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Short report

Resource impact of managing suspected Middle East respiratory syndrome patients in a UK teaching hospital

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SUMMARY

Clinical challenges exist in the management of hospitalized patients returning to the UK with potential Middle East respiratory syndrome coronavirus (MERS-CoV) infection, particularly with its clinical overlap with influenza, as demonstrated in this case-series and cost-analysis review of returning Hajj pilgrims. These patients were hospitalized with acute febrile respiratory illness, initially managed as potential MERS-CoV infections, but were eventually diagnosed with influenza. Additional costs were small, yet enhanced infection prevention measures created significant burdens on isolation rooms and staff time. Planning for predictable events such as Hajj is important for resource management. Here, in-house MERS-CoV diagnostic testing would have facilitated earlier diagnosis and discharge.

Introduction

Middle East respiratory syndrome coronavirus (MERS-CoV) first emerged in Saudi Arabia in 2012. It has established endemicity in the Arabian Peninsula and has been imported into other countries, including large hospital-related outbreaks in South Korea, demonstrating limited human-to-human transmission. There is no specific treatment or vaccine, and it carries an overall mortality of 30–40%.[1,2]

Current Public Health England (PHE) guidelines recommend that MERS-CoV infection should be considered in any symptomatic patient returning from an endemic area (or who has had contact with a confirmed case) within 14 days, with no alternative explanation.[3] Case definition criteria include cough, fever

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≥38°C, with clinical or radiological evidence of pneumonia or acute respiratory distress. However, MERS-CoV may present with a wide spectrum of clinical disease, indistinguishable from other respiratory virus infections.[4] Note that a history of camel contact is not included in these case definition criteria. The potential for aerosol as well as large droplet transmission make the additional healthcare resources required for managing patients with suspected MERS-CoV considerable, particularly the use of negative pressure isolation, enhanced personal protective equipment (PPE) and safe laboratory testing.[5,6]

Although there are few actual cases of MERS-CoV in returning pilgrims, the potential for transmission during large religious pilgrimages, especially Hajj, have raised concerns.[7,8] Given an incubation period of up to two weeks, asymptomatic patients may return unaware that they have contracted the disease.

This case series and cost analysis illustrates the clinical overlap between seasonal influenza and MERS-CoV in these returning Hajj pilgrims, together with the challenges of caring for these patients within an enhanced infection control environment.

Methods

Case reports

Table I supplies data for five patients hospitalized in the Infectious Diseases Unit, Leicester Royal Infirmary, during October 2015.

Two patients were male, three were female, with a mean age of 36 years. All patients developed symptoms within four days of returning to the UK, and presented after mean duration of four days (median: three days). All were febrile ≥37.8°C (5/5, 100%) with at least two respiratory symptoms (coryza, pharyngitis, cough, sputum, wheeze, dyspnoea), and three (60%) had diarrhoea and vomiting. The oldest patient, a female aged 57 years, developed hypoxia, respiratory failure and cardiac conduction abnormalities (2:1 heart block on electrocardiograph) and was transferred to intensive care. One of the female patients was 27 weeks pregnant and felt reduced fetal movements.

Two sets of nose swabs, throat swabs, and sputum were collected from each patient. One set was sent to our local reference laboratory for MERS-CoV polymerase chain reaction (PCR), the other was simultaneously tested in parallel (with appropriate initial sample inactivation) on our in-house assay for influenza/adenovirus/respiratory syncytial virus PCR. Routine bacteriological investigations were performed, including sputum culture and sensitivities.

Isolation precautions

Table II summarizes category of transmission-based precautions used during our admissions returning from Hajj.

All of our patients presented to the Emergency Department, Leicester Royal Infirmary, and were assessed in a single cubicle before transfer to one of two available medium-secure single negative-pressure rooms (negative-pressure isolation room with en-suite bathroom and antechamber) within the Infectious Diseases Unit, where medical and nursing staff should attend annual local training for PPE use and FFP3 respirator fit-testing. Visitors were restricted. Staff interactions were logged and restricted to essential attendances. Required PPE included the use of long-sleeved fluid repellent gown, plastic apron, double gloves, eye protection and FFP3 single valve respirator.

We estimated that it took an additional 15 min per patient contact (don and doff PPE, disposal, complete visitor logs) than standard precautions, for both nurses and doctors, with the consultant being present during the doctors' visits for suspected MERS patients.

Laboratory testing

Testing for routine respiratory viruses was performed at Leicester Royal Infirmary using in-house PCR assays based on previously published protocols.[9–11] This testing covered influenza A and B, respiratory syncytial virus, parainfluenza (types 1–4), and adenovirus.

Local practice is to process all respiratory samples in BSL 3 containment to allow safe inactivation of the suspected MERS-CoV sample in lysis buffer prior to RNA extraction for PCR testing. This in-house respiratory PCR test panel costs £21.60, and would be performed for any patient suspected of a possible respiratory infection, whether or not MERS-CoV infection was also suspected.

A separate set of samples for testing at the MERS-CoV reference laboratory in Birmingham was packaged and sent by courier under Category B (UN3373). The MERS-CoV testing at the Public Health England (PHE) Reference Laboratory in Birmingham was performed using an assay based on a previously published assay targeting the region upstream of the MERS-CoV E gene (upE).[12] This test panel also included non-MERS-CoV viruses, including respiratory syncytial virus (RSV), influenza A (H1, H3; not subtyped further), influenza B, parainfluenza virus (PIV types 1–4), rhinovirus (RV), human metapneumovirus (hMPV), and adenovirus (Adv).[9,10] The cost of the courier and the MERS-CoV testing was covered by PHE.

Results

Clinical cases

Throat swabs from all patients tested positive by in-house PCR assays for influenza A/H1N1, A/H3N2 or B viruses within 31 h (median: 23 h) from collection.

MERS-CoV PCR results were available to clinicians between 25 and 57 h from collection (median: 50 h) and patients remained in medium-secure negative-pressure isolation for a mean of 39 h (median: 45 h).

All patients received oseltamivir (oral, 75 mg, 12-hourly), and three (60%) received intravenous antibiotics as per hospital antimicrobial guidelines on admission. Two of these patients cultured *Haemophilus influenzae* from sputum and were treated with co-amoxiclav, and the third with clinical sepsis was given combination therapy (meropenem, doxycycline, linezolid) (Table I).

All patients recovered, with three (60%) being discharged within 48 h.

Overall cost of admitting and screening a suspected MERS-infected patient

Several aspects of the cost could not be quantified, such as the cost of the individual negative-pressure room ventilation and disposal of the enhanced PPE waste for any particular patient suspected of MERS-CoV infection. These costs were

Table I
Clinical features of returning travellers admitted to medium-secure negative pressure following return from Hajj in October 2015

No.	Age, sex	Time to onset of symptoms after return to UK (days)	Duration of symptoms pre admission (days)	Peak temperature (°C)	Symptoms and signs (including any history of contact with camels)	Chest radiograph	CRP (mg/mL)	WCC ($\times 10^9$/L)	Laboratory results (PCR), including MERS-CoV and other respiratory viruses[a] (time to non-MERS-CoV results for local/reference laboratory, h)[b]	Treatment	Time in medium-secure isolation; total time in hospital
1	57 years, female	3	2	38.7	Cough, sputum, pleuritic chest pain, diarrhoea, ECG: heart block	Multi-lobar consolidation	56	10.2	H1N1 (24/50)	Meropenem Doxycycline, Linezolid, Oseltamivir	48 h, 10 days
2	26 years, female	2	9	38.0	Cough, sputum, pharyngitis, diarrhoea	Clear	122	7.6	Influenza B, adenovirus (22/25)	Oseltamivir	24 h, 24 h
3	27 years, female (pregnant)	−1	3	38.8	Dyspnoea, cough, wheeze, diarrhoea, reduced fetal movements	Clear	72	14.7	H1N1; sputum isolated *Haemophilus influenzae* (16/40)	Co-amoxiclav Oseltamivir	45 h, 45h
4	28 years, male	0	3	37.8	Coryza, cough, inspiratory crackles	Clear	59	7.3	H3N2 (23/50)	Oseltamivir	28 h, 30 h
5	50 years, male	4	2	38	Cough, sputum, myalgia	Clear	122	4.5	H1N1; sputum isolated *H. influenzae* (31/57)	Co-amoxiclav Oseltamivir	48 h, 72 h

CRP, C-reactive protein; WCC, white cell count; PCR, polymerase chain reaction; MERS-CoV, Middle East respiratory syndrome coronavirus; ECG, electrocardiogram.

[a] The reference laboratory results include MERS-CoV, but also: respiratory syncytial virus (RSV), influenza A (H1, H3), influenza B, parainfluenza virus (PIV: not typed), rhinovirus (RV), human metapneumovirus (hMPV), and adenovirus (Adv). These are combined with our in-house respiratory virus PCR panel, which includes: influenza A/H1N1, A/H3N2, B, RSV, PIV types 1–4, Adv.

[b] The results for the non-MERS-CoV respiratory viruses were the same in both the local and reference laboratories.

Table II
Infection prevention measures used at University Hospitals of Leicester NHS Trust for patients with suspected respiratory illness or MERS-CoV infection

	Standard precautions for isolation of suspected respiratory pathogens	Enhanced precautions for isolation for suspected MERS-CoV
Category of infection prevention	Contact and droplet precautions	Contact, droplet and airborne precautions
Patient placement	Standard single cubicle if possible. Cohort if not available (same pathogen).	Medium-secure single negative-pressure room with en-suite and antechamber
Room restrictions	Access for visitors and staff	No visitors Essential staff visits only 'Don and doff' PPE-trained staff[a] Recording of staff contact (log)
Healthcare worker requirements (PPE)	Standard hand hygiene Single glove Plastic apron Surgical mask	Removal of rings, watches; standard hand hygiene Double gloves Disposable long-sleeved fluid-repellent gown Plastic apron Eye protection goggles Respirator FFP3 valved mask Domestic staff wear PPE
No. of staff visits per day	SpR or consultant once-daily visit until discharge. HCA/nurse visit six times per day (normal PPE).	SpR and consultant on admission (SpR clerk and consultant review). SpR or consultant daily visit until discharge. HCA/nurse visit six times per day day (enhanced PPE).
Additional staff time + PPE-related costs	Routine PPE costs (single layer of gloves, plastic apron, surgical mask)	Additional costs: One-off (once per year) 1.5 h enhanced PPE training course = £29.50/day for each nurse/doctor.[a] Enhanced PPE equipment costs (mask, gown, gloves, goggles) ~£2.50 per patient visit.[b] Additional time for don, doff and register ~15 min, assuming six patient visits/day, so for 6 × 15 min patient visits = @£29.50 for 1.5 h extra/day.[c] HCA/nurses: six patient visits per day = 2 × £29.50 + 6 × £2.50 = £74 extra/day,[c] using the two-nurse buddy system (as the 'buddy' observing nurse does not wear the enhanced PPE, but spends the same time in the isolation facility). Doctors: daily visit (using enhanced PPE, including don/doff time and buddy system as above) = 30 min extra per day = 0.5 × £(60+20) + 2 × £2.50 = £45 extra/day.[d]
Patient isolation/containment	Negative-pressure isolation room, where available. Single-bedded side-room is also used, where available.	Mandatory single-bedded isolation room with en-suite bathroom and negative-pressure ventilation.[e]
Cleaning	Regular surface cleaning	Daily surface cleaning (disposable equipment) Bag linen inside room[e]

(*continued on next page*)

Table II (*continued*)

	Standard precautions for isolation of suspected respiratory pathogens	Enhanced precautions for isolation for suspected MERS-CoV
Laboratory testing	BSL level 2 containment. In-house respiratory virus testing at £21.60.	BSL level 3 containment for sample inactivation. In-house respiratory virus testing at £21.60. MERS-CoV testing and courier (Category B/ UN3373) costs borne by the reference laboratory.
Total additional costs (mainly staff time/enhanced PPE costs)		£119/day

MERS, Middle East respiratory syndrome; PPE, personal protective equipment; BSL, biosafety level; HCA, healthcare assistant.
[a] Local training course for staff is available and mandatory, though this has not been included in the daily running cost total, as this will also cover the handling of other high-risk (e.g. suspected Ebola) patients.
[b] Costings from National Health Service supplies.
[c] This assumes a 50:50 regular (with salaries according to: https://www.rcn.org.uk/employment-and-pay/nhs-pay-scales-2015-16) and agency Band 5 staff nurse mix, which is typical in these situations.
[d] Assuming approximately midpoint-scale salary levels (http://careers.bmj.com/careers/static/advice-salary-scales.html).
[e] The additional cost of the removal of the enhanced PPE waste and ventilating a negative pressure room is not included, as these estimates are virtually impossible to separate from the general ward costs for these facilities.

impossible to separate from the whole ward costs. The courier and testing of the patient sample for MERS-CoV (and other respiratory viruses) at the Birmingham reference laboratory was covered by PHE and was not a cost burden to our hospital. The cost of the in-house respiratory PCR testing was the same as for any patient presenting with a respiratory infection, not just one suspected of MERS-CoV infection.

In terms of additional costs to the hospital, a set of single-use, enhanced PPE as compared to standard precautions cost an extra £2.50 per attendance, so up to £15 per day (data from NHS supplies), assuming six nursing staff entries and one doctor visit per day (Table II).

The donning/doffing procedure required two staff (using a 'buddy' system) and was both laborious and time-consuming. Assuming an additional 15 min for staff to don, doff, dispose of PPE, and complete the logbook register, for up to six attendances or entries per day, this deprives the nurses and doctors of time in which they could perform other duties.

For two nurses in a buddy system, this would then be $2 \times £29.50 = £59$ per patient, but only one of these nurses would use the enhanced PPE, giving a cost for six entries per day: $2 \times £29.50 + £15.00 = £74$. This time is doubled if two patients (e.g. a husband and wife) are admitted simultaneously, as we had in this case series, or if two nurses enter the patient room. This calculation is similar for the doctors (Table II).

In addition, there is a one-off (once per year) enhanced PPE training course that each nurse/doctor is required to attend before being permitted to care for these patients (i.e. a one-off £29.50 additional cost for each nurse), though this cost contribution is difficult to estimate because it also serves as training to manage other high-risk patients such as those suspected or confirmed to be infected with a viral haemorrhagic fever (VHF) (Table II). So this one-off cost is not considered specifically as an extra cost due to a suspected MERS-CoV infection.

Discussion

Our experience is currently not rare in UK hospitals and highlights several important points.

As with most assessments of returning Hajj pilgrims, none of our travellers actually had MERS-CoV, but were all managed as potential infections with strict isolation precautions until confirmed negative, even after an alternative diagnosis had been made.[7,8] A recent study, published by the same reference laboratory to which we send our samples for MERS testing, reported that out of the 202 patients tested during February 1st, 2013 to December 31st, 2015, none had laboratory-confirmed MERS-CoV infection. An alternative respiratory virus infection was diagnosed in half (50.3%) of the cases, including rhinoviruses, influenza A (H1N1 and H3N2), and influenza B, which were the most frequently detected. They found that peak testing occurred following the annual Hajj season and during other periods of increased national awareness.[13] The absence of any confirmed MERS-CoV-positive cases highlights the relevance and utility of the current study, but also highlights the need to encourage such pilgrims to increase their uptake of the seasonal influenza vaccine, as advised by one of their dedicated travel advice websites.[14]

However, with the increasing recognition that MERS-CoV causes a broader range of clinical illness, together with the potential for co-infection with other respiratory viruses leading to a delayed diagnosis of MERS-CoV, we felt that these patients justified the use of appropriate infection prevention measures until MERS-CoV infection had been excluded, as per published guidance.[4,5,8,14] Yet, the management of these patients using single, negative-pressure, isolation rooms, the limiting of staff interactions to essential duties with the use of enhanced PPE, and the secure transportation of laboratory specimens to an outside reference laboratory, posed significant resource and practical challenges in a busy hospital, particularly for patients (including one of ours) requiring intensive care.

In-house laboratory respiratory panel testing yielded results within 30 h at the most (assuming a worst-case scenario of a sample just missing the daily run which takes 6 h to complete, and no assay failure) and detected influenza A or B viruses in all of our patients. However, transportation of samples to the reference laboratory, with their once-a-day MERS-CoV testing

schedule, could potentially delay an exclusion of MERS-CoV by up to 24 h.

The testing of MERS-CoV in-house would reduce this waiting time by up to 27 h (assuming same-day sample receipt and testing, which will take about 6 h for most commercial assays), and allow the downgrading of infection prevention procedures, as well as possible patient discharge on influenza treatment. However, this is dependent on the local laboratory results being as reliable. Outside of the Hajj season our hospital sees patients returning from MERS-CoV endemic areas far less frequently. Ensuring that local results are valid would therefore require the local laboratory to regularly undergo quality assurance processes, which would slightly negate the cost-benefits of earlier MERS-CoV exclusion. In addition, the shelf-life of any commercial kit will also impact on the final overall costs of running this MERS-CoV testing service in-house. Unused, outdated test kits would need to be discarded and replaced to cope with any traveller returning sporadically throughout the years from a MERS-CoV-endemic area, with a clinical presentation that would make them eligible for MERS-CoV testing.

Our patients presented in early October 2015, ahead of the UK seasonal epidemic influenza activity. Thus, it is likely that their influenza viruses were acquired during Hajj from people who acquired their infection from other countries where influenza was already circulating, as has been previously described elsewhere.[7] Annual and, if possible, pre-travel influenza immunization of people attending Hajj pilgrimages may reduce their risk of influenza infection as is recommended on various websites, as well as by the Ministry of Health of Saudi Arabia.[14–16]

Although other pilgrimages occur throughout the year, the Hajj is a global event, attracting pilgrims from all over the world for a relatively short duration; our patients all presented within a four-week period. In order to facilitate timely transfer of high-risk patients from the emergency department into appropriate isolation, we planned to keep at least one single negative-pressure cubicle vacant at all times. However, this policy became impracticable during busy periods of high bed occupancy.

This case-series highlights the need to plan for predictable, yet potentially resource-challenging, events such as Hajj. In this particular situation, in-house MERS-CoV diagnostic testing would have facilitated earlier patient diagnosis with possible discharge, and a reduction in the level of PPE required, even if a longer inpatient stay were needed.

Conflict of interest statement
None declared.

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