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A systematic review of emerging respiratory viruses at the Hajj and possible coinfection with *Streptococcus pneumoniae*

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ABSTRACT

Background: The annual Hajj to the Kingdom of Saudi Arabia attracts millions of pilgrims from around the world. International health community's attention goes towards this mass gathering and the possibility of the development of any respiratory tract infections due to the high risk of acquisition of respiratory viruses.
Method: We searched MEDLINE/PubMed and Scopus databases for relevant papers describing the prevalence of respiratory viruses among Hajj pilgrims.
Results: The retrieved articles were summarized based on the methodology of testing for these viruses. A total of 31 studies were included in the quantitative/qualitative analyses. The main methods used for the diagnosis of most common respiratory viruses were polymerase chain reaction (PCR), culture and enzyme-linked immunosorbent assay (ELISA). Influenza, rhinovirus and parainfluenza were the most common viruses detected among pilgrims. Coronaviruses other than MERS-CoV were also detected among pilgrims. The acquisition of MERS-CoV remains very limited and systematic screening of pilgrims showed no infections.
Conclusions: Well conducted multinational follow-up studies using the same methodology of testing are necessary for accurate surveillance of respiratory viral infections among Hajj pilgrims. Post-Hajj cohort studies would further evaluate the impact of the Hajj on the acquisition of respiratory viruses.

1. Introduction

Religious events and festivals are types of mass gathering that draw large numbers of pilgrims from a large geographical region and people around the globe [1,2]. The annual Hajj pilgrimage to Makkah in the Kingdom of Saudi Arabia (KSA) attracts more than 2 million pilgrims from 184 countries around the world [1]. The climatic conditions and the inevitable overcrowding of pilgrims in Makkah and surrounding holy sites during the Hajj rituals create a situation that may promote the occurrence and spread of communicable diseases and possibly the spread of multi-drug resistance (MDR) bacteria [1,3–9]. Thus, the spread of respiratory illnesses during the Hajj is a major public health concerns with the potential of dissemination of these infectious diseases beyond the Hajj itself [10–12]. Risk factors for such an event to occur include close proximity between pilgrims, crowded accommodation, and congregation [1,6]. Studies had shown that respiratory tract infections occur commonly among the majority of pilgrims [10,13]. Also, it is estimated that more than 90% of pilgrims develop what is known as the “Hajj cough” during their stay in KSA [14–16]. Many studies showed that a variety of upper and lower respiratory tract infections due to viral and bacterial infections can cause infections among pilgrims [3–5,10,17–21]. A range of respiratory viruses were recovered from pilgrims, with influenza and rhinovirus the most common [10]. In this review, we summarize the available data about emerging respiratory viruses, including Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome (SARS), and other respiratory viruses such as influenza. We also discuss here the possible role of *Streptococcus pneumoniae* coinfection.

2. Search strategy

We searched MEDLINE and Scopus databases for articles published

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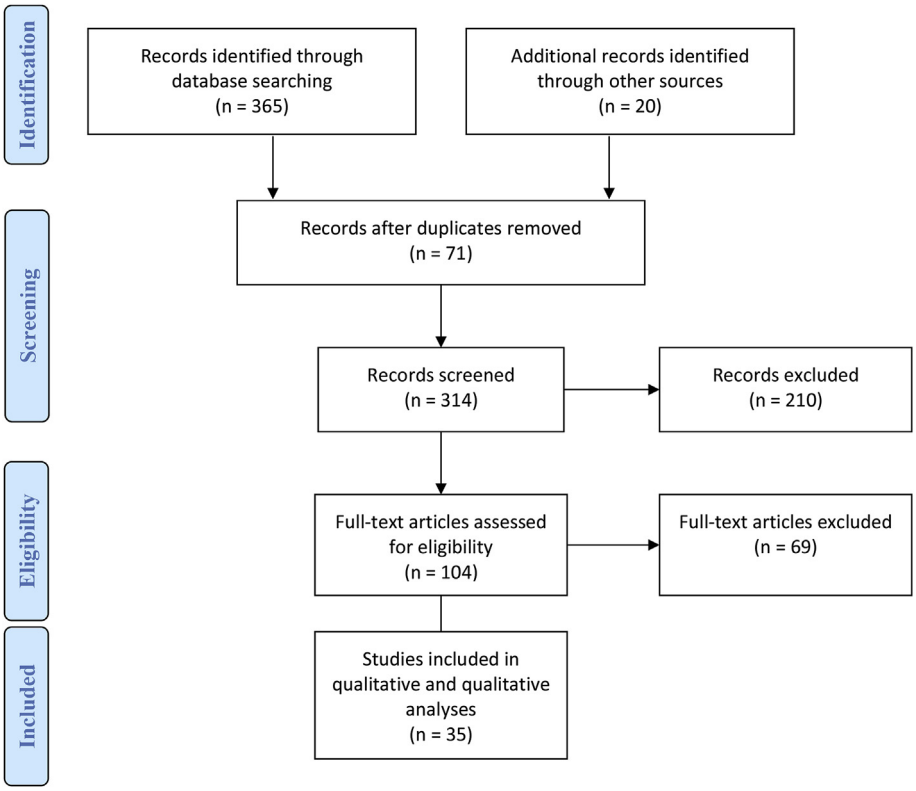

Fig. 1. Flow diagram of the search strategy.

in English using the following search strategy:

#1: "hadj" OR "hajj" OR "pilgrimage";

#2: "respiratory";

#3: "viral" OR "virus" OR "viruses" OR "pathogens" OR "infection" OR "infections";

#4: "influenza";

#5: "Middle East Respiratory Syndrome Coronavirus" OR "MERS-CoV";

#6: "Severe Acute Respiratory Syndrome" OR "SARS";

#7: "Pandemic H1N1";

#8: #1 AND #2 AND #3 AND #4 AND #5 AND #6 AND #7.

We also hand searched the Saudi Epidemiology Bulletin (available at: http://www.fetp.edu.sa/Bulletin.html) for additional articles for inclusion.

The search results were surveyed for methodological articles, and their titles and abstracts were then scanned. Additional studies were identified through bibliographies of original articles or relevant reviews. The search was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. One author (JAT) performed the searches, screened titles/abstracts for eligibility, selected relevant papers and reviewed each of the selected manuscripts in full. All authors were in agreement regarding the choice of papers.

3. Results

3.1. Included studies

The search strategy initially yielded 365 records of which 71 were duplicates. Twenty additional papers were identified through hand searching. Of the 104 full text articles reviewed, 31 studies were included in the final analysis. The results of the search strategy are shown in Fig. 1 according to the PRISMA methodology [22].

3.2. Types of included studies

The included studies were classified based on the methods used to detect respiratory viruses. Methods include polymerase chain reaction (PCR) [15,23–42] (Table 1), cell culture [26,27,43–45] (Table 2), direct immunofluorescence staining [46], and enzyme-linked immunosorbent assay (ELISA) [47–49] (Table 3).

3.3. Study designs

The included studies were cross-sectional studies, case-control studies, and prospective cohort studies. These studies had different designs and methodology, and varied widely in terms of the number of included pilgrims. We included studies addressing the prevalence of viral respiratory infections. Many of these studies reported the prevalence of clinical respiratory tract infections among pilgrims, including upper respiratory tract infection (URTI), acute respiratory infection (ARI) or influenza-like illness (ILI) [16,28,38,40,50–53]. We included in the analysis studies addressing microbiology and laboratory diagnosis of viral respiratory infections based on culture, ELISA or PCR methods.

3.4. Studies based on polymerase chain reaction methods

Included studies that used PCR methods for the detection of the respiratory viruses are summarized in Table 1 [15,23–42,54]. The overall analysis of these studies shows the most common viruses detected among pilgrims (Fig. 2), including influenza (A and B) virus (7.1%), influenza A (5.1%), rhinovirus (5.1%), and influenza B (1.9%).

Table 1
A Summary of Studies addressing the Prevalence of Respiratory Viruses among Pilgrims using PCR Methods, data presented as percentage of the total number of included pilgrims in each study.

Reference	[23]	[24]	[25]	[26]	[27]	[28]	[29]	[30]	[31]	[32]	[33]	[34]	[35]	[36]	[37]	[38]	[38]	[15]	[39]	[39]	[40]	[41]	[42]	[54]
Number of Included Pilgrims	202	555	110	255	275	80	112	38	7	551	305	2699	484	1600	839	169	129	129	692	470	3840	847	300	125
Influenza A-H1N1	0.5				1.8		0.9		0	0	1.6	0.1	3.5	0.5		0	0.8	0.7	1.6	3	6.7		3	
Influenza A-H3N2	9.9				2.9		3.6		28.6	1			5.6			0	6.2	6.2	2	1.7	2.6		4.3	
Influenza A (all)	10.4	8.2	8.1		4.7	6.3	4.5	15.8	28.6	1	2.6	0.3	9.1	7.5	1.3			6.9	3.6	4.7	9.3	7.2	7.3	3
Influenza B	3.5	2.3	2.3		7.3							0.1	5.4			1.3	0.8	0.7	0	0.2	3.5	3.3	3.6	2
Influenza overall	13.9	10.5	10.4		12	6.3	4.5	15.8	28.6	1		0.5	14.5	8		1.3	7.8	7.6	3.6	9.6	13	10.5	10.9	5
RSV	4.5		0.4									0.2			5.1		0.8		0.7	0.2				1
Parainfluenza 1			0			0	0.9	0				0							0	0				1
Parainfluenza 2			0			0	0	0				0							0.3	0.4				0
Parainfluenza 3			0.4			1.3	1.8	0				0							0.1	0.2				2
Parainfluenza overall			0.4			1.3	2.7	2.6				0					0.8		0.5	0.6				0
Rhinovirus			9.2	5.9		48.8	26.8	39.5	26.6								14.7		34.4	30.9				
Entero-rhino virus				2		0		0				12.9			16.8		2.3							47
CoV-229E								7.8				0.2					12.4		14.6	10.2				6
CoV-NL63								0				0.1					0.8		2	0.2				3
CoV-HKU1								0				0.1					3.9		1.3	1.5				0
CoV-OC43								2.6				0.5					3.9		1.6	1.9				3
CoV overall							2.7	10.4				0.9					21		19.5	13.8				12
Metapneumovirus								0				0.1					0.8		0.1	0.6				

These studies did not screen for the same surveyed viruses and there was a large variation in the screened viruses (see Fig. 2).

3.5. *Studies based on culture methods*

A number of studies have detected respiratory viruses among pilgrims using culture methods (Table 2). These studies included a total of 1866 pilgrims, and the most common viruses detected among them are shown in Fig. 3.

3.6. *Other studies using alternative methods for the detection of respiratory viruses*

Other studies, using alternative methods for the detection of respiratory viruses, have detected respiratory viruses (primarily influenza viruses) among pilgrims. ELISA was used in three studies [47–49] and direct immunofluorescence staining was used in one study [46]. A summary of the findings of these studies are presented in Table 3.

3.7. *2009 pandemic influenza A (H1N1) and the Hajj*

It was feared that the 2009 pandemic influenza A (H1N1) would result in a significant impact on the Hajj [55,56], especially that 200,000 pilgrims in 2008 were from resource-limited countries [56]. In total, six studies investigated the prevalence of H1N1 virus among pilgrims [27,32–34,36] and one study was conducted among healthcare workers at the pilgrimage sites [57] (Table 4). During the 2009 Hajj season, the prevalence of H1N1 virus among 275 symptomatic Iranian pilgrims was 1.8% [27]. However, none of the 184 screened healthcare workers was infected [57]. A large cross sectional study of 2699 departing pilgrims showed that 0.1% of them were positive for H1N1 virus [34]. Two other studies have also founded prevalence of 1.6% [33] and 1.8% [27], but none of the 551 Egyptian pilgrims survived in another study were positive for H1N1 virus [32].

3.8. *Threat of emerging coronaviruses*

In the last decade, two coronaviruses emerged, the SARS-CoV in 2003 and the MERS-CoV in 2012. Coronavirus infections were detected in 0.6–0.8% of tested population in regard to the Hajj seasons [3]. There were no cases of SARS linked to the Hajj [58].

3.8.1. *Systematic screening for MERS-CoV among attendees of the annual Hajj*

Despite the 2012 Hajj season started few weeks after the first case of MERS-CoV infection was reported, there were no reported cases among pilgrims in 2012 [5,25,32]. Systematic screening of pilgrims for MERS-CoV was done in multiple studies among > 10,000 pilgrims [5,14,29,31,35,37–39,41,42,54,59–63] (Table 5).

3.9. *Coinfection of respiratory viruses and S. pneumoniae*

In a recent study conducted among 129 French pilgrims in 2013, about 39% of those who tested positive for *S. pneumoniae* after the Hajj pilgrimage were co-infected with at least one virus [38]. However, there is no information on whether the pilgrims were carrying *S. pneumoniae* or were ill secondary to this organism.

4. Discussion

The most common viruses were rhinovirus, influenza A and coronavirus 229E. In addition, the acquisition of MERS-CoV remains very limited and systematic screening of pilgrims showed no infections. MERS-CoV is absent in all Hajj pilgrims tested so far. Different methods were used for the diagnosis of respiratory pathogens and included: PCR, culture methods and ELISA. The ease and rapidity of PCR method make

Table 2
A Summary of Studies addressing the Prevalence of Respiratory Viruses among Pilgrims using Cell Culture, data presented as percentage of the total number of included pilgrims in each study.

Reference	[43]	[44]	[49]	[26]	[27]
Study Design	Cross-sectional study (Saudi Arabia)	Cross-sectional study (Saudi Arabia)	Cross-sectional study (Saudi Arabia)	Cross-sectional airport study (Iran)	Cross-sectional airport study (Iran)
Number of Included Pilgrims	761	500	105	225	275
Influenza A	4.5	0.6	1.9	5.1	
H1N1					1.1
Influenza B	2	5.4	11.4	5.1	
Influenza overall	6.5	6	13.3	5.1	1.1
Parainfluenza 1	2				
Parainfluenza 2	1.7				
Parainfluenza 3	2.2				
Parainfluenza overall	5.9	0.8	0		
Adenovirus	4.7	0	36.2		
Respiratory syncytial virus	2.4	1.4	1.9		
Herpes virus	2.6				

Table 3
A Summary of Studies addressing the Prevalence of Respiratory Viruses among Pilgrims using Direct Immunofluorescence Staining or ELISA, data presented as percentage of the total number of included pilgrims in each study.

Reference	[46]	[47]	[48]	[49]
Methodology	Direct immunofluorescence staining	ELISA	ELISA	ELISA
Year	1994	2000	2004	2004–5
Number of Included Pilgrims	64	305	360	105
Influenza A	3.1	5.9		
H1N1				6.9
H3N2				6.1
Influenza B	1.6	11.5		20.8
Influenza overall	4.7	17.4	12.8	
Parainfluenza 1	0			
Parainfluenza 2	1.6			
Parainfluenza 3	0			
Parainfluenza overall	1.6			

this method an attractive method for further use in subsequent studies to detect respiratory viruses. Interestingly, it appears that some viruses are more prone to transmission during Hajj (influenza and Rhinoviruses). The difference in the transmission could be related to a predominant aerial transmission for Influenza and Rhinoviruses whereas other (less prevalent) could rely on direct contact (hands carry-over). Camels were not allowed in the Hajj areas due to the risk of MERS-CoV transmission and this strategy may further decrease the risk of MERS-CoV transmission. Different respiratory viruses might be acquired during the Hajj and these viruses might be introduced into pilgrims' home countries upon their return, thus contributing to the potential for international spread of these viruses.

Preventing influenza transmission during Hajj is an important target for public health. Influenza vaccination should be a priority for all Hajj pilgrims [64]. Vaccination is not so easy due to regulation on seasonal vaccine availability [65]. In addition, non-pharmacological preventive measures are needed for the prevention of respiratory infections during the Hajj: maintaining good infection control practice among healthcare

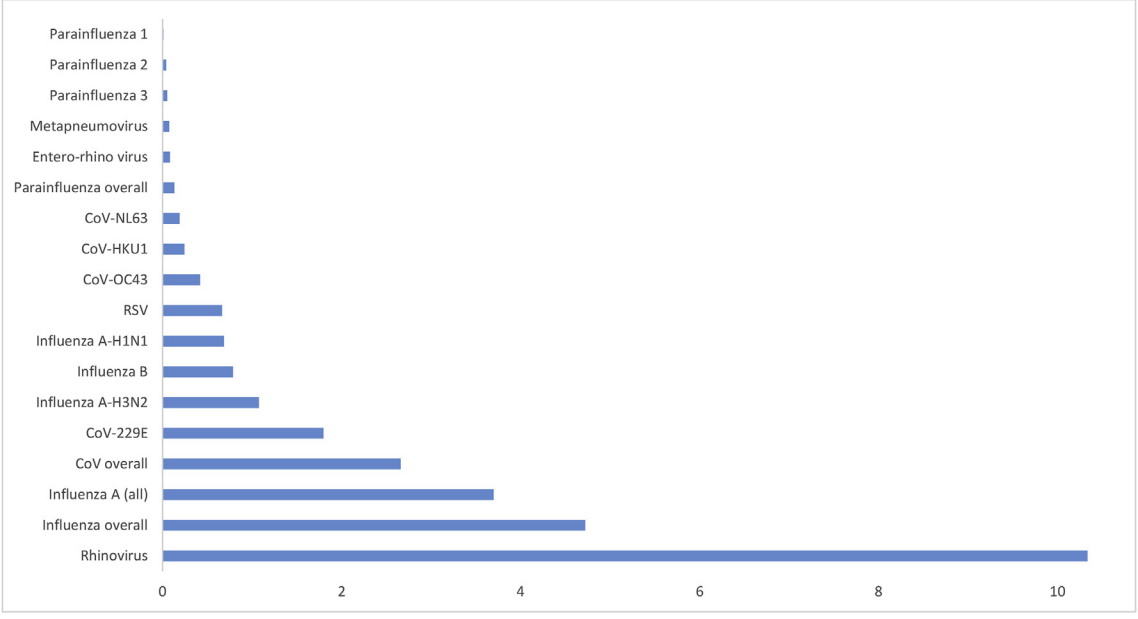

Fig. 2. A summary of studies among pilgrims showing the most common respiratory viruses using PCR based techniques.

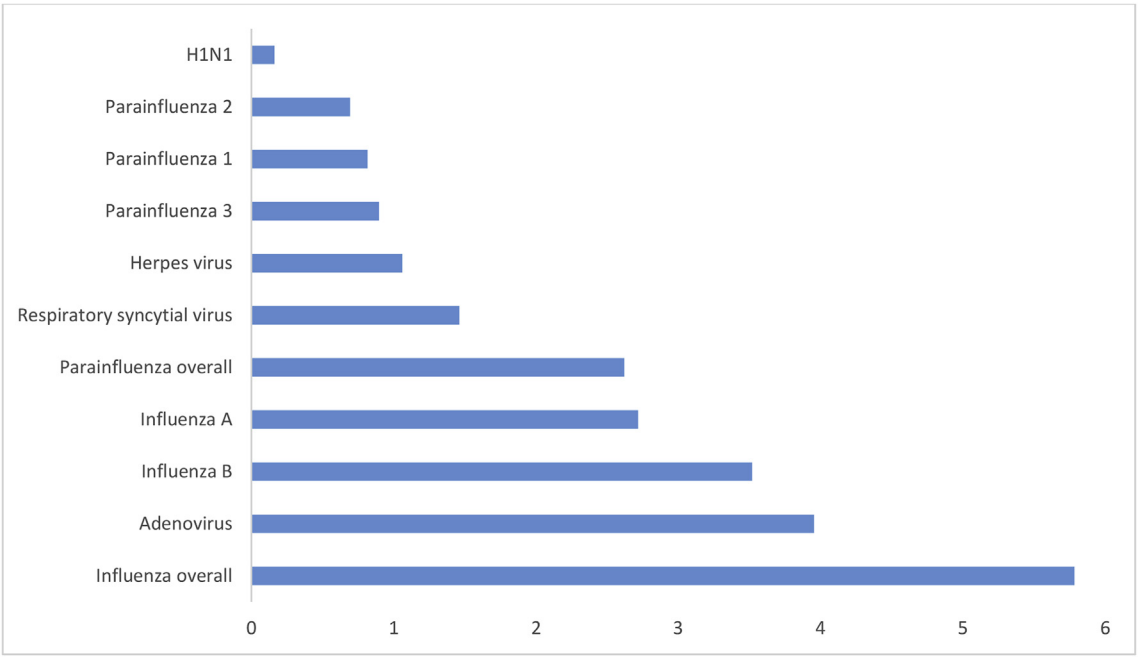

Fig. 3. A Summary of Studies among Pilgrims Showing the Most Common Respiratory Viruses Using Culture based Methods.

Table 4
A Summary of Studies addressing the Prevalence of Pandemic H1N1 Influenza among Pilgrims.

Reference	Study Design	Population	Number Tested	n (%) Positive
[27]	cross sectional	Returning Iranian pilgrims	275	5 (1.8)
[32]	cross sectional	Returning Egyptian pilgrims	551	0 (0)
[33]	cross sectional	Returning Iranian pilgrims	305	5 (1.6)
[34]	cross sectional	Departing pilgrims	2699	2 (0.1)
[36]	cross sectional	Pilgrims	1600	9 (0.5)
[57]	cross sectional	Healthcare workers	184	0 (0)

workers, the use of face masks or respirators, and hand hygiene [66,67]. The majority of viral respiratory infections acquired during pilgrimage are due to influenza viruses, and rhinoviruses [64]. The diagnosis of seasonal influenza during the hajj was a major focus of most studies addressing the prevalence of respiratory viruses among pilgrims [23,25,32–34,36,39,40,43,56,68–80]. In these studies, different methods were used to detect respiratory viruses, with PCR being the most common used method. There are multiple contributing factors for the transmission and acquisition of respiratory viruses during the Hajj and include the crowdedness, close proximity, and indoor or outdoor venue [80].

Consistent with few studies worldwide, entero-rhinovirus was the most common virus isolated among pilgrims. However, this result is related to a single study of 2699 departing pilgrims that showed a 13% acquisition rate [34]. It was shown that entero-rhinovirus the primary cause of common colds [81,82].

With the emergence of the pandemic 2009 H1N1, there was a fear of the significant impact on the Hajj [55,56]. However, different studies showed very low rate of acquisition of this virus during the 2009 Hajj. Also, the emergence of SARS-CoV and MERS-CoV was of major concerns for mass gatherings such as the Hajj [2,5]. However, to date neither SARS-CoV nor MERS-CoV was found to be transmitted among pilgrims. Systematic screening for MERS-COV among returning or departing pilgrims showed no positive cases [5,14,15,29–31,35,37–39,60,61,63]. However, four cases were linked to Umrah (also known as the lesser pilgrimage) [69,83–86]. It was estimated that the risk MERS-CoV transmission among pilgrims could be 1–7 cases per Hajj season and 3–10 per Umrah per year [87].

Various studies showed different acquisition rates of respiratory viruses, but only one study showed coinfection with *S. pneumoniae.* Recent studies showed a significant acquisition of *S. pneumoniae* and *Hemophilus influenzae* by returning pilgrims [3,10,12,66,88].

Viral respiratory tract infections, mainly rhinovirus, influenza A and coronavirus 229E, are of major concern during the Hajj. Despite extensive systematic screening, MERS-CoV had not been isolated from pilgrims. Continued surveillance for MERS-CoV is needed to ensure timely detection of any possible imported MERS cases [8,9,64]. Differential transmission of different viruses may play a role in the observed frequencies. Understanding these factors facilitate the development of preventive measures. Further paired prospective studies using a systematic evaluation of pilgrims for these viruses are needed in order to estimate the total burden of viral respiratory diseases during the Hajj. International collaboration would foster evidence-based practices and guidelines for implementation during mass gathering events [10].

Table 5
Systematic screening of MERS-CoV among pilgrims.

Reference	Year of the study	Study population	Method	Number Screened	N (%) positive
[5]	2012	Symptomatic French	Nasopharyngeal swab	300	0
[14]	2012	French cohort	Nasopharyngeal swab	154	0
[15]	2013	Departing Pilgrims	Nasal swabs	129	0
[29]	2013	Pilgrims from Saudi Arabia, Australia and Qatar	Nasal swabs	1038	0
[30]	2013	Admitted Pilgrims with Pneumonia	Sputum	38	0
[31]	2014	Symptomatic pilgrims returning to Austria	Sputum, throat swab, or bronchoalveolar lavage	7	0
[35]	2012–2015	Egyptian	Nasopharyngeal and oropharyngeal swabs	484	0
[37]	2013	Adult African Hajj pilgrims returning to Ghana, West Africa	Nasopharyngeal swab	839	0
[39]	2013	Departing Pilgrims, paired and non-paired cohort	Nasal swabs	692 (paired cohort), 514 (non-paired arriving cohorts); and 470 (non-paired departing cohort)	0
[38] [15]	2013	French pilgrims	Nasal and throat swab	129	0
[60]	2013	Multiple nationalities	Nasopharyngeal swab	3210 pre-Hajj	0
[60]	2013	Multiple nationalities	Nasopharyngeal swab	2025 post-Hajj	0
[61]	2013–2015	Symptomatic British Pilgrims	Upper and lower respiratory tract	202	0
[63]	2013–15	Ill French travelers	Not indicated	33	0
[41]	2013–2015	Chinese	Lower respiratory tract sputum, washes, and upper respiratory tract oropharyngeal swab	847	0
[54]	2015	Jordanian	Nasopharyngeal and oropharyngeal	125	0
[42]	2014–2015	Kashmir, north India	nasopharyngeal and throat swabs	300	0

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Conflicts of interest

The authors have no conflicts of interest to declare.

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