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Middle East respiratory syndrome coronavirus (MERS-CoV) — Surveillance and testing in North England from 2012 to 2019

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ABSTRACT

Background: Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in Saudi Arabia in 2012 and caused an epidemic in the Middle East. Public Health England (PHE) Manchester is one of the two PHE centres in the UK that perform testing for MERS-CoV. The results of the PHE Manchester MERS surveillance from 2012 to 2019 are presented in this report.
Methods: Retrospective data were collected for returning travellers from the Middle East fitting the PHE MERS case definition. Respiratory samples were tested for respiratory viruses and MERS-CoV using an in-house RT-PCR assay.
Results: Four hundred and twenty-six (426) samples from 264 patients were tested for MERS Co-V and respiratory viruses. No MERS-CoV infections were identified by PCR. Fifty-six percent of samples were PCR positive for viral or bacterial pathogen with Influenza A as the predominant virus (44%). Sixty-two percent of all patients had a pathogen identified with the highest positivity from sputum samples. Patients with multiple samples demonstrated a 100% diagnostic yield.
Conclusions: Although no cases of MERS were identified, the majority of patients had Influenza infection for which oseltamivir treatment was indicated and isolation warranted. Sputum samples were the most useful in diagnosing respiratory viruses with a 100% diagnostic yield from patients with multiple samples.

Introduction

A novel coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in Saudi Arabia in 2012. The first case was a Saudi national admitted in June 2012 with pneumonia and renal failure which resulted in a fatal outcome. The case was later identified in September 2012 as a novel betacoronavirus belonging to lineage C (Zaki et al., 2012). Retrospective testing of samples in the Middle East identified a further nine cases in Jordan (Hijawi et al., 2013). The disease was considered a clinical syndrome ranging from asymptomatic cases to respiratory failure to multisystem organ failure. The syndrome was termed “Middle Eastern Respiratory Syndrome” (MERS) and testing was performed accordingly in the Middle East and for return travellers from Middle East countries based on epidemiological risk factors.

The second global case of MERS was identified in a Qatari national who had previously travelled to Saudi Arabia in 2012. He was transferred from Qatar to a hospital in England where he clinically deteriorated and was placed on extracorporeal membrane oxygenation (ECMO) however, unfortunately had a fatal outcome (Bermingham et al., 2012). A second case in the UK was confirmed in February 2013, in a return traveler from Pakistan and Saudi Arabia who was admitted with severe acute respiratory symptoms. This patient required ECMO treatment, however also unfortunately died. This case resulted in onward transmission to two further cases, of which one subsequently died (The Health Protection Agency UK Novel Coronavirus Investigation team C, 2013). In August 2018, a fifth case of MERS was diagnosed in a return traveler from the Middle East. The patient was initially

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admitted to a hospital in Leeds and then transferred to a specialist infectious disease unit in Liverpool. The patient had a positive outcome and there was no onward transmission of MERS-CoV to the close contacts (PHE, 2018)

As of the end of November 2019, MERS Co-V has infected 2,494 people with a case fatality rate (CFR) of 37.1% (World Health Organization W, 2019; (WHO) WHO, 2019) and a notably higher CFR in ITU settings (Arabi et al., 2014). Nosocomial outbreaks have occurred in Saudi Arabia and South Korea demonstrating the need for stringent infection control polices (Park et al., 2015). In view of the high risk of imported cases, Public Health England (PHE) commissioned regional centers to perform MERS-CoV testing for possible MERS cases arriving in England. PHE Manchester laboratory is one of two centers that currently perform testing for MERS-CoV. It receives samples from the Greater Manchester region and surrounding counties of Lancashire, Merseyside, Cumbria and Cheshire. Additionally it receives samples from other areas of the North-West region of the United Kingdom which entails the counties of Yorkshire, Humber and also the counties of the North-East region.

The Greater Manchester (GM) region has a population of around 2.5 million people with a black and minority ethnic population of 33.4% (Manchester City Council M, 2011); some of whom are more likely to travel to the Middle East for visiting friends or family, business, religious pilgrimage or tourism. The GM region also has a Muslim population of 15.8% (Office for National Statistics O, 2019; Review WP, 2018) which is greater than the national average in the United Kingdom of 5% (Office for National Statistics O, 2019). The Muslim population will visit the Kingdom of Saudi Arabia (KSA) at least once in their lifetime to the holy cities of Mecca and Medina for the compulsory pilgrimage of Hajj. Over 2 million pilgrims from 188 countries attend the Hajj annually, which may result in dissemination of MERS-CoV or other pathogens to multiple countries, including to the United Kingdom. Muslims also travel to KSA for Umrah (mini-pilgrimage) and Ramadan which may increase the possibility of the spread of MERS.

Manchester has the UK's third busiest airport (UK Civil Aviation Authority C, 2017) with around 27.8 million passengers being processed in 2017. It was specially adapted to accommodate the Airbus A380 which has a capacity of 853 passengers per flight. As a result of this, a significant proportion of passengers return from the Middle East to the Greater Manchester region.

Manchester also hosts the North-West region's tertiary Infectious Disease unit. The Regional Infectious Diseases Unit (RIDU) at North Manchester General Hospital accepts direct admissions of returning travelers with fever and consequently assesses a multitude of patients for possible MERS-CoV infection. The PHE Manchester laboratory works closely with RIDU and both provide a 7-day service.

We present a detailed analysis of the results of the surveillance for MERS-CoV testing at the PHE Manchester laboratory initially between 2012 to 2013 and then from 1st September 2015 to 1st February 2019.

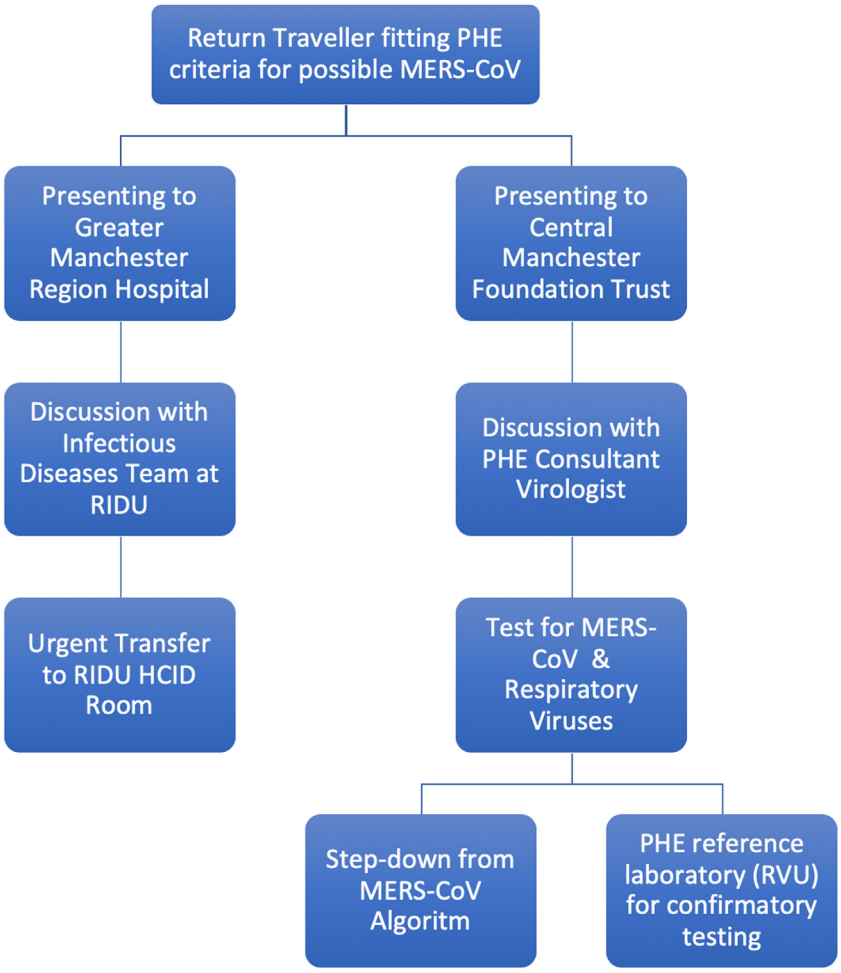

Figure 1. Greater Manchester MERS pathway.

Methods

Data collection of patients

Initial testing was carried out in 2012–2013 when the first MERS-CoV case was identified in the UK. There was pause in testing from June 2013 to September 2015 when testing was carried out at PHE Birmingham.

From 1st September 2015 to 1st February 2019, returning travellers presenting to any hospital in the North West region with respiratory symptoms from the Middle East were risk assessed for potential MERS-CoV infection. This risk assessment was performed utilizing the PHE MERS criteria with a possible case defined as:

1. A person with severe acute respiratory infection requiring admission to hospital with symptoms of fever ($\geq$38 °C) or history of fever and evidence of pulmonary parenchymal disease; and at least one of the following:

- History of travel to, or residence in an area where infection with MERS-CoV could have been acquired in the 14-days before symptom onset
- Close contact during the 14-days before onset of illness with a symptomatic confirmed case of MERS-CoV infection
- Person is a healthcare worker based in ICU caring for patients with severe acute respiratory infection, regardless of travel or PPE use
- Part of a cluster of two or more epidemiologically linked cases within a two-week period requiring ICU admission, regardless of history of travel

2. Acute influenza-like-illness symptoms (ILI), and contact with camels, camel environments or consumption of camel products in the 14-days prior to onset.

3. Acute respiratory illness (ARI) and contact with a confirmed case of MERS-CoV in the 14 days prior to onset.

Those meeting the PHE case definition were discussed with the Regional Infectious Diseases team and/or the Consultant Virologist and then tested for infection ((PHE) PHE, 2018a) (Figure 1).

The majority of cases were initially discussed with the RIDU team and then transferred to North Manchester General Hospital for further assessment in the negative pressure rooms with appropriate personal protective equipment (PPE) use. Some local hospital cases were discussed directly with the PHE Manchester Consultant virologist. In these scenarios, the risk assessment was directly carried out by the PHE Virologist and advice on infection control, use of PPE and FFP 3 masks was given to reduce the chance of nosocomial transmission in case the test was found to be positive (Figure 1). Local Health Protection Teams were involved throughout the process from the time of presentation to the referring hospital until the result of the testing.

Data were extracted from the laboratory information management system (LIMS) into MS Excel. After initial screening, data were extracted and analysed in SPSS. Utilising SPSS and Tableau Desktop, the results and figures were produced.

Samples

Respiratory samples were taken by the referring physician from the patient whilst in PPE. Both Upper Respiratory Tract (URT) samples (nose and throat swabs or nasopharyngeal aspirates) and Lower Respiratory Tract (LRT) sample (sputum or Bronchoalveolar lavage) were submitted. In addition, clotted blood was also requested and stored for possible serological testing in the future.

Other samples (urine for legionella and pneumococcal antigen, URT and LRT samples for bacterial culture) were submitted for investigation of other pathogens. All samples were processed at the appropriate containment level in accordance with national guidance. Samples were transported and packed in accordance with UN3373 (category B, biological substance) regulations (Public Health England P, 2016).

MERS-CoV and respiratory virus testing

URT and LRT samples were initially tested for MERS Co-V by a quantitative real time reverse transcription polymerase chain

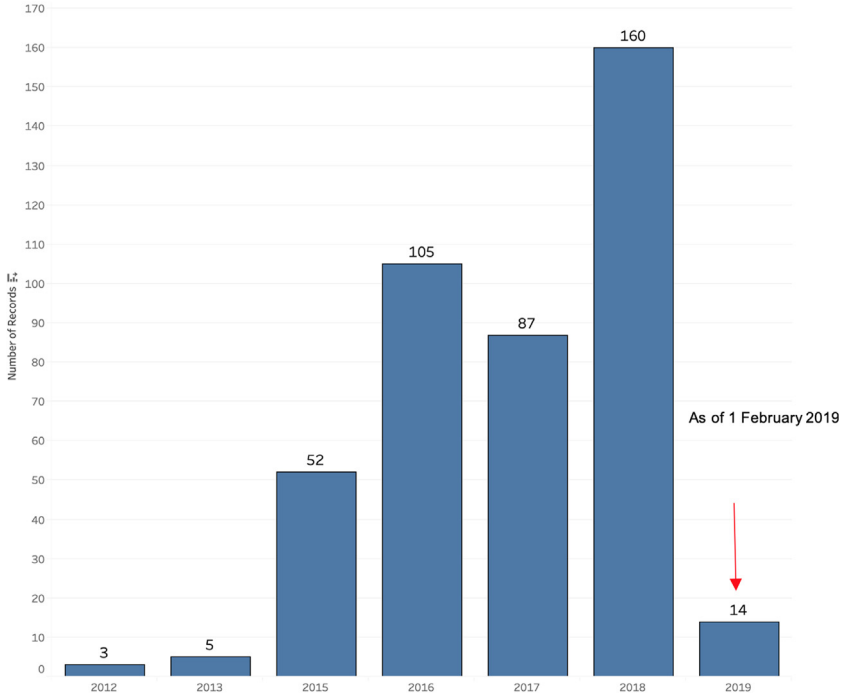

Figure 2. Number of samples received at PHE Manchester during the study period.

reaction (rRT-PCR) from 1st January 2012 to 31st December 2016 in all PHE centers.

An assay verification of CE marked commercially available testing kits for MERS-CoV across five PHE laboratories led to selection of the Altona RealStar MERS RT-PCR Kit for patient testing from January 2017 (Diagnostics A, 2019). All samples were also tested for Influenza A (Flu A -H1 and H3), Influenza B (Flu B), Respiratory syncytial virus (RSV), Rhinoviruses, Adenovirus (Adeno), Human Metapneumovirus (MPV) and Parainfluenza Virus (PF Types 1-3). Testing is performed using a mixture of triplex (FluA/FluB/RSV, PF1-3), duplex (Adeno/Rhino) and singleplex (MPV) PCR assays.

Results

Samples

Four hundred and twenty-six samples (426) were received for two hundred and sixty-four (264) patients who fulfilled the criteria of MERS Co-V testing under the PHE case definition algorithm ((PHE) PHE, 2018a) (Figure 2). Samples were sent from locations throughout the North-West of England with the majority sent from the regional infectious disease unit and from university teaching hospitals (Supplementary Figures S1 and S2).

Patient demographics

Patient age ranged from 18 weeks to 89 years old. Patient demographic characteristics are shown in Table 1. Fifty-five percent of patients were of Asian background with 23% and 19% of Arab and Caucasian backgrounds, respectively (Supplementary Figure S3).

Travel history

The travel history as noted on the LIMS system and request forms showed the majority of patients returned from KSA (102) and the UAE (Refaey et al., 2017) as demonstrated by Figure 3 and Supplementary Figure S4.

Results of testing

Of 426 samples, 55% (234) were positive for a viral pathogen. 44% were negative via viral PCR testing and considered of bacterial origin (Supplementary Figure S5). Of note, 18 samples were positive for dual viral infections with 1 sample positive for a triple viral infection (Supplementary Figures S6 and S7).

Sample types and number of samples per patient

The majority of samples sent were nose and throat swabs (179), sputum samples (120) and throat swabs (60), as demonstrated by Figure 4.

Sputum samples had the highest positivity rate for viral pathogens (69.17%) followed by BAL samples (57.14%) as shown by Supplementary Figure S8.

Patient end-diagnosis positivity for a viral pathogen is 100% when more than 4 samples are sent. This is in contrast to an end-diagnosis positivity of 51.1% when 1 sample is sent for a patient (Supplementary Figures S9 and S10).

Total results by patient

Four hundred and twenty-six (426) samples were sent for 264 patients. Hence, if the results were viewed according to patient numbers, the percentage of total patients with positive microbiological end-diagnoses increases to 62% (Figure 5)

Viral results

Supplementary Figures S11 and S12 demonstrates the number of positive viral results of patients and the subsequent positive dual and triple viral infections.

Bacterial results

Of the 10% bacterial aetiology patients, 29% of patients were positive for Legionella initially via urinary antigen testing and then confirmed via reference laboratory testing. 15% of total patients were positive for co-infection with Methicillin Sensitive *Staphylococcus aureus* (MSSA) and Group G Streptococcus. The rest were equally divided for *Escherichia coli* (*E.coli*), Haemophilus influenza, PCP and Mycoplasma (Supplementary Figure S13).

Peak testing for MERS-CoV

The dates for Hajj, Umrah and Ramadan fluctuates every year as the Islamic calendar is lunar based; the dates usually change by 10 days annually (Table 2). Supplementary Figures S10 to 183 demonstrate the testing for MERS-CoV and subsequent results at PHE Manchester during the period of 2012 to 2013 and then from 2015-2018 demonstrating seasonal variation.

Discussion

During the surveillance period, there were no MERS-CoV detected at PHE Manchester from travellers returning from the Middle East. This correlates with PHE Birmingham's data during a similar period (Atabani et al., 2016) and the wider global findings via the WHO and Pro-Med monitoring reports. However, as discussed previously, in August 2018, a MERS-CoV case was diagnosed positive by PHE Birmingham highlighting the need for continued vigilance ((PHE) PHE, 2018b). Of the patients whose travel history was known (145), the majority travelled to the Kingdom of Saudi Arabia and the United Arab Emirates. Unfortunately, 123 patients had no travel history documented on the databases, demonstrating the need for improving travel history documentation on clinical laboratory request forms. Other patients had travelled to various countries in the Middle East (Supplementary Figure S4).

When analysing the sample type, of note is that the highest positivity is of sputum samples, followed by BAL. Although the lowest positivity of samples is of nasopharyngeal aspirates (NPA), the number of samples was too low for this to be considered significant as only one NPA sample was received.

Table 1
Patient demographics of referred samples to PHE Manchester (2012–2019).

Age	0–16	17–30	31–45	46–60	60–75	>75	Total
Male	11	22	27	46	36	19	161 (61%)
Female	5	12	17	31	25	13	103 (39%)
Total	16 (6%)	34 (13%)	44 (17%)	77 (29%)	61 (23%)	32 (12%)	264 (100%)

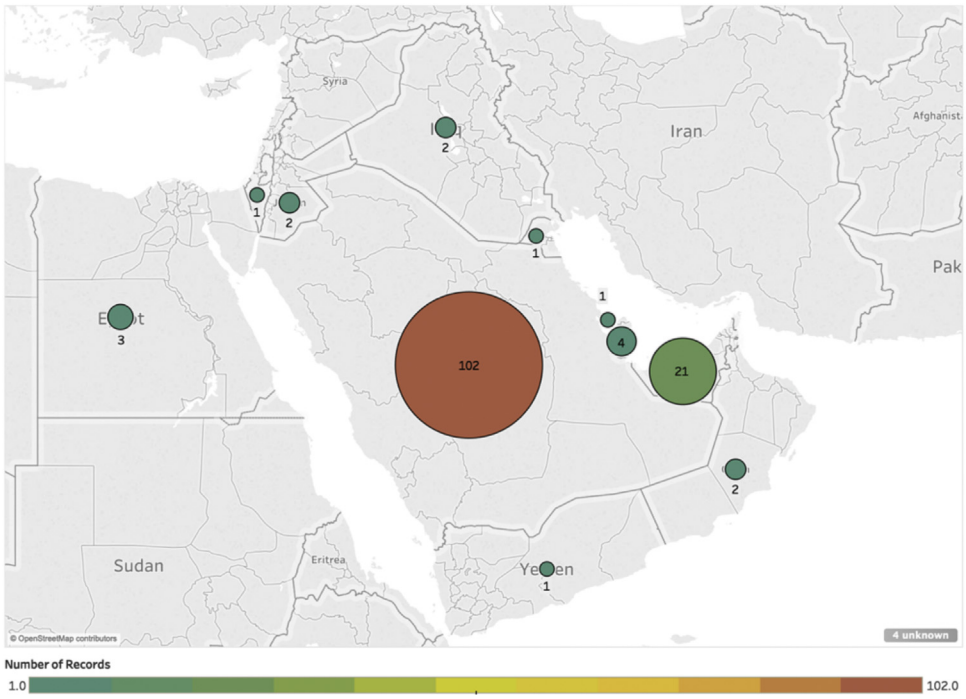

Figure 3. Travel history of patients to PHE Manchester during the study period.

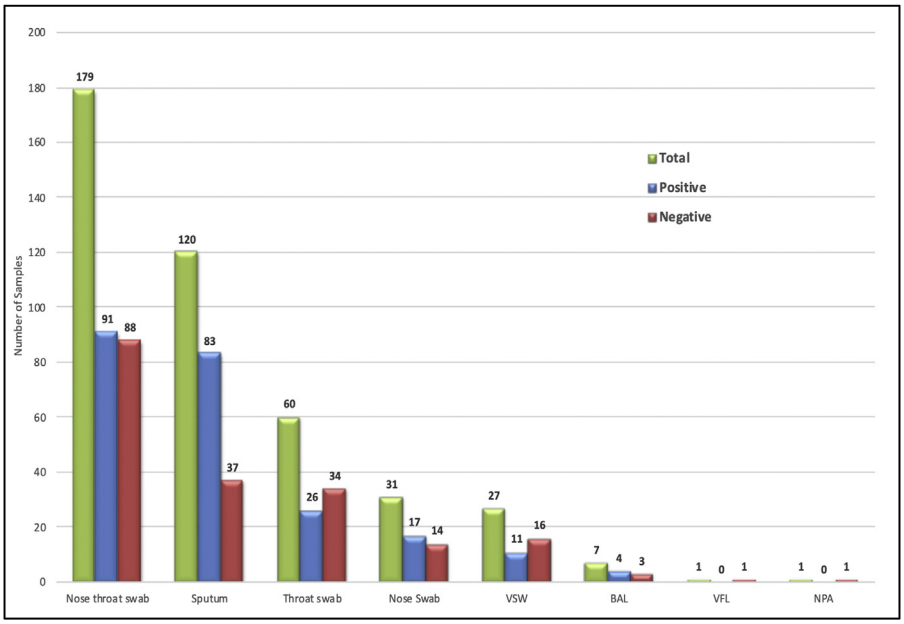

Figure 4. Type of samples sent patients to PHE Manchester during the study period.

Four hundred and twenty-six samples were sent for a total of 264 patients, as some of the referring hospitals sent multiple samples per patient as advised to ensure a PCR confirmed end-diagnosis for the patient. Patients with four or more samples sent had a confirmed end-diagnosis, contrasting with an end-diagnosis in only half of patients with one sample sent. However, a limitation in this study is a low number of patients who have had greater than four samples sent.

Although 56% of all samples were PCR positive for a pathogen, if the results were viewed according to patient numbers, 62.1% of all patients had a positive microbiological result. This was due to the bacterial investigations eliciting a positive diagnosis and higher pathogen positivity in patients who have had more than two samples sent. For patient numbers, the most common viral pathogen for the tested patients was Influenza A followed by Rhinovirus. Of total patients, 10% were positive for a bacterial pathogen via PCR testing or culture/antigen results.

During 2015, PHE Manchester received the greatest number for MERS Co-V testing in October. This correlates with the post Hajj period (21st to the 26th of September 2015 - Supplementary Figure S16). During 2016, the greatest number of samples received was during July (Supplementary Figure S17). This did not correlate with Hajj (10th–15th September 2016), however, it did correlate with the post Ramadan period (6th June–5th July 2016) and post

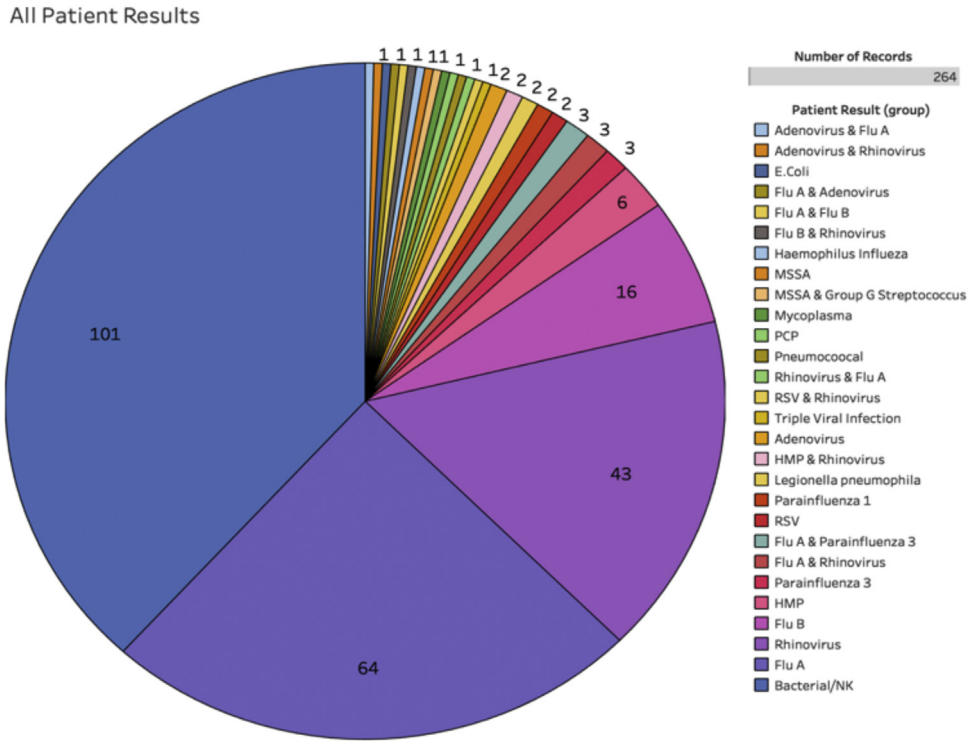

Figure 5. Patient end-diagnoses of referred samples to PHE Manchester during the study period.

Table 2
Dates of Hajj and Ramadan during PHE Manchester testing periods (2012–2018).

Year	Hajj dates	Ramadan dates
2012	25th October 2012	20/7/12–19/8/12
2013	14th October 2013	9/7/13–8/8/13
2015	23th September 2015	18/6/15–18/7/15
2016	11th September 2016	7/6/16–6/7/16
2017	31st August 2017	27/5/17–26/6/17
2018	20th August 2018	16/5/18–15/6/17

vacation period with tourism travel to Dubai and the UAE. A secondary peak was in April which could correlate to the period after the Easter school holidays (25th March–10th April 2016) when travellers may be returning to the UK after travel to the Middle East for tourism purposes. The peak testing for 2017 was during the months of September and November. This occurred post-Ramadan (26th May–24th June 2017) and Hajj (30th August–4th September 2017). This is longer than the 14-day incubation period for MERS which may be explained by pilgrims extending their stay for the holy festival of Eid, thus, resulting in possible increased exposure to other MERS-infected people and/or camel exposure.

It is likely there will be more testing after these periods, especially as travellers might also be returning via the Middle East after the summer vacation months. Similarly the peak testing was September and June in 2018 correlating post Hajj (19th–24th August 2018) and Ramadan (16th May–14th June 2018). Combined with the UK school vacation periods this resulted in more returning travellers, causing a higher testing rate after these periods.

As the clinical spectrum of MERS is broad, there is the possibility that some cases may be missed in asymptomatic patients who do not fit the PHE criteria and those patients who do not attend hospital. However, the risk of transmission from asymptomatic cases is considered lower than symptomatic cases, thus there is less of a need to focus on these patients from a public health perspective (Moon and Son, 2017). Furthermore, attempting to screen every traveller returning from a MERS-CoV endemic country would be very difficult from both logistical and financial perspectives. In this scenario, it would be prudent to test for seroprevalence of MERS-CoV in travellers returning from the Middle East to establish if there are any MERS-CoV cases which do not fit the PHE MERS-CoV criteria.

The primary finding of this study is that 56% of the samples had a viral aetiology with 62.1% of total patients being positive. Influenza A was the most common viral cause followed by Rhinovirus. Although no patient was positive for MERS-CoV, this positivity for Influenza A amongst travellers returning from the Middle East demonstrates the need to carry out infection control measures with isolation in side-rooms to reduce nosocomial spread of Influenza A and other respiratory viruses. It also demonstrates the need for empirical use of Neuraminidase inhibitors pending the viral result for the assessed patients. Previous studies (Refaey et al., 2017; Annan et al., 2015; Benkouiten et al., 2014; Assiri et al., 2014; Zumla et al., 2016) in the Middle East have also demonstrated the high positivity for Influenza A virus in returning Hajj pilgrims. This gives more evidence that influenza vaccination should be advised before travel for people considering Hajj.

A secondary finding was the high positivity of sputum samples compared to BAL samples. Previous studies have demonstrated the higher yield of BAL testing to sputum testing (Sing et al., 2000) for PCP testing and of the higher yield of sputum compared to nasopharyngeal swabs (Falsey et al., 2012). This study demonstrates the higher yield of sputum but not of BAL testing. However, the limitation here is of the higher number of sputum samples (n = 120) submitted compared to BAL samples (n = 7). Additionally, it is

noted that sputum PCR positivity is higher than the combined pool positivity of all nose, throat and combined nose-throat swabs. However the total number of sputum samples received is 120 compared to 270 samples received for nose, throat or combination NT swabs. This finding demonstrates the need for further studies on sample type and PCR positivity of respiratory viruses.

Also of note is the higher positivity rate when a higher number of samples is sent by the referring hospital. For diagnosis of MERS-CoV, PHE Manchester requests samples for sputum, nose ± throat swabs, BAL (if available) and clotted blood. Due to the high clinical workload of the referring hospitals, we received a variable number of samples per patient. In this study we have seen that patients who have greater than four samples sent demonstrated a 100% diagnostic yield compared to 51.1% when one sample per patient was sent. In one specific patient case, six samples were sent, of which only 1/6 was positive for Influenza A. We conclude from our observation that four samples or more from a patient should be taken to ensure a viral diagnosis.

Conclusion

Although no cases of MERS Coronavirus were identified at PHE Manchester, the majority of patients identified under the PHE MERS criteria had a viral respiratory pathogen for which Neuraminidase inhibitors treatment was indicated and for whom nosocomial isolation was warranted. Respiratory tract viral infections post travel to the Middle East are common and vaccination for influenza is strongly recommended for people travelling to the Middle East for religious purposes.

With the positive MERS-CoV case in August 2018 in the UK and previous devastating nosocomial outbreaks of MERS in the world, it is essential to raise awareness of this fatal pathogen. We need to continue proactive investigation and rapidly identify and isolate possible MERS-CoV patients after return from the Middle East. We need to continue surveillance of returning travellers at risk for MERS-CoV infection not only to further the knowledge of this important syndrome but also to facilitate the public health response and management of cases. MERS-CoV is a high consequence infectious disease which requires the highest vigilance to ensure preventing its spread and lethal outcomes.

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Conflicts of interests

All authors declare they have no conflicts of interests or anything to declare.

Ethical approval

Ethical approval was not obtained as this study is an analysis of laboratory surveillance data. However, patient identifiable information was anonymized to ensure patient confidentiality during the data analysis.

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Appendix A. - Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.01.043.

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