

Accepted Manuscript

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PII: S0195-6701(18)30286-X

DOI: [10.1016/j.jhin.2018.05.021](https://doi.org/10.1016/j.jhin.2018.05.021)

Reference: YJHIN 5446

To appear in: *Journal of Hospital Infection*

Received Date: 2 April 2018

Accepted Date: 27 May 2018

Please cite this article as: Al-Tawfiq JA, Auwaerter PG, Healthcare-associated Infections: The Hallmark of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) With Review of the Literature, *Journal of Hospital Infection* (2018), doi: 10.1016/j.jhin.2018.05.021.

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Healthcare-associated Infections: The Hallmark of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) With Review of the Literature

Jaffar A. Al-Tawfiq, MD^{1,2,3*}, Paul G. Auwaerter, M.B.A., MD⁴

Specialty Internal Medicine, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia¹, and Indiana University School of Medicine, Indiana, USA², Johns Hopkins University School of Medicine, Baltimore, MD, USA³ and The Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, MD, USA⁴

Corresponding author:

Dr. Jaffar A. Al-Tawfiq*

P.O. Box 76; Room A-428-2, Building 61, Dhahran Health Center,
Saudi Aramco, Dhahran 31311, Saudi Arabia.

E-mail address: jaffar.tawfiq@jhah.com; jaltawfi@yahoo.com

Tel: +966-13-877-3524; Fax: +966-13-877-3790

Key words: Middle East Respiratory Syndrome Coronavirus; MERS; Healthcare-associated outbreaks

Financial support: all authors have no funding

Conflict of interest: all authors have no conflict of interest to declare

Abstract:

The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is a coronavirus capable of causing acute respiratory illness. Laboratory confirmed MERS-CoV cases may be asymptomatic, have mild disease or life-threatening infection with a high case fatality rate. There are three patterns of transmission: sporadic community cases from presumed non-human exposure, family clusters arising from contact with the infected family index case, and healthcare-acquired infections among patients and from patients to healthcare workers. Healthcare-acquired MERS infection has become a well-known characteristic of the disease and a leading means of spread. Contributing factors foremost to such healthcare-associated outbreaks include delayed recognition, inadequate infection control measures, inadequate triaging and isolation of suspected MERS or other respiratory illness patients, crowding, and patients remaining in the emergency department for many days. A review of the literature suggests effective control of these hospital outbreaks was accomplished in most instances by the application of proper infection control procedures. Prompt recognition, isolation, and management of suspected cases are key factors for the prevention of the spread of MERS. Repeated assessments of infection control and monitoring of corrective measures contribute to changing the course of an outbreak. Limiting the number of contacts and hospital visits are also important factors to decrease the spread of infection.

Introduction:

The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is a viral infection capable of causing acute respiratory infection though its spectrum ranges from asymptomatic laboratory-confirmed cases, or mild infection to a life-threatening disease with a high case fatality rate [1,2]. Initially described in 2012 in a 60-year old man hospitalized with suspected community-acquired pneumonia developed renal and respiratory failure, ultimately succumbing to progressive disease [3]. The first reported healthcare-associated infection was described among multiple facilities in Al-Hasa, Saudi Arabia [4]. However, a later retrospective analysis of a respiratory outbreak occurring in a Jordan public hospital determined that this cluster dated back earlier, becoming the first recognized healthcare-associated MERS-CoV infection in April 2012 [5]. The disease was also recognized internationally in many countries with secondary transmissions. The first MERS-CoV infection in France caused one secondary transmission among 123 contacts [6]. In a study of 51 outbreaks, nosocomial transmissions were observed in 80.4% of the clusters [7]. Another study found 37.5% of 1797 cases were ascribed to healthcare-associated infections [8]. The percentage of healthcare workers (HCWs) involved in different outbreaks is variable and ranges between 14% and 64% [9]. There seems to be a higher risk of severe disease in people with comorbid diseases and older age [8].

As of March 2018, the WHO reported 2189 laboratory-confirmed cases from 27 countries, including 782 (35.7%) deaths [10]. Among the reported cases, peaks occurred in 2014 (due to the Jeddah outbreak) and 2015 (South Korea outbreak) (figure 1).

There are three patterns of MERS-CoV transmission [1]: sporadic community cases from presumed non-human exposure [1], family clusters resulting from contact with an infected

family index case [11–13], and healthcare-acquired infections between patients and from patients to healthcare workers [1,4,5,14–31].

Though MERS-CoV has a documented ability to transmit between humans, even in healthcare settings there does not appear to be sustained human-to-human transmission. This is likely due to the MERS-CoV relatively low reproduction number of 0.8-1.3 [29,30]. The South Korean MERS outbreak was thought to have a low reproduction number of 1 % [31]. However, the reproduction number was estimated to be as high as 2-5% in some MERS outbreaks in Saudi Arabia and South Korea [32]. The upper reproduction estimates were probably derived from lack of sufficient infection control measures, and the estimates were lowered with improved detection and prevention practices over time. In this review, we review the available literature on healthcare-associated infections and transmission of MERS-CoV to elucidate the contributing risk factors.

Search strategy

The search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (<http://www.prismastatement.org>). The search included MEDLINE and Scopus databases for articles published in English as follows:

#1: “MERS” OR “MERS-CoV” OR “Middle East Respiratory Syndrome Coronavirus”

#2: “Transmission” OR “Outbreak” OR “Healthcare associated infection” OR “Nosocomial” or “cluster”;

#3: #1 AND #2.

In addition, we searched the Saudi Ministry of Health website for updates and the World Health Organization website and ProMed websites for any listed outbreaks.

We included published papers written in English if the studies described any healthcare-associated outbreak and included contributing factors to the outbreak or factors that were used to limit and control the spread of the infection. We excluded case reports and reports of clinical presentations. We also excluded outbreaks with no specific descriptions of contributing factors to the outbreaks [10,18,26]. Of the 40 full-text articles assessed for eligibility, 18 articles were excluded as these did not describe factors related to outbreaks. A total of 22 articles were included in the final analyses for contributing factors for MERS-CoV outbreaks in healthcare settings.

Timeline of Healthcare-Associated Infections:

Many healthcare-associated outbreaks have occurred in Saudi Arabia, though a large outbreak arose in South Korea in 2015 [1]. A timeline of these outbreaks is shown in figure 2, the most recent updated figure from the World Health Organization. The first outbreak in Saudi Arabia occurred in Al-Hasa [4], followed by a significant epidemic in Jeddah in 2014 [14,16]. Other outbreaks in 2014 were in King Faisal Specialist Hospital [17], King Fahad Medical City in Riyadh [18] and Al-Madinah Al-Mounawarh [21]. There were no specific factors listed contributing to an outbreak at Prince Sultan Military Medical City, Riyadh [18–20]. In 2015, there were three outbreaks in Saudi Arabia in three public hospitals in Al-Hasa region [22], King Abdulaziz Medical City in Riyadh [23–25], and King Fahad Cardiac Center [26]. A multi-facility outbreak of MERS-CoV infection occurred in September 2014-January 2015 in Taif, Saudi Arabia in four healthcare facilities [27].

Observed Infection Control Practices among Various Outbreaks:**Jordan Hospital Outbreak, April 2012:**

The outbreak in Zarqa, Jordan involved 13 healthcare workers with pneumonia [5]. Following the identification of MERS-CoV, specimens from two fatal cases were retrospectively confirmed to be MERS-CoV by real-time RT-PCR [5]. Based on serology and PCR testing, the attack rate was 10% among potentially exposed healthcare workers [15]. In this outbreak, multiple infection control issues were observed and included: absence of physical barriers between different beds in intensive care units apart from cloth drapes, lack of isolation and negative pressure rooms, and non-adherence to infection control measures [15]. Patients were transferred to two other hospitals with no further evidence of intra-hospital transmissions believed due to adequate infection control measures in the accepting institutions [15].

Al-Hasa 2013 Outbreak, April-May 2013:

The outbreak involved four hospitals with 21 of the 23 cases acquired by person-to-person transmission within hemodialysis units, intensive care units, or other in-patient areas [4]. Contributing factors to this outbreak included the use of aerosol-generating procedures and the performance of resuscitations [4]. The outbreak abated by emphasizing primary infection control measures: hand hygiene, droplet and contact precautions for febrile patients, testing all febrile patients for MERS-CoV, surgical mask use for all patients undergoing hemodialysis, and N95 respirators for healthcare workers during aerosol-generating procedures. Additional measures included enhanced environmental cleaning and excluding non-essential staff and visitors [4]. A super-spreading event might also have occurred in the Al-Hasa outbreak where one patient infected seven secondary cases [4].

France Cases, May 2013:

A French patient contracted MERS-CoV while traveling, requiring hospitalization. Of the 123 contacts of this index patient, only one (0.8%) hospitalized patient tested positive and 39 contacts of the second patient tested negative [6].

Abu Dhabi Outbreak, July 2013

A patient developed community-acquired infection through camel contact, receiving care in two different hospitals. Of the 277 healthcare contacts, four (1.4%) had healthcare-associated infections. These four patients were exposed to the index case before the MERS-CoV diagnosis and institution of any respiratory protection measures [28].

Al-Madinah Al-Munawwarah August 24 to September 3, 2013:

From August 24 to September 3, 2014, 18 cases were linked to one cluster involving 11 healthcare-associated infections [21]. The outbreak was thought to be secondary to under-recognition and poor infection control measures [21].

Abu Dhabi Outbreak, March–April 2014:

In this cluster, the index case arose from camel exposure. Only 2 (2.2%) of 90 hospital contacts were positive for MERS-CoV [28].

Another cluster was traced to a community member who visited an emergency room three times and was then subsequently admitted to a regular unit. Evaluation of 224 contacts identified 15 (6.7% positive cases) [28].

Prince Sultan Military Medical City, March and April 2014

Among multiple outbreaks in this hospital, the largest outbreak came from 15 patients acquiring infection within the emergency room [20]. The outbreak abated after application of infection control measures.

Jeddah 2014 Outbreak, March 2-May 10, 2014:

Involving 14 hospitals and more than 200 cases, 60% of infected cases resulted from healthcare-associated transmission [14,16] [33]. Factors contributing to intra-hospital transmission included inadequate separation of suspected MERS patients, crowding, and inconsistent use of infection control precautions [33]. There was no triaging or isolation of patients with respiratory illness, and patients remained in the emergency department for many days [33]. In addition, uncontrolled patient movements, and high visitor traffic also contributed to the spate [23].

Taif, Saudi Arabia Outbreak, September 2014-January 2015:

The outbreak in Taif, Saudi Arabia included four healthcare settings with the largest number traced to a hemodialysis unit involving 15 patients [27]. The implicated cause was close spacing between patients of less than two meters [27].

South Korea Outbreak, May-July 2015:

The most prominent outbreak outside the Arabian Peninsula, about 17,000 contacts were quarantined by the summer of 2015 [34]. The index patient had been in contact with 742 people between May 11 to 20, 2015 in one hospital, subsequently infecting 28 patients [35]. An additional 186 MERS-CoV cases were identified in more than 17 healthcare settings [31,36–39]. Among the many contributory reasons for MERS-CoV advancing within South Korea included healthcare workers unfamiliar with MERS, suboptimal infection prevention and control

measures, overcrowded emergency departments, multi-bed hospital rooms, “medical shopping” by patients, presence of visitors to infected patients, extensive MERS patient movements, and the use of aerosol-generating procedures [40–42]. Particularly problematic factors in the South Korea outbreak were contributions of overcrowding, medical shopping and super-spreaders [1,43,35,40,44,45]. The first case in the Republic of Korea infected 27 secondary cases, and one of the secondary patients then infected 24 tertiary cases, and another secondary patient infected 73 tertiary cases [43]. Another report from South Korea found 85, 28, 23, 11, and 6 secondary cases arising from individual patients with MERS-CoV [40]. A secondary patient was described causing 91 tertiary MERS cases of which 39% occurred within the emergency department and 13% of cases were healthcare workers [45]. Delayed isolation of suspected patients was an important factor that contributed to the spread of MERS-CoV. This was higher in super-spreaders compared to other patients (mean, 6.6 vs. 2.9 days; $P = 0.061$) [46]. Multi-bedded rooms and nebulization treatments may have also contributed to the spread of MERS-CoV in South Korea [47].

King Abdulaziz Medical City in Riyadh in June–August 2015

One of the largest MERS outbreaks occurred in the King Abdulaziz Medical City, Riyadh. Transmission appeared related to care in the emergency department before a MERS suspicion or diagnosis, causing 130 cases [23–25]. A major contributing factor was overcrowding in the emergency department [48].

Jordan Outbreak, August 2015:

Amman, Jordan during August-October 2015 experienced 16 laboratory-confirmed cases from nine hospitals [36]. There were human-to-human transmissions in both cardiac care and

intensive care units of two hospitals [36]. Analyzed viral isolates were similar to those recovered in Riyadh except for deletions in open reading frames 4a, though its impact on transmissibility or virulence remains unknown [49].

Riyadh, June 2016:

A nosocomial MERS outbreak was reported in Riyadh, Saudi Arabia during 19-22 June 2016. This appeared to start with a woman admitted to the vascular surgery ward through the emergency room. Her initial symptoms were not characteristic of MERS-CoV infection. After confirmation of the diagnosis, active screening revealed 24 positive contacts (HCWs = 20), and of all contacts, 20 (83.3%) were asymptomatic [50].

Riyadh June 1-July 3, 2017 Outbreaks:

The index case was a 47-year-old male who underwent emergency intubation in the emergency room. From 220 contacts, 33 additional cases were identified as positive including 16 HCWs [10]. This cluster was linked to a smaller cluster of five cases in another hospital with the involvement of three household contacts, one patient contact, and one health-care worker [10]. A third unrelated outbreak also occurred in Riyadh in June 2017 and involved nine cases, with eight HCWs (4 asymptomatic and four had mild disease) [10].

Discussion:

The WHO continues to tally laboratory-confirmed MERS-CoV infections. In the recent update from September 2012 to July 2017, there were 2040 cases with health-care facility associated infections (40 HCWs, patients, and visitors) representing 31% of cases [10]. The initial symptoms of MERS-CoV are non-specific, often thought to be pedestrian respiratory

infections and thus may go unnoticed. Adherence to standard precautions at all times, given the unpredictability of MERS-CoV infection, appears to be the critical factor for the prevention of transmission in health-care facilities [10]. Additionally, environmental contamination may play a role in some transmission of MERS as viral RNA has been detected for up to five days on surfaces [36].

A well-characterized outbreak in Abu Dhabi, United Arab Emirates offers insights into important infection control issues. The overwhelming reason for MERS-CoV spread centered on the delayed diagnosis of MERS-CoV as 93% of infected contacts were exposed before the patient's diagnosis. Also, use of personal protective equipment (PPE) use during care was inconsistent among these HCWs, especially during aerosol-generating procedures. Although improved PPE use would benefit, a larger preventative impact would be placing patients presenting with respiratory complaints and potential MERS-CoV infection in proper isolation with infection control practices until MERS-CoV infection is ruled out using the standard PCR diagnostic method.

Protocols to address such patients in emergency departments or patients developing an apparent viral illness while hospitalized for other conditions should include the ability to rapidly isolate patients and run laboratory testing which would likely mitigate spread within healthcare systems. Proper triaging of patients with acute respiratory illness is a fundamental step towards the application of a unified process to deal with such patients as suggested by the World Health Organization and the United States Centers for Disease control and preventions [51,52]. Despite such advice, not all healthcare systems in regions endemic for MERS-CoV or in non-endemic regions caring for a potentially infected traveller follow these steps. In a simulation of a "mystery" infectious patient, 95 drills including 42 drills specifically for patients with possible

MERS were conducted in 49 emergency departments in New York City, USA. Hospitals were variable in the identification of potentially infectious patients and implementation of appropriate infection control measures such as suboptimal adherence to hand hygiene, PPE use and isolation signage posting [53].

The Saudi Ministry of Health had recently introduced visual triage using a scoring system to aid in the assessment of patients presenting with respiratory symptoms in emergency departments, dialysis units, and other clinical settings [54]. Also, the Saudi Ministry of Health had developed a rapid response team that visits hospitals upon the identification of any positive MERS cases to help streamline contact tracing and implementation of infection control measures[55]. A similar rapid response team was also formed following the MERS outbreak in South Korea [56]. An interesting observation of the outbreaks of MERS-CoV infection is the variability of the intra-hospital transmission of the virus. The South Korea and Jeddah outbreaks witnessed patients causing significant spread of secondary cases while in others the index patient resulted in few secondary cases despite lack of infection control practices [1]. One reason may lie with prolonged viral shedding, observed more commonly in patients with multiple comorbidities [1]. One study found that 30% of contacts and 76% of cases were still positive for MERS-CoV by PCR 12 days from initial positive samples [57]. A case report showed that a healthcare worker shed MERS-COV for about 42 days after initial sampling for diagnosis [58]. Whether viral detection by molecular methods always equates with an infectious risk remains unclear. An additional factor likely rests in patient movements. Intra-hospital and inter-hospital transmission were documented arising from patient movements within and between hospitals [4] [42,45]. Control of patient flow within and between healthcare settings with proper infection prevention measures is necessary to decrease the chance of transmission of MERS-CoV.

How much asymptomatic and mildly symptomatic patients contribute to viral dissemination in the healthcare setting is not clear. Studies have found variable percentages of asymptomatic individuals from 7-66% [10][59] [23,24] [33] [16] [59]. Data from South Korea showed that none of 82 contacts of an asymptomatic carrier was positive [60], and data showed that transmission occurred from asymptomatic individuals [11,61] [62]. These differences do not yet have defined answers for variability in intra-hospital transmission; however, they do highlight the need to review and refine infection control practices to help prevent the spread of infection within healthcare settings and prevent unwitting spread especially by asymptomatic individuals by screening healthcare worker contacts by PCR.

What is the contribution of the persistence of the MERS-CoV virus in the environment to the spread of the virus? As an RNA virus, MERS-CoV survives surprisingly well on surfaces and in the air especially at low temperature and low humidity [63]. Sixty minutes after aerosolization, the virus remains infectious at 63.5% at 25 °C and 79% humidity compared to only 4.7% at conditions of 38 °C and 24% humidity [64]. Up to day 18-27 after symptom onset, MERS-CoV was detected by RT-PCR and viral culture from most of the touchable environments in patients rooms [65]. Bed controller devices and thermometers were PCR positive until five days after the last positive PCR result from the patient's respiratory specimen [65]. MERS-CoV was cultured in 4 of 7 air samples from patients' rooms, restroom, and common corridor and from 15 (22%) of 68 surface swabs [37]. The MERS-CoV RNA was detected from anterooms, medical devices, air-ventilating equipment, bed sheets, bed rails, IV fluid hangers, and X-ray devices [66]. These data suggest that environmental cleaning needs to be meticulous and that laboratory data may be required to prove adequate disinfection to allow discontinuation of

isolation procedures. Further studies are required to assess infectious risks of the environment in the presence of molecularly detected MERS-CoV RNA.

The prospect for control of MERS-CoV relies on multi-faceted programs to educate HCWs on the disease, to identify potential patients early in their course of illnesses, to isolate suspected and confirmed cases appropriately, and to implement proper infection control. The best prospect for MERS prevention and control rests in basic principles of infection prevention and control in the healthcare settings. Balkhy argues that three pillars are necessary: policies and procedures, facility and human resources, and accountability and leadership [67,68]. How these goals could be achieved is partly found in one study using a core group of nurses for an education program consisting of an online skill module, donning and doffing of personal protective equipment, and hands-on practice to obtain nasopharyngeal swabs [69]. Another study called for the use of the “3Is” (Identify-Isolate-Inform) tool in the emergency room to rapidly identify and isolate suspected cases with any emerging infectious disease [70].

Table 2 provides a summary of potential concerns in infection prevention and control to halt MERS-CoV transmission with appropriate interventions. Some listed items are by nature parochial including facility structure, knowledge and skills of HCWs, and patient-related issues. These can be individualized incorporating strategies that include education, feedback, and tackling facility related issues [71]. In a survey of 607 HCWs, hospital infrastructure and design, staffing shortfalls, and absence of infection control training were cited as the primary contributing factors for the spread of MERS-CoV infection in healthcare facilities [72]. In a study from Saudi Arabia of 228 trainees, half of the respondents indicated that their hospital had

a clear plan while 28% did not feel they were well prepared for MERS [73]. A targeted educational strategy increased HCWs knowledge, skills and attitudes in Saudi Arabia private hospitals [74]. Raising public awareness and recognition of the disease will also assist in preventing transmission [75].

MERS-CoV presents with a variety of clinical and laboratory findings [4,13,76]. There are notable challenges in diagnosis through laboratory and radiological methods, including the possibility of negative swab results by PCR methodology. Currently, the diagnosis of MERS-CoV infection best relies on viral detection by real-time reverse-transcription polymerase chain reaction (PCR) methodology [76–78]. Lower respiratory samples had been shown to yield better diagnostic results than nasal or oral swabs. In two studies, lower respiratory samples showed higher Ct values than upper respiratory samples and MERS-CoV virus was detected later in the course of the disease [77,79]. The WHO recommends that both upper and lower respiratory tract specimens be collected whenever possible [80]. Improved diagnostic tools are needed for early diagnosis of the disease.

In conclusion, MERS-CoV like SARS requires leadership insisting on formal and continued training of HCWs to be sufficiently prepared for emerging respiratory infectious diseases. Hospitals have varied in their ability to identify correctly potentially infectious patients and quickly implement appropriate infection control measures [53]. Prompt recognition, isolation, and management of the suspected cases are vital factors for the prevention of MERS transmission. It has been shown that MERS-CoV nucleic acid was detected by PCR in serum, feces and urine [81–85]. Thus, it is important to maintain proper infection control practices when caring for those patients.

Repeated assessments of infection control and monitoring implementation of corrective measures leading to constant readiness will change the course of an outbreak or halt it before it starts [86]. Limiting the number of contacts and hospital visits are also important factors to decrease the spread of infection [87]. Healthcare facilities should take all the steps to learn from past experiences and build capacities for the prevention of outbreaks such as MERS, SARS, and Ebola. Healthcare leadership and workers should strive to prevent future outbreaks. Failure to do so would mean that lessons learned from SARS, MERS and Ebola would be relegated to history--leaving patients, hospitals and HCWs vulnerable. Many infection control questions remain requiring further research, including a better understanding of the disease dynamics. Leading concerns include the role of asymptomatic individuals in the transmission of the disease and precise risk factors for the transmission in the healthcare. Although data accrued has concentrated on respiratory transmission, the role of other body fluids and the built environment in transmission remains unknown. As zoonotic reservoirs for MERS-CoV may continue to produce sporadic human infections, rigorous infection control practices should prevent the virus from spreading past the hospital door

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Table 1: Contributing factors to the hospital outbreaks

Infection control issues	Examples	number of instances where this was an issue	Involved Hospitals	Reference
Hospital Design	absence of physical barriers between different beds, inadequate separation of suspected MERS patients, lack of isolation and negative pressure rooms	3	Jordan, Jeddah, Taif	[5,14,16,27,33,88]
Healthcare Workers Adherence	Sub-optimal adherence to infection control measures	4	Jordan, Al-Madinah Al-Muwnawarah, Jeddah, Riyadh	[5,14,16,21,23–25,33,88]
	Contacts prior to MERS diagnosis and under-recognition	1	Abu Dhabi	[28]
	contact without respiratory protection	1	Abu Dhabi	[28]
	Overcrowding	2	South Korea,	

				[1,14,16,33,35,36,40–45,88]
Patients flow	No triaging and isolation of patients with respiratory illness, patients remained in the emergency room for many days, use of multi-bed rooms, extensive patients movements,	2	South Korea,	[1,14,16,33,35,36,40–45,88]
	Unfamiliarity with MERS infection	1	South Korea	[1,43,35,36,40–42,44,45]
	Under-recognition	2	Al-Madinah Al-Muwnawarah	[10,21,50]
Aerosol generating procedures	use of CPAP and nebulized medications and the performance of resuscitations	3	South Korea, Al-Hasa	[1,4,10,35,36,40–45]
Patients' characteristics	Contribution of super-spreaders	1	South Korea	[1,43,35,36,40–42,44,45]

Social Norms	“medical shopping”, presence of multiple friends and family members with patients	1	South Korea	[1,43,35,36,40–42,44,45]
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Table 2: A Summary of Highlights of Areas for Concern and Possible Interventions to Control MERS Infection

Infection Control Domain	Infection control issues	Suggested Interventions
Environmental	Absent physical barriers between beds, inadequate isolation of suspected MERS patients	Establish respiratory triage areas, adequate isolation of suspected patients: Contact and airborne
	Lack of isolation and negative pressure rooms	Build capacity to accommodate increasing number of patients with respiratory illness
System	Unfamiliarity and under-recognition of MERS infection	Education and periodic review of MERS case definitions
	Insufficient compliance with infection control measures	Strengthening education, compliance monitoring and feedback
	Aerosol generating procedures	Include training of HCWs on how to protect themselves during these procedures and to carry them in an airborne infection isolation room

Personal	Presence of multiple friends and family members with patients	Limiting visitors to suspected and confirmed cases until patients are no longer infectious
	“Medical Shopping”	Education of the public on the risk of exposure to multiple medical venues

Figure 1: A flow diagram of the search strategy according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [89]

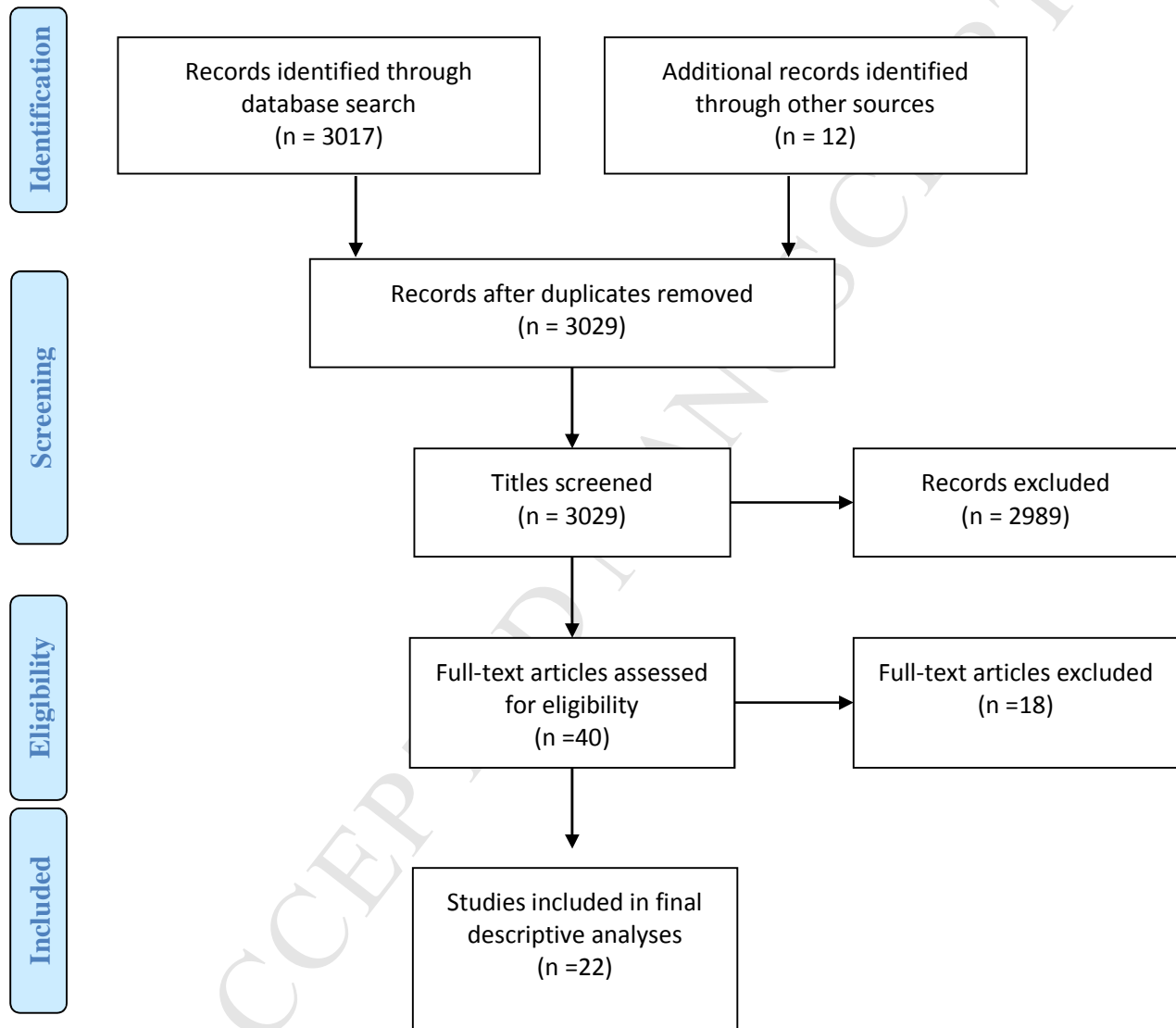


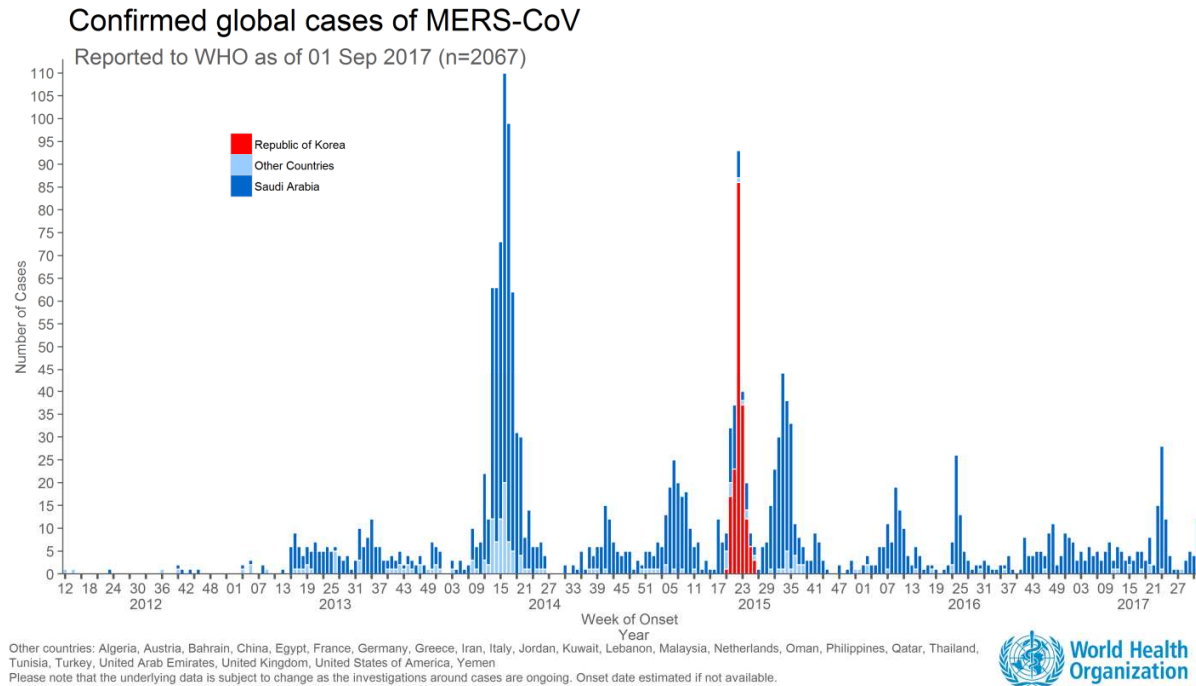
Figure 2: Most Recent Updated Figure of Timeline of Reported MERS-CoV Cases to the World Health Organization

Figure 3: Timeline of Major Healthcare Associated Outbreaks