pelt's pouched bat, *Saccoleucus pelii*
- Naked-rumped pouched bat, *Saccoleucus saccoleucus*

Genus Saccopteryx
- Antilopan sac-winged bat, *Saccopteryx antilopae*
- Greater sac-winged bat, *Saccopteryx hildegardeic*
- Frosted sac-winged bat, *Saccopteryx canescens*
- Amazonian sac-winged bat, *Saccopteryx gymnea*
- Lesser sac-winged bat, *Saccopteryx leucura*

Genus Taphochoerus
- Indonesian tomb bat, *Taphochoerus achatos*
- Coastal sheath-tailed bat, *Taphochoerus australis*
- Common sheath-tailed bat, *Taphochoerus georgianus*
- Hamilton's tomb bat, *Taphochoerus hamiltonii*
- Hildegarde's tomb bat, *Taphochoerus hildegardei*
- Hill's sheath-tailed bat, *Taphochoerus hillii*
- Amhbita sheath-tailed bat, *Taphochoerus rapincaus*
- Long-winged tomb bat, *Taphochoerus longipennis*
- Mammuth tomb bat, *Taphochoerus mammuthus*
- Black-billed tomb bat, *Taphochoerus melanosomus*
- Naked-rumped tomb bat, *Taphochoerus multicornis*
- Egyptian tomb bat, *Taphochoerus pachypus*
- Theobold's tomb bat, *Taphochoerus theobaldi*
- Trougthou's sheath-tailed bat, *Taphochoerus trouchtoni*
Occasional Human-to-human transmission

- Has been observed to a limited extent in households
  - Rate of transmission among household contacts approximately 5% based on 2013 findings
- More common in health care settings
  - In Middle East mid 2014
  - Korean “superspreading events”
- To date, there is no evidence of sustained human-to-human transmission.

WHO MERS-CoV Summary of Current Situation, Literature Update and Risk Assessment, 7 July 2015
### Table 1

<table>
<thead>
<tr>
<th>Author/country/year</th>
<th>Setting</th>
<th>Number of cases (labouratory confirmed/probable)</th>
<th>Number of HCWs (% of total cases)</th>
<th>Nurses (% of HCWs)</th>
<th>Median age of cases, years (range)</th>
<th>Median age of HCWs, years (range)</th>
<th>Fatal cases (% of total)</th>
<th>Fatalities in HCWs (% of HCWs)</th>
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</thead>
<tbody>
<tr>
<td>Hijawi et al. and Al-Abdallat et al. [20]</td>
<td>ICU, CCU, medical and emergency wards</td>
<td>13 (8/5)*</td>
<td>10 (76.9)</td>
<td>8 (80)</td>
<td>33 (25-65)</td>
<td>31.5 (25-47.5)</td>
<td>2 (15.4)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Arabi et al. [21]</td>
<td>Saudi Arabia/2012-2013 Medical-surgical ICUs, 1 cardiac ICU</td>
<td>15 (14/1)</td>
<td>4 (26.7)</td>
<td>4 (100)</td>
<td>59 (36-83)</td>
<td>36 (1 HCW with data)</td>
<td>7 (46.6)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Assiri et al. [22]</td>
<td>Saudi Arabia/2013 Hemodialysis unit, ICUs, medical wards</td>
<td>34 (23/11)</td>
<td>2 (5.9)</td>
<td>1 (50)</td>
<td>56 (24-94)</td>
<td>43.5 (42-45)</td>
<td>15 (65)</td>
<td>0 (0)</td>
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<td>Memish et al. [23]</td>
<td>Saudi Arabia/2012-2013</td>
<td>NR</td>
<td>7 (7/0)</td>
<td>7 (100)</td>
<td>6 (86)</td>
<td>n/a</td>
<td>42 (28-59)</td>
<td>n/a</td>
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<td>Guery et al. [24]</td>
<td>France/2013 Medical ward</td>
<td>2 (2/0)</td>
<td>0 (0)</td>
<td>n/a</td>
<td>57.5 (51-64)</td>
<td>n/a</td>
<td>1 (50)</td>
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<td>Omran et al. [25]</td>
<td>Saudi Arabia/2013 Emergency department/rooms</td>
<td>3 (2/1)</td>
<td>0 (0)</td>
<td>n/a</td>
<td>40 (39-51)</td>
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<td>2 (66.7)</td>
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<td>Tsiodrias et al. [26]</td>
<td>Greece/2014 Extensive contact with the health care environment in Jeddah</td>
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<td>69</td>
<td>n/a</td>
<td>0 (0)</td>
<td>n/a</td>
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</table>

CCU, coronary care unit; HCW, health care worker; ICU, intensive care unit; MERS-CoV, Middle East respiratory syndrome coronavirus; n/a, nonapplicable; NR, not reported; PPE, protective equipment; WHO, World Health Organization.

*Data about laboratory confirmation were obtained from Al-Abdallat et al. [20]; the remaining data were obtained from Hijawi et al. [20].

*Median age and range concerns the 12 critically ill patients out of the 15 MERS-CoV infected cases.
Routes of Transmission

- **Inhalation**
  - Most infected patients develop prominent respiratory symptoms
  - Virus easily found in respiratory tract
  - Coronavirus is mainly spread by the inhalational route
  - Asymptomatic healthcare worker contact has been reported to shed for more than 5 weeks

- **Direct contact**
  - Vomitus, feces, urine
  - Fomite

*Important implications for Infection Control*
Viability over time of Middle East respiratory syndrome coronavirus (MERS-CoV) and Influenza A/Mexico/4108/2009 (H1N1) virus under different environmental conditions

More stable at low temp & humidity

No decrease in stability upon aerosolisation
How transmissible is MERS-CoV?

- Not very transmissible in general
  - Negative serological evidence among camel herders and slaughterhouse workers in Saudi Arabia
  - No sustained human-to-human transmission apart from small clusters in healthcare and household settings
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

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.

Cases of Middle East respiratory syndrome (MERS) in humans continue to be reported from the Arabian

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

Group 1 comprised 4 herdsmen who were in daily contact with the infected herd (feeding, grooming, administering treatment when needed). They frequently consumed fresh unboiled milk from the camels, of which at least 1 dam and 7 calves were retrospectively confirmed to have been MERS-CoV infected (4).

Group 2 comprised 8 persons who had intermittent but regular (several times/week) direct contact with the infected herd (animal management, feeding, manure removal) and included veterinary staff and attendants. Because this
Interhuman transmissibility of Middle East respiratory syndrome coronavirus: estimation of pandemic risk

Romulus Breban, Julien Riou, Arnaud Fontanet

Summary

Background The new Middle East respiratory syndrome coronavirus (MERS-CoV) infection shares many clinical, epidemiological, and virological similarities with that of severe acute respiratory syndrome (SARS)-CoV. We aimed to estimate virus transmissibility and the epidemic potential of MERS-CoV, and to compare the results with similar findings obtained for prepandemic SARS.

Methods We retrieved data for MERS-CoV clusters from the WHO summary and subsequent reports, and published descriptions of cases, and took into account 55 of the 64 laboratory-confirmed cases of MERS-CoV reported as of June 21, 2013, excluding cases notified in the previous 2 weeks. To assess the interhuman transmissibility of MERS-CoV, we used Bayesian analysis to estimate the basic reproduction number ($R_0$) and compared it to that of prepandemic SARS. We considered two scenarios, depending on the interpretation of the MERS-CoV cluster-size data.

Results With our most pessimistic scenario (scenario 2), we estimated MERS-CoV $R_0$ to be 0.69 (95% CI 0.50–0.92); by contrast, the $R_0$ for prepandemic SARS-CoV was 0.80 (0.54–1.13). Our optimistic scenario (scenario 1) yielded a MERS-CoV $R_0$ of 0.60 (0.42–0.80). Because of recent implementation of effective contact tracing and isolation procedures, further MERS-CoV transmission data might no longer describe an entire cluster, but only secondary infections directly caused by the index patient. Hence, we calculated that, under scenario 2, eight or more secondary infections caused by the next index patient would translate into a 5% or higher chance that the revised MERS-CoV $R_0$ would exceed 1—ie, that MERS-CoV might have pandemic potential.

Interpretation Our analysis suggests that MERS-CoV does not yet have pandemic potential. We recommend enhanced surveillance, active contact tracing, and vigorous searches for the MERS-CoV animal hosts and transmission routes to human beings.
Figure 1: Stages of the Hajj

1 Makkah
Pilgrims circumambulate the Ka’aba (Tawaf) seven times, while reciting prayers, and then briskly walk between the hills of Safa and Marwah seven times (Sa’i). Afterwards, the pilgrims proceed to Mina.

2 Mina
Pilgrims do five daily prayers, starting with Fajr (morning prayer) and ending with Isha (evening prayer), and spend most of their time reading the Quran. Pilgrims then make their way to Mount Arafat.

3 Mount Arafat
Pilgrims devote their time to prayer from sunrise to dusk, while living in tents. They leave for Muzdalifah after sunset.

4 Muzdalifah
Pilgrims gather pebbles for the Jamarat ceremony in which pebbles are thrown at three stone pillars (symbolic of the devil). Before the sun rises, the pilgrims set off on their return to Mina.

5 Mina

6 Makkah
Pilgrims return to Makkah for the final Tawaf (seven times) and Sa’i (seven times).

On return to Mina, at the start of Eid-al-Adha festival, pilgrims participate in the Jamarat ceremony. An animal sacrifice is made and the meat is distributed to people who are poor. Men shave off the hair on their heads before doing prayers for Eid-al-Adha.
When to suspect MERS?

- Incubation period:
  - outbreak in Saudi Arabia, the median incubation period was 5.2 days (95% CI 1.9-14.7 days)
  - outbreak in South Korea, the median incubation period was 6.3 days

- For epidemiological purposes, the incubation period is taken as **2-14 days** before onset of illness
Case definition for reporting: Middle East Respiratory Syndrome  
(last updated on 8 June 2015)  

In view of the evolving situation in Korea, the epidemiological criteria for reporting of suspected case of MERS is updated as follows:

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Epidemiological criteria</th>
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<tbody>
<tr>
<td>A person with fever not explained by any other aetiology;</td>
<td>One or more of the followings within 2-14 days before onset of illness</td>
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<tr>
<td>OR</td>
<td>close contact* with a confirmed or probable case of Middle East Respiratory Syndrome while the case was ill</td>
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<tr>
<td>A person with clinical feature(s) of lower respiratory tract infection not explained by any other aetiology; OR</td>
<td>OR</td>
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<tr>
<td>An immunocompromised patient with diarrhoea not explained by any other aetiology</td>
<td>residence in or history of travel to the Arabian Peninsula or neighboring countries (i.e., Bahrain, Iran, Iraq, Israel, Jordan, Kingdom of Saudi Arabia, Kuwait, Lebanon, Oman, Qatar, State of Palestine, Syria, United Arab Emirates, and Yemen) or Korea</td>
</tr>
</tbody>
</table>

*Close contact is defined as
Anyone who provided care for the patient, including a health care worker or family member, or who had other similarly close physical contact;
Anyone who stayed at the same place (e.g. lived with, visited) as a probable or confirmed case while the case was ill.
Among 47 patients with MERS-CoV infection in Saudi Arabia:

- **Fever** (>38°C) – 46 patients (98 %)
- **Fever with chills or rigors** – 41 patients (87 %)
- **Cough** – 39 patients (83 %)
- **Shortness of breath** – 34 patients (72 %)
- **Hemoptysis** – 8 patients (17 %)
- **Sore throat** – 10 patients (21 %)
- **Myalgias** – 15 patients (32 %)
- **Diarrhea** – 12 patients (26 %)
- **Vomiting** – 10 patients (21 %)
- **Abdominal pain** – 8 patients (17 %)
- **Abnormal chest radiograph** – 47 patients (100 %)

42 (89 %) required intensive care and 34 (72 %) required mechanical ventilation

Can be the presenting symptom in immunocompromised patients
<table>
<thead>
<tr>
<th>Patient</th>
<th>Comorbid Condition</th>
<th>Presenting Symptoms</th>
<th>Sex</th>
<th>Age, y</th>
<th>Health Care-Associated</th>
<th>Invasive Ventilation</th>
<th>NIPPV</th>
<th>HFOV</th>
<th>ECMO</th>
<th>NO</th>
<th>Prone Positioning</th>
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<td>Fever, cough, dyspnea</td>
<td>M</td>
<td>83</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>B</td>
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<tr>
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</tr>
<tr>
<td>D</td>
<td>Neuromuscular disease</td>
<td>Fever, cough, dyspnea, myalgia, sputum production, sore throat</td>
<td>M</td>
<td>66</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>E</td>
<td>DM, hypertension</td>
<td>Fever, cough, dyspnea, bloody sputum, rhinorrhea</td>
<td>M</td>
<td>69</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>F</td>
<td>DM, hypertension</td>
<td>Fever, cough, dyspnea, sputum production</td>
<td>F</td>
<td>40</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>G</td>
<td>DM, renal insufficiency</td>
<td>Cough, dyspnea, wheezing</td>
<td>M</td>
<td>57</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>H</td>
<td>Dialysis, kidney and liver transplant, pericardectomy</td>
<td>Diarrhea, myalgia, cough, dyspnea</td>
<td>M</td>
<td>50</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>I</td>
<td>DM, MI, CABG</td>
<td>Fever, dyspnea, abdominal pain, diarrhea, decreased level of consciousness</td>
<td>F</td>
<td>66</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>J</td>
<td>MI, CHF, renal insufficiency</td>
<td>Fever, cough, dyspnea, myalgia, headache</td>
<td>M</td>
<td>41</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>K</td>
<td>DM, hypertension, CHF, post-AVR and CABG</td>
<td>Dyspnea</td>
<td>F</td>
<td>59</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>L</td>
<td>Asthma</td>
<td>Fever, cough, dyspnea, headache, wheezing</td>
<td>M</td>
<td>36</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

+ = yes; - = no; AVR = aortic valve replacement; CABG = coronary artery bypass graft; CHF = congestive heart failure; CVA = cerebrovascular accident; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; F = female; HFOV = high-frequency oscillation ventilation; M = male; MI = myocardial infarction; NIPPV = noninvasive positive-pressure ventilation; NO = nitric oxide.
A summary of demographics of major MERS-CoV studies

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Median age (range)</th>
<th>Male-to-female ratio</th>
<th>Percentage asymptomatic</th>
<th>Percentage severe cases</th>
<th>Case fatality rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>56 (24–94)</td>
<td>2.8:1</td>
<td>0</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>47</td>
<td>NA</td>
<td>3.3:1</td>
<td>0</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>133</td>
<td>NA</td>
<td>1.5:1</td>
<td>13.5</td>
<td>86.5</td>
<td>45</td>
</tr>
<tr>
<td>161</td>
<td>50 (14–94)</td>
<td>1.8:1</td>
<td>11.1</td>
<td>63.4</td>
<td>–</td>
</tr>
<tr>
<td>402</td>
<td>46 (0.75–94)</td>
<td>1.4:1</td>
<td>28.6</td>
<td>44.5</td>
<td>28.3</td>
</tr>
<tr>
<td>113</td>
<td>41 (0.25–89)</td>
<td>1.3:1</td>
<td>28.9</td>
<td>NA</td>
<td>30</td>
</tr>
</tbody>
</table>
MERS in children

- Mostly mild or asymptomatic presentation, though severe disease can occur in children with underlying conditions
- Appears to be uncommon among children < 2 years of age in the Middle East in 2010 - 2012
- However, only a very small number of cases have been reported
Comparison with SARS

- Both are zoonotic diseases originating from bats
- Human receptor for SARS is hACE receptor -2
- Clinical features are similar, but MERS progresses to respiratory failure much more rapidly than SARS, which affects young people more
- Although the estimated pandemic potential of MERS is lower than SARS, case fatality rate of MERS is higher, likely due to older age and presence of comorbidities

Perlman S, Zhao J. 2013. Human coronavirus EMC is not the same as severe acute respiratory syndrome coronavirus. mBio 4(1)
### Table 1. Comparison of demographic, clinical and laboratory features between MERS-CoV and SARS-CoV outbreaks

<table>
<thead>
<tr>
<th></th>
<th>MERS-CoV [8,36**–39**]</th>
<th>SARS-CoV [1,28,40]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of first case report (place)</strong></td>
<td>April 2012 (Jordan)</td>
<td>November 2002 (China)</td>
</tr>
<tr>
<td><strong>Incubation period</strong></td>
<td>Mean: 5.2 days (95% CI: 1.9–14.7) Range: 2–13 days</td>
<td>Mean: 4.6 days (95% CI: 3.8–5.8) Range: 2–14 days</td>
</tr>
<tr>
<td><strong>Serial interval</strong></td>
<td>7.6 Days</td>
<td>8.4 Days</td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td>Adults (98%)</td>
<td>Adults (93%)</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td>Children (2%)</td>
<td>Children (5–7%)</td>
</tr>
<tr>
<td><strong>Age (years): range, median</strong></td>
<td>Range: 1–94; median: 50</td>
<td>Range: 1–91; mean: 39.9</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Case fatality rate (CFR)—overall</strong></td>
<td>41.8%</td>
<td>9.6%</td>
</tr>
<tr>
<td><strong>CFR in patients with comorbidities</strong></td>
<td>13.3%</td>
<td>1–2%</td>
</tr>
<tr>
<td><strong>Time from onset to death</strong></td>
<td>Median 11.5 days</td>
<td>Mean 23.7 days</td>
</tr>
<tr>
<td><strong>Sex [M, F]</strong></td>
<td>M: 64.5%, F: 35.5%</td>
<td>M: 43%, F: 57%</td>
</tr>
<tr>
<td><strong>Presenting symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fever &gt;38°C</strong></td>
<td>98%</td>
<td>99–100%</td>
</tr>
<tr>
<td><strong>Chills/rigors</strong></td>
<td>87%</td>
<td>15–73%</td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td>83%</td>
<td>62–100%</td>
</tr>
<tr>
<td><strong>Dry</strong></td>
<td>56%</td>
<td>29–75%</td>
</tr>
<tr>
<td><strong>Productive</strong></td>
<td>44%</td>
<td>4–29%</td>
</tr>
<tr>
<td><strong>Haemoptysis</strong></td>
<td>17%</td>
<td>0–1%</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>11%</td>
<td>20–56%</td>
</tr>
<tr>
<td><strong>Myalgia</strong></td>
<td>32%</td>
<td>45–61%</td>
</tr>
<tr>
<td><strong>Malaise</strong></td>
<td>38%</td>
<td>31–45%</td>
</tr>
<tr>
<td><strong>Shortness of breath</strong></td>
<td>72%</td>
<td>40–42%</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>21%</td>
<td>20–35%</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>21%</td>
<td>20–35%</td>
</tr>
<tr>
<td><strong>Diarrhoea</strong></td>
<td>26%</td>
<td>20–25%</td>
</tr>
<tr>
<td><strong>Sore throat</strong></td>
<td>14%</td>
<td>13–25%</td>
</tr>
<tr>
<td><strong>Rhinorrhoea</strong></td>
<td>6%</td>
<td>2–24%</td>
</tr>
</tbody>
</table>

---

Cont’d

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>76%</th>
<th>10–30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>10%</td>
<td>24%</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>13%</td>
<td>2–6%</td>
</tr>
<tr>
<td>Chronic heart disease</td>
<td>7.5%</td>
<td>10%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34%</td>
<td>19%</td>
</tr>
<tr>
<td>Obesity</td>
<td>17%</td>
<td>N/A</td>
</tr>
<tr>
<td>Smoking</td>
<td>23%</td>
<td>17%</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>Not known</td>
<td>27%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory results</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR abnormalities</td>
<td>100%</td>
<td>94–100%</td>
</tr>
<tr>
<td>Leukopenia (≤4.0 × 10⁹/l)</td>
<td>14%</td>
<td>25–35%</td>
</tr>
<tr>
<td>Lymphopenia (≤1.5 × 10⁹/l)</td>
<td>32%</td>
<td>68–85%</td>
</tr>
<tr>
<td>Thrombocytopenia (≤140 × 10⁹/l)</td>
<td>36%</td>
<td>40–45%</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>48%</td>
<td>50–71%</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>11%</td>
<td>20–30%</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>14%</td>
<td>20–30%</td>
</tr>
<tr>
<td>Ventilatory support required</td>
<td>80%</td>
<td>14–20%</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CXR, chest X-ray; KSA, Kingdom of Saudi Arabia; LDH, lactate dehydrogenase; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus.
Molecular pathology of emerging coronavirus infections

Figure 2. Model of an infected alveolus in the lung. Type I and type II pneumocytes make up the alveolar walls and resident alveolar macrophages and pulmonary surfactant exist in the airspace (A). In the acute phase of SARS-CoV infection (B), type I and type II pneumocytes are infected and secrete inflammatory cytokines, while surfactant levels decrease. During the late stage/tissue damage portion of viral infection, viral titres decrease, while airway debris, pulmonary oedema and hyaline membrane formation all impede respiration (C).
Severe acute respiratory syndrome (SARS) coronavirus pneumonia

Chest radiograph shows asymmetric bilateral consolidation involving mainly the middle lung zones.


High-resolution computed tomography (CT) scan shows extensive bilateral ground-glass opacities. The patient was a 48-year-old man with SARS coronavirus pneumonia.

Imaging findings at presentation in Saudi patients with Middle East respiratory syndrome coronavirus infection
Diagnostic tests

- **Lower + Upper respiratory tract specimens for RT-PCR**
- Blood test for serology (1st one taken within first week of illness and 2nd one taken 10-14 days later)
- Other adjunctive tests: stool for RT-PCR (unexplained diarrhea in an immunocompromised host)
- Repeat testing is helpful for confirming clearance of the virus. Tested every two to four days until two consecutive negative results
- Also repeat testing in case of clinical suspicion but initial testing is negative
<table>
<thead>
<tr>
<th>Patient</th>
<th>Test</th>
<th>Type of sample</th>
<th>Timing</th>
<th>Storage and transportation</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>RT-PCR</td>
<td>Lower respiratory tract</td>
<td>Collect on presentation. To confirm clearance of the virus, sample collection to be repeated until the results are negative on 2 sequential samples.</td>
<td>If the specimen will reach the laboratory in less than 72 hours, store and ship at 4°C. If the specimen will reach the laboratory in more than 72 hours, store at -80°C and ship on dry ice or liquid nitrogen.</td>
<td>Follow international regulations and triple package system for transportation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper respiratory tract</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- nasopharyngeal and oropharyngeal swabs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- nasopharyngeal wash/nasopharyngeal aspirate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum for virus detection</td>
<td>(particularly if lower respiratory tract specimens are not available.) For monitoring the distribution of virus in the body: other sample types, stool, urine.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Serology</td>
<td>Serum for serological testing.</td>
<td>Paired samples are necessary for confirmation with the initial sample collected in the first week of illness and the second ideally collected 2-3 weeks later. If only a single serum sample can be collected, this should occur at least 14 days after onset of symptoms for determination of a probable case.</td>
<td>As above.</td>
<td>As above.</td>
</tr>
<tr>
<td>Asymptomatic Contact</td>
<td>PCR</td>
<td>Nasopharyngeal and oropharyngeal swabs; sputum if possible.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-----</td>
<td>------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Within 14 days of last documented contact.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology</td>
<td>Serum</td>
<td>Baseline serum taken within 14 days of last documented contact and convalescent serum taken 2-3 weeks later. If only a single sample is possible, collect at least 14 days after last documented contact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>As above.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>As above.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. Algorithm for testing cases under investigation for MERS-CoV by rRT-PCR

Case under investigation

Screening assay (e.g. Up E gene rRT-PCR)

Positive

Confirmatory assay (e.g. ORF 1a, ORF 1b, or N gene rRT-PCR)

Positive

Confirmed case

Further specimens should be collected, and if necessary, referred to a laboratory with greater experience of testing for MERS-CoV

Negative

RdRp-Seq or NSeq sequencing assay

Indicates MERS-CoV

Confirmed case

Indicates other sequences

Negative

Confirmed case

Negative

Collect further specimens and repeat tests if clinical or epidemiological evidence is suggestive, or if initial specimen was of poor quality
Potential treatment and prevention

- No effective antiviral treatment and vaccination yet
- Treatment is mainly **supportive**
  - Oxygen supplement
  - Mechanical ventilation +/- ECMO
  - IV fluids
  - Organ support
  - Antipyretics
  - Empirical antibiotics for community acquired pneumonia
<table>
<thead>
<tr>
<th>Anticipated Outcome</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce days of invasive mechanical ventilation (IMV)</td>
<td>• Weaning protocols that include daily assessment for readiness to breathe spontaneously.</td>
</tr>
<tr>
<td></td>
<td>• Sedation protocols to titrate administration of sedation to a target level, with or without daily interruption of continuous sedative infusions.</td>
</tr>
<tr>
<td>Reduce incidence of ventilator-associated pneumonia</td>
<td>• Oral intubation is preferable to nasal intubation in adolescents and adults.</td>
</tr>
<tr>
<td></td>
<td>• Perform regular antiseptic oral care.</td>
</tr>
<tr>
<td></td>
<td>• Keep patient in semi-recumbent position.</td>
</tr>
<tr>
<td></td>
<td>• Use a closed suctioning system; periodically drain and discard condensate in tubing.</td>
</tr>
<tr>
<td></td>
<td>• Use a new ventilator circuit for each patient; once patient is ventilated, change circuit if it is soiled or damaged but not routinely.</td>
</tr>
<tr>
<td></td>
<td>• Change heat moisture exchanger when it malfunctions, when soiled or every 5–7 days.</td>
</tr>
<tr>
<td></td>
<td>• Reduce days of IMV.</td>
</tr>
<tr>
<td>Reduce incidence of venous thromboembolism</td>
<td>• Use pharmacological prophylaxis (for example, heparin 5000 units subcutaneously twice daily or a low molecular-weight heparin) in adolescents and adults without contraindications. For those with contraindications, use mechanical prophylactic device such as intermittent pneumatic compression devices.</td>
</tr>
<tr>
<td>Reduce incidence of catheter-related bloodstream infection</td>
<td>• Use a simple checklist during insertion as reminder of each step needed for sterile insertion and daily reminder to remove catheter if no longer needed.</td>
</tr>
<tr>
<td>Reduce incidence of pressure ulcers</td>
<td>• Turn patient every two hours</td>
</tr>
<tr>
<td>Reduce incidence of stress ulcers and gastric bleeding</td>
<td>• Give early enteral nutrition (within 24–48 hours of admission), administer histamine-2 receptor blockers or proton-pump inhibitors.</td>
</tr>
<tr>
<td>Reduce incidence of ICU-related weakness</td>
<td>• Early mobility</td>
</tr>
</tbody>
</table>
Exceptionally Potent Neutralization of Middle East Respiratory Syndrome Coronavirus by Human Monoclonal Antibodies


Protein Interactions Group, Laboratory of Experimental Immunology, Cancer and Inflammation Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Frederick, Maryland, USA; Lindsley F. Kimball Research Institute, New York Blood Center, New York, New York, USA; Basic Science Program, Leidos Biomedical Research, Inc., Frederick National Laboratory, Frederick, Maryland, USA; Department of Microbiology, University of Hong Kong, Pokfulam, Hong Kong; Key Laboratory of Medical Molecular Virology of Ministries of Education and Health, Shanghai Medical College and Institute of Medical Microbiology, Fudan University, Shanghai, China

ABSTRACT

The recently discovered Middle East respiratory syndrome coronavirus (MERS-CoV) continues to infect humans, with high mortality. Specific, highly effective therapeutics and vaccines against the MERS-CoV are urgently needed to save human lives and address the pandemic concerns. We identified three human monoclonal antibodies (MAbs), m336, m337, and m338, targeting the receptor (CD26/DPP4) binding domain (RBD) of the MERS-CoV spike glycoprotein from a very large naïve-antibody library (containing ~10^11 antibodies). They bound with high affinity: equilibrium dissociation constants for the three MAbs were equal to 4.2, 9.3, and 15 nM, respectively, as measured by Biacore for Fabs binding to RBD. The avidity for IgG1 m336, m337, and m338 was even higher: 99, 820, and 560 pM, respectively. The antibodies bound to overlapping epitopes that overlap the receptor binding site on the RBD as suggested by competition experiments and further supported by site-directed mutagenesis of the RBD and a docking model of the m336-RBD complex. The highest-affinity MAb, m336, neutralized both pseudotyped and live MERS-CoV with exceptional potency, 50% neutralization at 0.005 and 0.07 µg/ml, respectively, likely by competing with DPP4 for binding to the S glycoprotein. The exceptionally high neutralization activity of these antibodies and especially m336 suggests that they have great potential for prophylaxis and therapy of MERS-CoV infection in humans and as a tool for development of vaccine immunogens. The rapid identification (within several weeks) of potent MAbs suggests a possibility to use the new large antibody library and related methodology for a quick response to the public threat resulting from emerging coronaviruses.
Interferon-α2b and ribavirin treatment improves outcome in MERS-CoV-infected rhesus macaques

Darryl Falzarano1, Emmie de Wit1, Angela L. Rasmussen2, Friederike Feldmann3, Atsushi Okumura2, Dana P. Scott3, Doug Brining3, Trenton Bushmaker4, Cynthia Martellaro1, Laura Baseler1, Arndt G. Benecke2,6, Michael G. Katze2, Vincent J. Munster4, and Heinz Feldmann1,7

Abstract

The emergence of Middle East respiratory syndrome coronavirus (MERS-CoV) is of global concern – causing severe respiratory illness with 97 confirmed cases and 46 deaths1. Therapeutic interventions have not been evaluated in vivo, thus patient management relies exclusively on supportive care, which given the high case-fatality rate is not highly effective. The rhesus macaque is the only known disease model for MERS-CoV, developing an acute localized-to-widespread pneumonia with transient clinical disease2,3 that recapitulates mild-to-moderate human MERS-CoV cases4,5. The combination of interferon-α2b and ribavirin was effective in reducing MERS-CoV replication in vitro6; therefore, this strategy was initiated 8 h post-infection in the rhesus macaque model. Treated animals did not develop breathing abnormalities and showed no-to-very mild radiographic evidence of pneumonia. Moreover, treated animals showed reduced levels of systemic (serum) and local (lung) proinflammatory markers in addition to reduced viral genome copies, altered gene expression and less severe histopathological changes in the lungs. Taken together, these data suggest that treatment of MERS-CoV infected rhesus macaques with IFN-α2b and ribavirin reduces virus replication, moderates the host response and improves clinical outcome. As these two drugs are already used in combination in the clinic, IFN-α2b and ribavirin should be considered for management of MERS-CoV cases.
IFN-α2a or IFN-β1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study

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¹Infectious Diseases Division, Department of Medicine, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia; ²King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), King Abdullah International Medical Research Center (KAIMRC), Infection Prevention and Control, King Abdullah Medical City, Saudi Arabia; ³Infection Prevention and Control, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia; ⁴Microbiology Laboratory, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia; ⁵Department of Critical Care, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia; ⁶Department of Nephrology, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia

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Received 29 December 2014; returned 31 January 2015; revised 4 March 2015; accepted 14 March 2015

Objectives: Middle East respiratory syndrome coronavirus (MERS-CoV) is associated with significant mortality. We examined the utility of plasma MERS-CoV PCR as a prognostic indicator and compared the efficacies of IFN-α2a and IFN-β1a when combined with ribavirin in reducing MERS-CoV-related mortality rates.

Methods: We retrospectively analysed 32 patients with confirmed MERS-CoV infection, admitted between April 2014 and June 2014, by positive respiratory sample RT-PCR. Plasma MERS-CoV RT-PCR was performed at the time of diagnosis for 19 patients.

Results: The overall mortality rate was 69% (22/32). Ninety percent (9/10) of patients with positive plasma MERS-CoV PCR died compared with 44% (4/9) of those with negative plasma MERS-CoV PCR. Mortality rate in patients who received IFN-α2a was 85% (11/13) compared with 64% (7/11) in those who received IFN-β1a (P = 0.24). The mortality rate in patients with renal failure (14), including 8 on haemodialysis, was 100%. Age >50 years and diabetes mellitus were found to be significantly associated with mortality (OR = 26.1; 95% CI 3.58–190.76; P = 0.001 and OR = 15.74; 95% CI 2.46–100.67; P = 0.004, respectively). The median duration of viral shedding in patients who recovered was 11 days (range 6–38 days). Absence of fever was noted in 5/32 patients.

Conclusions: Plasma MERS-CoV RT-PCR may serve as an effective tool to predict MERS-CoV-associated mortality. Older age and comorbid conditions may have contributed to the lack of efficacy of IFN-α2a or IFN-β1a with ribavirin in treating MERS-CoV. Absence of fever should not exclude MERS-CoV.
Testing of Middle East Respiratory Syndrome Coronavirus Replication Inhibitors for the Ability To Block Viral Entry

Qi Liu, a, c Shuai Xia, a Zhiwu Sun, a Qian Wang, a Lanying Du, b Lu Lu, a Shibo Jiang a, b

Key Lab of Medical Molecular Virology of MOE/MOH, Shanghai Medical College, Fudan University, Xuhui District, Shanghai, China; Lindsley F. Kimball Research Institute, New York Blood Center, New York, New York, USA; Department of Medical Microbiology and Immunology, School of Basic Medicine, Dali University, Dali, China

As of 23 July 2014, 837 laboratory-confirmed cases of Middle East respiratory syndrome (MERS-CoV) infection, including 291 deaths, had been reported to the WHO (http://www.who.int/csr/disease/coronavirus_infections/en/), raising concerns about its pandemic potential and calling for the development of vaccines and therapeutics against MERS-CoV infection.

We previously identified peptidic HIV-1 and severe acute respiratory syndrome coronavirus (SARS-CoV) fusion inhibitors (1, 2), which led to the development of MERS-CoV spike (S) protein-mediated cell-cell fusion and six-helix bundle (6-HB) formation assays. Using these assays, we identified a peptide from the MERS-CoV S protein HR2 region, termed HR2P, that inhibited 6-HB formation, cell-cell fusion, and MERS-CoV replication (3).

To identify small-molecule MERS-CoV fusion inhibitors, we used a cell-cell fusion assay to screen 1,280 compounds from an FDA-approved drug library obtained from MicroSource Discovery Systems, Inc. (Gaylordsville, CT), but none of the compounds at 10 μM could significantly inhibit MERS-CoV S-mediated membrane fusion.

fluphenazine), which were moderate inhibitors of cell-cell fusion with IC_{50}s of about 20, 20, and 29 μM, respectively (Table 1).

Subsequently, we determined the inhibitory activities of these compounds (40 μM) on 6-HB formation between HR1P and HR2P-fluorescein isothiocyanate (FITC) by using a fluorescence native polyacrylamide gel electrophoresis (FN-PAGE) assay adapted from the FN-PAGE assay for testing of HIV fusion inhibitors (7). As expected, HR1P showed no band because it carries net positive charges, thus migrating up and off the gel under native electrophoresis conditions, which is consistent with the results of HR1 peptides from HIV-1 (7) and SARS-CoV (2), while HR2P-FITC showed a band at a lower position. The mixture of HR1P and HR2P-FITC showed a band at a higher position, suggesting the formation of an HR1P/HR2P-FITC complex, possibly the 6-HB band (Fig. 1). In the presence of HR2P, the upper band disappeared while the lower HR2P-FITC band was displayed, suggesting that HR2P binds to HR1P and blocks 6-HB formation between HR2P-FITC and HR1P. However, none of the MERS-CoV replication inhibitors at 40 μM could block 6-HB formation by HR2P-FITC and HR1P (Fig. 1 and Table 1).
Panel: Potentially useful antiviral agents for Middle East respiratory syndrome coronavirus (MERS-CoV) infection

- Neutralising antibody
  - Convalescent plasma
  - Polyclonal human immunoglobulin from transgenic cows
  - Equine F(ab’), antibody fragments, camel antibodies
  - Anti-S monoclonal antibodies
- Interferons
  - Interferon alfa
  - Interferon beta
- Repurposed drugs
  - Ribavirin (with or without interferon)
  - HIV protease inhibitors (lopinavir, nelfinavir)
  - Cyclophilin inhibitors (ciclosporin, alisporivir)
  - Chloroquine (active in vitro)
  - Mycophenolic acid
  - Nitazoxanide
  - Recombinant human mannose-binding lectin
  - siRNA to key MERS-CoV genes
8. Experimental virus-specific therapeutics

At this time, there is no conclusive evidence from rigorous clinical trials in humans to recommend any virus-specific treatments for patients with suspected or confirmed MERS-CoV infection.

Treatment with investigational therapeutic agents should use standard research treatment protocols, employ systematic clinical and virologic data collection, and occur in the context of controlled research trials and with local ethics review and approval.

9. Special considerations for pregnant patients

Pregnant women with MERS-CoV infection should be treated with supportive therapies as described above taking into account the physiologic adaptations of pregnancy.

Experimental, virus-specific treatments should be guided by individual risk-benefit analysis based on potential benefit for mother and safety to fetus, with consultation of obstetric specialist and ethics committee.

Ribavirin has been shown to be genotoxic in vitro and teratogenic in animal models. Some other compounds considered for experimental treatments of MERS have not been tested for safety in pregnancy. Use of any of these compounds in pregnancy should be considered only when the benefit outweighs the risk of treatment.

Emergency delivery/pregnancy termination decisions are challenging and based on many factors: gestational age, maternal condition, and fetal stability. Consultations with obstetric, paediatric and intensive care specialist are essential.
Candidate vaccines in development

Novavax Produces MERS-CoV Vaccine Candidate

Rockville, MD (June 6, 2013)—GlobeNewswire, Inc. /-Novavax, Inc. (NASDAQ: NVAX) announced today that it had successfully produced a vaccine candidate designed to provide protection against the recently emerging Middle East Respiratory Syndrome Coronavirus (MERS-CoV). The vaccine candidate, which was made using Novavax’ recombinant nanoparticle vaccine technology, is based on the major surface spike (S) protein. The Company believes that its MERS-CoV vaccine candidate may provide a path forward for a vaccine for this emerging threat.

Engineering a Replication-Competent, Propagation-Defective Middle East Respiratory Syndrome Coronavirus as a Vaccine Candidate

Fernando Almazán, Marta L. DeDiego, Isabel Sola, Sonia Zuñiga, Jose L. Nieto-Torres, Silvia Marquez-Jurado, German Andrés, Luis Enjuanes

Department of Molecular and Cell Biology, Centro Nacional de Biotecnología (CNB-CSIC), Campus Universidad Autónoma de Madrid, Cantoblanco, Madrid, Spain; Centro de Biología Molecular Severo Ochoa (CBM-CSIC-UM), Campus Universidad Autónoma de Madrid, Cantoblanco, Madrid, Spain

F.A. and M.L.D. contributed equally to this work.

ABSTRACT  Middle East respiratory syndrome coronavirus (MERS-CoV) is an emerging coronavirus infecting humans that is associated with acute pneumonia, occasional renal failure, and a high mortality rate and is considered a threat to public health. The construction of a full-length infectious cDNA clone of the MERS-CoV genome in a bacterial artificial chromosome is reported here, providing a reverse genetics system to study the molecular biology of the virus and to develop attenuated viruses as vaccine candidates. Following transfection with the cDNA clone, infectious virus was rescued in both Vero A66 and Huh-7 cells. Recombinant MERS-CoVs (rMERS-CoVs) lacking the accessory genes 3, 4a, 4b, and 5 were successfully rescued from cDNA clones with these genes deleted. The mutant viruses presented growth kinetics similar to those of the wild-type virus, indicating that accessory genes were not essential for MERS-CoV replication in cell cultures. In contrast, an engineered mutant virus lacking the structural E protein (rMERS-CoV-ΔE) was not successfully rescued, since viral infectivity was lost at early passages. Interestingly, the rMERS-CoV-ΔE genome replicated after cDNA clone was transfected into cells. The infectious virus was rescued and propagated in cells expressing the E protein in trans, indicating that this virus was replication competent and propagation defective. Therefore, the rMERS-CoV-ΔE mutant virus is potentially a safe and promising vaccine candidate to prevent MERS-CoV infection.

IMPORTANCE  Since the emergence of MERS-CoV in the Arabian Peninsula during the summer of 2012, it has already spread to 10 different countries, infecting around 94 persons and showing a mortality rate higher than 50%. This article describes the development of the first reverse genetics system for MERS-CoV, based on the construction of an infectious cDNA clone inserted into a bacterial artificial chromosome. Using this system, a collection of rMERS-CoV deletion mutants has been generated. Interestingly, one of the mutants with the E gene deleted was a replication-competent, propagation-defective virus that could only be grown in the laboratory by providing E protein in trans, whereas it would only survive a single virus infection cycle in vivo. This virus constitutes a vaccine candidate that may represent a balance between safety and efficacy for the induction of mucosal immunity, which is needed to prevent MERS-CoV infection.
Middle East Respiratory Syndrome Coronavirus Spike Protein Delivered by Modified Vaccinia Virus Ankara Efficiently Induces Virus-Neutralizing Antibodies

Fei Song, a Robert Fux, a Lisette B. Provacia, b Asisa Volz, a Markus Eickmann, c Stephan Becker, c, d Albert D. M. E. Osterhaus, b Bart L. Haagmans, b Gerd Sutter a, d

Institute for Infectious Diseases and Zoonoses, LMU University of Munich, Munich, Munich, Germany a; Department of Viroscience, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands b; Institute of Virology, Philipps University Marburg, Marburg, Germany c; German Centre for Infection Research (DZIF) d

Middle East respiratory syndrome coronavirus (MERS-CoV) has recently emerged as a causative agent of severe respiratory disease in humans. Here, we constructed recombinant modified vaccinia virus Ankara (MVA) expressing full-length MERS-CoV spike (S) protein (MVA-MERS-S). The genetic stability and growth characteristics of MVA-MERS-S make it a suitable candidate vaccine for clinical testing. Vaccinated mice produced high levels of serum antibodies neutralizing MERS-CoV. Thus, MVA-MERS-S may serve for further development of an emergency vaccine against MERS-CoV.
Difficulty of drug development: Lack of suitable animal models

- Lab mice, guinea pigs are not easily affected
- Macaques do not reflect extent of disease severity in humans
- Marmosets data are not reproducible
- These animals are very expensive and in limited supply
- One way is to use transgenic mice expressing the functional receptor

Courtesy of Prof. D Hui
Infection control
Suspected/Confirmed case of MERS

Bundle of immediate isolation, prompt notification and quick diagnosis on suspected cases has to be strictly observed

1. Nurse in Airborne Infection Isolation Room (AIIR) (i.e. with negative pressure and at least 12 ACH) en-suite with toilet facility, in an isolation ward setting; (The use of AIIR without toilet facility in a general ward setting should be avoided).

2. Patient care: Standard, Contact, Droplet and Airborne precautions

3. PPE: N95, goggles/face shield, gown, gloves, and cap (optional) for aerosol generating procedures and routine patient care
<table>
<thead>
<tr>
<th>Clinical areas</th>
<th>Recommended PPE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Routine patient care / provision of clinical services</strong></td>
<td><strong>High-risk areas</strong> <em>(for caring suspected or confirmed MERS patients)</em>&lt;br&gt;• N95 respirator (Surgical mask could be an alternative for triage stations based on nature of encounter upon risk assessment), eye protection, gown, gloves and cap (optional)</td>
</tr>
<tr>
<td>Other patient areas</td>
<td>• Surgical mask, Standard precautions +/- transmission based precautions</td>
</tr>
<tr>
<td><strong>Performing aerosol-generating Procedures (AGPs)</strong></td>
<td><strong>High-risk areas</strong> <em>(for performing intubation or ventilation)</em>&lt;br&gt;• N95 respirator, eye protection, gown, gloves and cap (optional); Place patient in a negative pressure airborne infection isolation room (AIIR).</td>
</tr>
<tr>
<td>Other patient areas</td>
<td><strong>For NIV</strong>&lt;br&gt;• Please refer Risk assessment for patient required Non-invasive ventilation (NIV).&lt;br&gt;• NIV beds: Surgical mask, eye protection, gown, gloves and cap (optional)</td>
</tr>
<tr>
<td><strong>No patient contact</strong></td>
<td><strong>High-risk areas</strong> <em>(outside suspected or confirmed MERS patient’s room)</em>&lt;br&gt;Other patient areas (e.g. waiting areas in SOPC, GOPC and A&amp;E)</td>
</tr>
</tbody>
</table>

*High-risk areas refer to triage stations of out-patients clinics and Accident & Emergency department, designated clinics (if activated) and isolation rooms (including isolation rooms in ICU and AEDs) and clinical laboratories.
Aerosol-generating procedures** (AGP)

AGP such as:

- Endotracheal intubation#
- CPR
- Bronchoscopy
- Open suctioning of respiratory tract (including tracheostomy care)
- Autopsy
- Non-invasive positive pressure ventilation (BiPAP & CPAP)
- High-frequency oscillatory ventilation
- Nebulizer therapy
- Sputum induction

** NPA and high flow oxygen (6L/min) are theoretically at risk of dispersal of infectious respiratory droplets, therefore they should be performed in conditions as required for AGP in high-risk patient areas

# Taking into consideration of patient’s factors under OT setting, where the patient has undergone pre-operative screening and under sedation, staff is advised to follow Standard Precautions or transmission based precautions (if indicated) when performing intubation for elective surgery

Other procedures should be assessed on discretion of hospital Infection Control Officers.
Correct sequence for PPE removal

- Doffing (taking off):
  - Glove
  - Gown
  - Cap and eye protection
  - Surgical mask or N95 respirator

- Hand hygiene should be performed after each step (i.e. palmful of alcohol-based hand rub applied for 15-20 seconds, or wash with soap under running tap water if hands are visibly soiled)
N95口罩正確佩戴方法：

1. 潔手
   - 洗手
   - 佩戴護目鏡
   - 戴上口罩

2. 擦手
   - 用酒精棉擦拭口罩

3. 調整
   - 調整口罩至舒適位置

4. 佩戴
   - 將口罩戴在頭部
   - 調整口罩至舒適位置

5. 口罩佩戴
   - 將口罩戴在頭部

6. 檢查
   - 檢查口罩是否緊貼

N95口罩正確卸除方法：

1. 濕手
   - 洗手
   - 佩戴護目鏡
   - 戴上口罩

2. 擦手
   - 用酒精棉擦拭口罩

3. 除口罩
   - 除下口罩

4. 檢查
   - 檢查口罩是否緊貼

備註：
- 個人防護裝備必須穿戴妥當才可進入隔離區
- 離開隔離區時，必須卸除所有個人防護裝備及潔手
5 moments for hand hygiene

1. BEFORE TOUCHING A PATIENT 直接接觸病人之前
2. BEFORE CLEAN / AEROBIC PROCEDEURE 進行無菌操作或護理程序之前
3. AFTER BODY FLUID EXPOSURE RISK 接觸血液或體液之後
4. AFTER TOUCHING A PATIENT 直接接觸病人之後
5. AFTER TOUCHING PATIENT SURROUNDINGS 接觸病人直接範圍之後

WHO Guidelines on Hand Hygiene in Health Care

First Global Patient Safety Challenge Clean Care is Safer Care
In the primary care clinic

- Triage patients in clinic in a separate area if possible
- Adopt basic standard and droplet precautions e.g. Surgical masks, hand hygiene
- Enquire on travel and contact history within 14 days prior to symptom onset
- For suspected cases fulfilling reporting criteria, notify CHP immediately. Transport will be arranged to escort them directly to hospital for further testing and management
- Environmental cleaning and disinfection (e.g. 1:49 diluted household bleach) for potentially contaminated area
- May consider posting notices to inform the public that testing for MERS is not available so that they will consider going directly to A&E
Droplet precautions

Droplet precautions should be used if there is a risk of infectious microorganisms being transmitted by droplets generated by coughing, sneezing or talking (eg patients with influenza). To prevent droplet transmission, the following items and actions are recommended:

• Offer staff appropriate immunisation for vaccine-preventable diseases.
• If not immune, use a fluid repellent surgical mask to protect the mouth and nose.
• Clean hands immediately after attending patient and removing mask (and face shield if used) before leaving the area.
• Segregate patients (social distancing) with these types of infectious diseases if possible – move the patient from the general waiting area to a vacant area, or maintain a 1-metre gap between the infectious patient and other patients in the waiting area.
• Ask the infectious patient to wear a surgical mask. In this instance, advise patients how to remove and dispose of the mask safely.
• Ask the patient to attend to respiratory etiquette (see Chapter 5, Section 5.2).
• Consider explaining the situation to nearby patients.
• Communicate the patient’s infectious status to other doctors and health professionals involved in the care of the patient (eg ambulance and emergency department staff if the patient is transferred to another healthcare facility) so that appropriate transmission-based precautions can be maintained.
• Staff known to be immune to particular infectious diseases do not need to use a mask and goggles when exposure is possible.
Recent outbreak in South Korea
**Index patient: M/68**

- Visited Bahrain/KSA/UAE from April 18 to May 3, participated in agricultural business
- Returned to Korea via Qatar on May 4
- Developed fever and cough on May 11, hospitalised on May 12
- Confirmed to have MERS on May 20
重要: Never give false / inaccurate travel hx!!

No confirmed case in HK so far
"Red" outbound travel alert is still in force
Middle East respiratory syndrome coronavirus (MERS-CoV)

MERS-CoV in Republic of Korea at a glance
as of 16 July 2015

TOTAL CONFIRMED
186
Republic of Korea
185
China
1
DEATHS
36

Please refer to the link below for up to date MoHW summary of MERS statistics and list of health facilities where confirmed MERS cases were reported in the Republic of Korea.
http://www.mers.go.kr/mers/html.jsp/Menu_C/list_C4.jsp
Press Release

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<td>2015-07-15</td>
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<td>2015-07-14</td>
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<td>2015-07-13</td>
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<td>MERS Statistics (July 13)</td>
<td>2015-07-13</td>
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</table>
List of healthcare facilities with confirmed case(s) of Middle East Respiratory Syndrome reported (Based on announcement by the World Health Organization on 17 June 2015)

1. Asan Seoul Clinic
   牙山首爾醫院

2. Pyeongtaek St. Mary's Hospital
   平澤聖母醫院

3. 365 Yeol Lin Clinic
   365首爾開院醫院

4. Samsung Medical Centre
   三星首爾醫院

5. KonYang University Hospital
   建陽大學醫院

6. Dae Cheong Hospital
   大田大邱醫院

7. Asan Medical Centre
   首爾城山醫院

8. Yeouido St. Mary's Hospital
   法矣島聖母醫院

9. KonKuk University Medical Centre
   建國大學醫院

10. Hallym University Medical Centre
    現林大學東湖心靈醫院

11. Pyeongtaek Good Morning Hospital
    平澤早安醫院

12. Yangji Seoul Samsung Clinic
    YANGJI首爾三星醫院

13. 365 Gangdong
    江東慶熙大學醫院

14. Songtaeul Clinic
    SONG JAEYI內科醫院

15. South Chungcheong

16. North Chungcheong

17. North Jeollanam

18. South Jeollanam

19. South Gyeongsang

20. North Gyeongsang

21. Jeju

22. Jeonju

23. Gumi

24. Yangpyeong

25. Gwangju

26. Incheon

27. Gwangju

28. Yeongju

29. Gyeongju

30. Suwon

31. Icheon

32. KonKuk University Medical Centre
    建國大學醫院
<table>
<thead>
<tr>
<th>Specified visiting period (date/month)</th>
<th>Name in Korean 韓語名稱</th>
<th>Name in Chinese translation* 中文翻譯名稱*</th>
<th>Name in English translation* 英文翻譯名稱*</th>
<th>Location 位置</th>
</tr>
</thead>
<tbody>
<tr>
<td>15/5 – 29/5 梨花女子大學 農意科</td>
<td>평택성모병원</td>
<td>Pyeongtaek St. Mary’s Hospital</td>
<td>Segyo-dong, Pyeongtaek-si (平澤市), Gyeonggi-do (京畿道)</td>
<td></td>
</tr>
<tr>
<td>27/5 – 31/5 三星首爾綜合</td>
<td>삼성서울병원</td>
<td>Samsung Medical Centre</td>
<td>Irwon-dong, Gangnam-gu (江南區), Seoul (首爾)</td>
<td></td>
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<tr>
<td>28/5 – 30/5 建陽大學醫科</td>
<td>건양대학교병원</td>
<td>KonYang University Hospital</td>
<td>Gasuwon-dong, Seogu (西區), Daejeon (大田)</td>
<td></td>
</tr>
<tr>
<td>22/5 – 30/5 大田大邱醫院</td>
<td>대천병원</td>
<td>Dae Cheong Hospital</td>
<td>Jeonglim-dong, Seogu (西區), Daejeon (大田)</td>
<td></td>
</tr>
<tr>
<td>5/6 - 9/6 賀林大學江東聖心醫科 14層小兒科</td>
<td>한림대학교 감동성심병원 14층 소아청소년과</td>
<td>Hallym University Gangdong Sacred Heart Hospital 14th floor (Pediatrics Unit)</td>
<td>Gil-dong (吉洞)</td>
<td></td>
</tr>
<tr>
<td>10/6, 11/6, 12/6 金字串手卷和針灸</td>
<td>MOKCHASOO 內科醫院, JONGRO 光明路店</td>
<td>Mokchassoo Internal Medicine Clinic, Jongro Guangnyung Pharmacy</td>
<td>Sangil-dong</td>
<td></td>
</tr>
<tr>
<td>12/6 青田景安院</td>
<td>ILSUNDANG 韓醫院</td>
<td>Ilsundang Korean Traditional Medical Clinic</td>
<td>Sangil-dong</td>
<td></td>
</tr>
<tr>
<td>15/6 仁荷大學附設，SMILE</td>
<td>BON 耳鼻咽喉科, SMILE 醫院</td>
<td>Bon Otorhinolaryngology Clinic, Smile Pharmacy</td>
<td>Godeok-dong</td>
<td></td>
</tr>
<tr>
<td>16/6 桑南永佳醫院, 興安路</td>
<td>GANGDONG 神經外科醫院, TUNTUN (健康)</td>
<td>Gangdong Neurosurgery Clinic, Tuntun Pharmacy</td>
<td>Myeonggil-dong</td>
<td></td>
</tr>
<tr>
<td>17/6 天使郵輪</td>
<td>sWithPHEM 天使郵輪</td>
<td>Withpharm Angel Pharmacy</td>
<td>Gil-dong (吉洞)</td>
<td></td>
</tr>
<tr>
<td>17/6 (PM 下午) - 22/6 仁荷大學附設</td>
<td>Withpharm 天使郵輪</td>
<td>Hallym University Gangdong Sacred Heart Hospital</td>
<td>Gil-dong (吉洞)</td>
<td></td>
</tr>
</tbody>
</table>

*According to Korea, the English and Chinese translation may not be official name.

*根據韓國，英文及中文翻譯名稱可能不是正式名稱。
Epidemic curve of MERS-CoV infections, South Korea, 11 May–19 June 2015 (n = 166)

predicted Case Fatality Rate = 21% (95% CrI: 14–31) (allowing for the uncertain outcomes of cases that remained in hospital)


<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All cases (n = 166)</th>
<th>Fatal cases (n = 24)</th>
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<tbody>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–18 years</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>19–39 years</td>
<td>31 (19%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>40–59 years</td>
<td>64 (39%)</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>60–79 years</td>
<td>61 (37%)</td>
<td>16 (67%)</td>
</tr>
<tr>
<td>≥ 80 years</td>
<td>9 (5%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>101 (61%)</td>
<td>17 (71%)</td>
</tr>
<tr>
<td>Female</td>
<td>65 (39%)</td>
<td>7 (29%)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthcare personnel</td>
<td>30 (18%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Not healthcare personnel</td>
<td>136 (82%)</td>
<td>24 (100%)</td>
</tr>
</tbody>
</table>

MERS-CoV: Middle East respiratory syndrome coronavirus.
Epidemiological data

- Mean incubation period 6.3 days
- Reproductive number is still likely to be <1
  - However, there is substantial risk of superspreading event
  - Occasional cluster sizes of >150 cases as in the Korean outbreak is not unexpected
  - Due to these superspreading events, it would not be accurate to characterize the transmissibility of MERS-CoV simply based on measuring the average reproductive number
- Experience in Saudi Arabia, UAE, China and Thailand has shown that the reproduction number can be brought under one with early isolation of cases and adequate infection prevention and control measures
Figure 2
Simplified transmission diagram illustrating the superspreading events associated with Cases 1, 14, 16 and fourth-generation infections of MERS-CoV, South Korea, 11 May–19 June 2015 (n = 166)

MERS-CoV: Middle East respiratory syndrome coronavirus.
Contributing factors in the Korean outbreak

- Poor infection control and lack of awareness
- Suboptimal contact tracing, patient not immediately forthcoming with travel history
- Overcrowding in AED and multiple-bed rooms
- Inadequate isolation rooms
- Doctor shopping and visiting several hospitals sequentially
- Family and friends staying overnight in ward
Has the transmission patterns of MERS-CoV changed?

The overall transmission patterns previously observed remain unchanged. There is no evidence of sustained human-to-human transmission in the community or evidence of airborne transmission.

Supporting evidence:
- 1. The clinical picture seen in recent outbreaks appears similar to that observed throughout previous outbreaks.
- 2. The cases recently exported to countries outside the Middle East have not resulted in sustained onward transmission to persons in close contact with these cases in the community.
- 3. Intensive screening of MERS contacts revealed very few instances of household transmission and there has been no identified transmission on airplanes.
- 4. There has been no increase in the size or number of observed household clusters.
Should we be worried?

No need to be overly worried if we adhere to infection control practices and stay alert.
Welcome to CENO On-line!

Central Notification Office (CENO) has been set up under the Centre for Health Protection (CHP) to centralize communicable diseases notifications and monitoring in Hong Kong. CENO On-line is literally CENO on the internet. In this website, using designated login ID and password, registered medical practitioners practising in Hong Kong* can access the secure and convenient web-based notification system to report cases online.

What to report?

(a) **Statutory notifiable diseases**
(b) **Other communicable diseases of topical public health concern**
(c) Poisoning related to heavy metal or traditional Chinese medicine
(d) **Suspected institutional outbreaks**
(e) **Unusual clustering of communicable diseases**

NB Anonymous HIV/AIDS reporting is handled by Special Preventive Programme, Public Health Services Branch, Centre for Health Protection. Please click [here](#) for details.

### How to report?

<table>
<thead>
<tr>
<th>Notification channels</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CENO On-line</td>
<td><a href="http://www.chp.gov.hk/cono">www.chp.gov.hk/cono</a></td>
</tr>
<tr>
<td>Fax</td>
<td>2477 2770</td>
</tr>
<tr>
<td>Telephone</td>
<td>2477 2772</td>
</tr>
<tr>
<td>Email</td>
<td><a href="mailto:diseases@dh.gov.hk">diseases@dh.gov.hk</a></td>
</tr>
<tr>
<td>Mail</td>
<td>Central Notification Office, 3/F., 147C Argyle Street, Kowloon. The above channels are preferable to mail, as the latter takes considerably longer time to reach CENO.</td>
</tr>
</tbody>
</table>

Statutory notifiable diseases

These are the infectious diseases specified in the First Schedule (Cap 599). Notification of suspected or confirmed cases of these figures are available at the CHP website. Please click [here](#) for details.

- Acute poliomyelitis
- Amoebic dysentery
- Anthrax
- Bacillary dysentery
- Botulism
- Chickenpox
- Chikungunya fever
- Cholera
- Community-associated meticillin-resistant Staphylococcus aureus
- Creutzfeldt-Jakob disease
- Dengue fever
- Diphtheria
- Enterovirus 71 infection
- Food poisoning
- *Haemophilus influenzae* type b infection (invasive)
- Hantavirus infection
- Invasive pneumococcal disease
- Japanese encephalitis
- Legionnaires' disease
- Leprosy
- Leptospirosis
- Listeriosis
- Malaria
- Measles
- Meningococcal infection (invasive)
- **Middle East Respiratory Syndrome**
- Mumps
- Novel influenza A infection
- Paratyphoid fever
- Pneumonia
Where can I get updated information?

<table>
<thead>
<tr>
<th>Organization</th>
<th>Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Authority</td>
<td><a href="http://ha.home">http://ha.home</a></td>
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</tbody>
</table>
Thank you