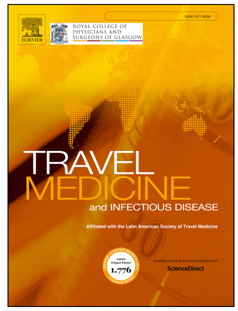

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Respiratory virus detection in returning travelers and pilgrims from the Middle East

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Abstract: Background: Pilgrims travelling to Saudi Arabia are commonly infected with respiratory viruses. Since the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) emerged in 2012, patients with acute respiratory symptoms returning from an endemic area can be suspected to be infected by this virus. Methods: 98 patients suspected to have MERS-CoV infection from 2014 to 2019 were included in this retrospective cohort study. Upper and lower respiratory tract samples were tested by real time RT-PCR for the detection of MERS-CoV and other respiratory viruses. Routine microbiological analyses were also performed. Patient data were retrieved from laboratory and hospital databases retrospectively. Results: All patients with suspected MERS-CoV infection travelled before their hospitalization. Most frequent symptoms were cough (94.4%) and fever (69.4%). 98 specimens were tested for MERS-CoV RNA and none of them was positive. Most frequently detected viruses were Enterovirus/Rhinovirus (40/83 - 48.2%), Influenzavirus A (34/90 - 37.8%) and B (11/90 - 12.2%), H-CoV (229E and OC43 10/83 - 12% and 7/83 - 8.4%, respectively). Conclusion: From 2014 to 2019, none of 98 patients returning from endemic areas was MERS-CoV infected. However, infections with other respiratory viruses were frequent, especially with Enterovirus/Rhinoviruses and Influenzaviruses.

Keywords: Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Pilgrims, Saudi Arabia, Enterovirus, Influenzavirus, respiratory virus, PCR, SARS-CoV2

Highlights:

- Most frequent symptoms leading to MERS-CoV infection suspicion were cough and fever
- No MERS-CoV detected in travelers returning from Middle East from 2014 to 2019
- Most frequently detected viruses were Enterovirus/Rhinovirus, Influenzavirus A and B

Abbreviations:

- CNIL: Commission nationale de l’informatique et des libertés
- HCoV: Human Coronavirus
- MERS-CoV: Middle East Respiratory Syndrome Coronavirus
- SARS-CoV: Severe-Acute Respiratory Syndrome Coronavirus

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Conflicts of Interest

The authors declare no conflict of interest.

1. Introduction

Human coronaviruses (HCoV) are enveloped, positive-sense non-segmented RNA viruses and are characterized by the presence of spikes on the envelope that remind the aspect of solar corona. They belong to the *Coronaviridae* family of the *Nidovirales* order and infect multiple mammals and birds. They cause respiratory, digestive and neurologic infections. *Coronavirinae* are divided in four genera, namely Alpha-, Beta-, Gamma- and Deltacoronavirus according to their phylogenetic characteristics [1].

7 *Alpha-* and *Betacoronaviruses* infect humans. Four cause respiratory infections in immunocompetent hosts: HCoV 229E, HCoV NL63, HCoV OC43 and HCoV HKU1. The other three are highly pathogenic and cause severe respiratory syndromes such as: SARS-CoV (Severe-Acute Respiratory Syndrome Coronavirus), MERS-CoV (Middle East Respiratory Syndrome Coronavirus) and more recently SARS-CoV-2 (Severe-Acute Respiratory Syndrome Coronavirus 2) [2,3].

MERS-CoV has first been detected in a patient hospitalized in Saudi Arabia who died 11 days later due to kidney and respiratory failures [4]. This virus, discovered in 2012, caused 886 deaths (in 2574 MERS-CoV positive patients) until 11 March 2021 [5]. It spread in neighboring countries essentially in Qatar, Jordan and cases have been detected worldwide. In 27 countries that reported infected patients, the majority came from Saudi Arabia [6]. However, a MERS-CoV epidemic was also observed in South Korea [7].

The aim of this work was to study epidemiological, clinical and microbiological characteristics of patients with suspected MERS-CoV infection returning from endemic areas from 2014 to 2019.

2. Materials and Methods

2.1. Patients and specimens

98 patients with suspicion of MERS-CoV infection from March 2014 to September 2019 were retrospectively retrieved from the laboratory database and included in this retrospective cohort study. Clinical data of 72 patients that were hospitalized at Lille University Hospital were retrospectively collected from medical files.

Data collected were: specimen type, detected viruses, results of bacterial cultures, travel history, symptoms, comorbidities and anti-infectious treatment mentioned in medical files.

Upper respiratory tract specimens were defined as nasal swabs, sputum and nasopharyngeal aspirations.

Lower respiratory tract specimens were defined as induced sputum, bronchoalveolar lavages and tracheal aspirations.

Fever was defined as body temperature > 38°C or documented as fever by medical staff.

The definition used to define a patient as a possible MERS-CoV infection was the French definition written by the High Council of Public Health. There were three definitions used since the outbreak: June 2013 [8] April 2015 [9] and May 2018 [10] with several differences between each other. The definition of 2013 did not refer to the animal contacts nor to the stay in a hospital of the listed countries. This definition is based on a 10-day period upon return from endemic zones. The definition of 2015 differs with the 2018 definition only on one point: signs of pulmonary parenchyma infection had not to be confirmed by a thoracic radiography.

For the present study, we decided to use the latest definition to classify patients retrospectively. This definition [10] contains:

1/ each person who traveled or lived, in a restricted list of countries (i. e. Saudi Arabia, Bahrein, United Arab Emirates, Kuwait, Oman, Qatar, Yemen, Iraq and Jordan), who presented within 14 days after the return:

- signs of acute distress respiratory syndrome (ARDS)
- or signs of pulmonary parenchyma infection confirmed by a thoracic radiography with fever ≥38°C and cough

2/ each contact of a possible or confirmed case who presented an acute respiratory infection within 14 days following the last contact with an infected patient.

3/ each person who worked in or was admitted to a hospital in the restricted list of countries and who presented an acute respiratory infection within 14 days following the last contact with the Institution.

4/ each person who was in contact with camels or related products (non pasteurized milk, raw meat, urine) in a restricted list of countries and who presented an acute respiratory infection within 14 days.

For immunosuppressed people or people affected by a chronic disease, it needed to consider a fever syndrome with diarrhea and/or a severe clinical situation.

2.2. Laboratory procedures

RT-PCR for the detection of MERS-CoV RNA was performed on all specimens. Different assays were used during the study period: (1) a real-time RT-PCR targeting the upE, Orf1a or Orf1b regions of the MERS-CoV genome [11,12] was used from 2014 to 2019 and (2) the Filmarray Respiratory Panel 2 Plus (RP2 Plus) was used in 2018 and 2019.

In addition, as prescribed by the physician in charge of the patients, different commercially available RT-PCR assays (Table 1) were used for routine diagnostics of respiratory viruses when patients presented a suspicion of MERS-CoV infection. Bacteriological analyses were performed for routine diagnostics as prescribed by the physician in charge of the patients by using blood culture, serology, sputum and pulmonary cultures, urine culture, urine antigens.

Table 1: Multiplex RT-PCR assays

Assay	Years of application	Viruses included
Xpert Flu A/B (Cepheid®)	2014	Influenzavirus A, B
AnyplexTM II RV16 Detection (Seegene)	2014, 2015	Influenzavirus A, B, Parainfluenzavirus 1, 2, 3, 4, RSV A, B, Adenovirus,Metapneumovirus,Rhinovirus A/B/C, Enterovirus, Coronaviruses 229E, NL63, OC43, Bocavirus
AllplexTMRespiratory Panel (Seegene)	2016 - 2018	Influenzavirus A, B, Parainfluenzavirus 1, 2, 3, 4, RSV A, B, Adenovirus, Metapneumovirus, Rhinovirus,Enterovirus, Coronaviruses 229E, NL63, OC43, Bocavirus.
Film Array Respiratory Panel® (bioMérieux)	2016 - 2019	Influenzavirus A, B, Parainfluenzavirus 1, 2, 3, 4, RSV, Adenovirus, Metapneumovirus,Rhinovirus/Enterovirus, Coronaviruses HKU1, NL63, 229E, OC43, Bordetella pertussis, Chlamydophila pneumoniae, Mycoplasma pneumoniae
Filmarray Respiratory Panel 2 Plus (RP2 Plus) (bioMérieux)	2018, 2019	Influenzavirus A, B, Parainfluenzavirus 1, 2, 3, 4, RSV, Adenovirus, Metapneumovirus, Enterovirus/Rhinovirus, Coronaviruses HKU1, NL63, 229E, OC43, MERS Coronavirus, Bordetella pertussis, Bordetella

	parapertussis, Chlamydophila pneumoniae, Mycoplasma pneumoniae,

RSV = Respiratory syncytial virus

2.3. Statistical analysis

Descriptive statistics were performed by using IBM SPSS Statistics 22. Results were reported as numbers and percentages.

2.4. Ethics, consent and approval

It was a retrospective noninterventional study with no additional procedures. This study was registered by the CNIL (Commission nationale de l'informatique et des libertés) under study number DEC21-197.

3. Results

3.1. Study population and specimens

98 patients with suspected MERS-CoV infection were included in the study and had at least one specimen tested for MERS-CoV (mean number of specimens per patient 1.3, median 1.0). Most patients had only one lower respiratory tract (LRT) specimen (64.3% - 63/98) tested while 88.2% (77/98) of sampling contained at least one LRT specimen.

3.2. Micro-organisms detected

Of the 98 patients tested from 2014 to 2019, 80.1% (79/98) had an infection with a documented microorganism. No specimen was found positive for MERS-CoV (0% - 0/98) (Figure 1). Most frequently detected viruses were Enterovirus/Rhinovirus (48.2% - 40/83) followed by Influenzavirus A and B (37.8% - 34/90 and 12.2% - 11/90 respectively). Other viruses were less frequently detected, such as, by order of frequency, H-CoV (229E and OC43 12% - 10/83 and 8.4% - 7/83 respectively), Adenovirus (8.4% - 7/83), Metapneumovirus (3.6% - 3/83), Parainfluenzavirus 1 (1.2% - 1/83), RSV (1.2% - 1/84).

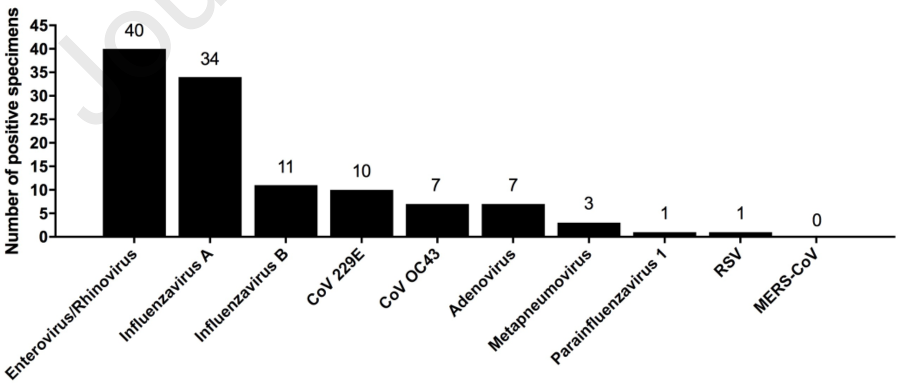

Figure 1: Detection of viruses in 98 returning travelers and pilgrims from the Middle East.

In 69/72 (95.8%) patients hospitalized at Lille University Hospital microbiological investigations were undertaken simultaneously. These were most often negative (79.2%). However, *Streptococcus pneumoniae* and *Haemophilus influenzae*were detected in 5 (7.2%) and 3 (4.3%) patients respectively. Other bacteria such as *Escherichia coli*, *Legionella pneumophila* and *Micrococcus luteus* were detected in three different patients (1.5% each).

39 patients were had coinfections. Most coinfections were virus/virus and Enterovirus/Rhinovirus were the most frequent viruses detected in coinfections (in 64.1% of coinfections). Table 2 summarizes detected viruses and coinfections found in our study.

Table 2: Pathogens detected in patients with suspected MERS-CoV infection

Coinfection / Virus	None	EV/RV	Inf. A	Inf. B	CoV 229E	CoV OC43	AdV	HMpV	Parainf. 1	RSV	MERS-CoV	Bacteria	Yeasts	Total
EV/RV	15		12	1	6	4	3	2	1	1	0	3	0	40
Inf. A	14	12		0	2	2	2	0	1	1	0	2	1	34
Inf. B	6	1	0		0	1	0	0	0	0	0	3	0	11
CoV 229E	3	6	2	0		1	2	1	0	0	0	2	0	10
CoV OC43	1	4	2	1	1		0	0	0	0	0	0	0	7
AdV	3	3	2	0	2	0		0	0	0	0	0	0	7
HMpV	0	2	0	0	1	0	0		0	0	0	1	0	3
Parainf 1	0	1	1	0	0	0	0	0		1	0	0	0	1
RSV	0	1	1	0	0	0	0	0	1		0	0	0	1
MERS-CoV	0	0	0	0	0	0	0	0	0	0		0	0	0

Abbreviations: EV/RV = Enterovirus/Rhinovirus, Inf. A = Influenzavirus A, Inf. B = Influenzavirus B, CoV = Coronavirus, AdV = Adenovirus, HMpV = Human Metapneumovirus, Parainf 1 = Parainfluenzavirus 1, RSV = Respiratory Syncytial virus

3.3. Patient characteristics

Of the 72 patients who were hospitalized at Lille University Hospital, 27 did not fulfill the case definition of 2018 (Table 3).

Clinical data of MERS-CoV suspected patients are summarized in table 3. 55.6% of patients were female and the median age was 65.5 years old (range 22-83 years). 54.2% (39/72) of patients were 65 years old or older. Many patients had comorbidities (87.5% - 63/72). 40.3% of patients had cardiovascular and metabolic comorbidities and 41.7% chronic pulmonary pathologies (Table 3).

Of the 72 patients with clinical information available, 100% (72/72) travelled before their hospitalization. 95.8% (69/72) came back from Saudi Arabia, 2.8% (2/72) from Jordan and 1.4% (1/72) reported a trip to Czech Republic, Dubai and Turkey. In most cases (93.0% - 66/71) there was no contact with camels (Table 3).

Most common symptoms were cough and fever, found in 94.4% and 69.4% of patients, respectively. Nausea was found in 22.2% (16/72) of patients. Dyspnea or respiratory distress were found in 36.1% of cases. Myalgia was reported in 22.2% (16/72) of patients. Pulmonary abnormalities on clinical examination were observed in 74.3% of patients.

Imaging examination was available for 67 (of 72) patients. The most used exam (94.0% - 63/67) was chest x-ray. 77.6% of imaging examinations found pulmonary parenchyma lesions.

88.9% of patients were treated with antibiotics, 54.7% received multiple antibiotics (Table 3). Most of antibiotics prescribed were ß-lactam and the most used was the association of a ß-lactam with a ß-lactamase inhibitor (Amoxicillin/Clavulanic acid, 48.6%). Other antibiotics included Amoxicillin (25.0%), third-generation cephalosporins (Cefotaxime, 38.9%; Ceftriaxone, 15.3%; Cefixime, 1.4%), quinolones (Levofloxacin; 13.9%), Macrolides (Spiramycin, 8.3%; Clarithromycin, 2.8%; Roxithromycin, 2.8%; Azithromycin, 1.4%), Streptogramins (Pristinamycin, 4.2%) and aminoglycosides (Gentamicin, 2.8%).

Antiviral therapy with oseltamivir was prescribed in 63.9% of patients.

Most of patients were treated with a combination of antibiotics and oseltamivir (59.7%). 21/72 (29.2%) were treated only with antibiotics. 5/72 (6.9%) of patients received no antimicrobial treatment while 3/72 (4.2%) were treated with oseltamivir only.

41.7% of patients received oxygen treatment (Table 3).

Table 3: Clinical characteristics of patients with suspected MERS-CoV infection

Characteristics		Criteria of 2018 definition fulfilled (n=45)	Not all criteria fulfilled 2018 definition (n=27)	Total (n = 72)
Sex ratio (F/M) (number, %)		0.51/1 (23/45 – 51.1%/ 48.9%)	1.70/1 (17/10 - 63.0%/37.0%)	1.25/1 (40/32 – 55.6%/ 44.4%)
Age, median (range)		66 years (22 – 83)	63.0 years (26 – 77)	65.5 years (22 - 83)
Comorbidities	Chronic CMP*	16/45 (35.6%)	13/27 (48.1%)	29/72 (40.3%)
	Chronic PP	23/45 (51.1%)	7/27 (25.9%)	30/72 (41.7%)
	HBP	15/45 (33.3%)	11/27 (40.7%)	26/72 (36.1%)
	T2D	17/45 (37.8%)	10/27 (37.0%)	27/72 (37.5%)
Clinical examination	Fever	35/45 (77.8%)	15/27 (55.6%)	50/72 (69.4%)
	Cough	42/45 (93.3%)	26/27 (96.3%)	68/72 (94.4%)
	Dyspnea	18/45 (40.0%)	8/27 (29.6%)	26/72 (36.1%)
	Pulmonary abnormalities	36/43 (83.7%)	16/27 (59.3%)	52/70 (74.3%)
Radiological	Pulmonary parenchyma lesions	44/45 (97.8%)	10/22 (45.5%)	54/67 (80.6%)
Exposition	Travel before hospitalization	45/45 (100%)	27/27 (100%)	72/72 (100%)
	Return from Saudi Arabia	43/45 (95.6%)	26/27 (96.3%)	69/72 (95.8%)
	Contact with camels	3/45 (6.7%)	2/26 (8.3%)	5/71 (6.9%)
Use of antibiotics		44/45 (97.8%)	20/27 (74.1%)	64/72 (88.9%)
When use of antibiotics → combination used		26/44 (59.1%)	9/20 (45.0%)	35/64 (54.7%)
Antiviral treatment		30/45 (66.7%)	16/27 (59.2%)	46/72 (63.9%)
Combination antibiotics + antiviral treatment		30/45 (66.7%)	13/27 (48.1%)	43/72 (59.7%)
Oxygen therapy		22/45 (48.9%)	8/27 (29.6%)	30/72 (41.7%)

Abbreviation: CMP: cardiovascular and metabolic pathologies / HBP: High Blood Pressure / PP: Pulmonary pathologies / T2D: Type 2 Diabetes
* Chronic CMP except HBP and T2D

4. Discussion

In this study, we showed that MERS-CoV suspicion was evoked in 98 patients who returned from a journey to the Arabian Peninsula and had clinical respiratory signs (cough was the most represented symptom) from March 2014 to September 2019. However, MERS-CoV infection was confirmed in none of them.

Our clinical data show that MERS-CoV diagnostic testing was performed even if all criteria of the definition were not present. Indeed, some patients benefited from MERS-CoV diagnostic testing with no or prior to radiological examinations because of the delay in carrying out radiologic examinations in clinical practice. The subgroup of patients who did not fulfill all criteria of the case definition of 2018 were therefore shown in a separate column in table 3.

In France, 2 MERS-CoV were hospitalized in Lille University Hospital in 2013 [13]. No MERS-CoV infections have been detected in Lille University Hospital since 2013 but other respiratory viruses were detected frequently in patients with suspected MERS-CoV-infection. The three most frequently detected viruses in the present study were, in order of frequency, Enterovirus/Rhinovirus, Influenzavirus A and Influenzavirus B.

Influenzavirus infection among pilgrims is well described but no Enterovirus infections were found in the study of Balkhy and colleages [14. This study used cell culture coupled with immunofluorescence. The lack of sensitivity of this technique in comparison with RT-PCR could explain this finding.

Our data are in agreement with other studies reporting that mainly Enterovirus/Rhinovirus, Influenzavirus and non-MERS human coronaviruses were detected in returning travelers and pilgrims from the Middle East with acute respiratory symptoms [15–18]. Enteroviruses and Rhinoviruses belong to *Enterovirus* genus of the *Picornaviridae* family. This genus is diversified with many species that cause various acute and chronic diseases [19]. These viruses were found in nearly 50% of specimen tested when MERS-CoV infection was suspected.

Most of patients suspected to have MERS-CoV infection were treated with a combination of antibiotics and oseltamivir, an antiviral medication used to treat and prevent influenzavirus (A and B) infections[20,21].

Mass gatherings, for example religious gatherings like the Hajj, or others, such as Olympics, are a recognized for their role in the spread of respiratory pathogens [22]. Since the end of 2019, another human coronavirus, named SARS-CoV-2, emerged and caused the ongoing COVID-19 pandemic [23]. Mass gatherings also played an important role in the initial spread of SARS-CoV-2 [24]. Rapidly preventive measures, such as cancellation of mass gatherings, travel restrictions and other containment measures were taken to slow down spread of SARS-CoV-2 [25] and the government of Saudi Arabia canceled the entrance of international Hajj pilgrims in 2020 in order to avoid massive spread of SARS-CoV-2 [26]. Taken together, this shows that well-known and emerging respiratory pathogens represent a challenge for public health authorities in the context of mass gatherings and international travel.

Study limitations: due to the retrospective nature of the study, there are missing data. Furthermore, different techniques were used for the detection of MERS-CoV and other respiratory viruses during the study period. In addition, the diagnostic techniques did not allow us to discriminate *Enterovirus* species.

5. Conclusions

We found no MERS-CoV infections in hospitalized travelers returning to the north of France from endemic areas from 2014 to 2019. These results are in accordance with earlier studies from other geographic regions. However, other viruses were frequently detected such as Enterovirus/Rhinovirus, Influenzavirus A/B and H-CoV.

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