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Signature:

Roaa Jumbi

Date:

April 21, 2017

Systematic Narrative Review of MERS-CoV Risk of Severe Disease and Death, Kingdom of Saudi Arabia, 2017

by

Roaa Jumbi

Master of Public Health

Hubert Department of Global Health

Scott JN McNabb, PhD, MS
Thesis Committee Chair

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Roaa Jumbi

MBBS, King Abdulaziz University 2010

Scott JN McNabb, PhD, MS
Thesis Committee Chair

An abstract of a thesis submitted to the Faculty of the Rollins School of Public Health of Emory University in partial fulfillment of the requirements for the degree of Master of Public Health in Hubert Department of Global Health, 2017

Abstract

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Introduction: The factors leading to severe life-threatening manifestations and death associated with Middle East respiratory syndrome coronavirus (MERS-CoV or MERS) are not well defined. As with any newly emerging pathogen, this study aims to systematically review the risk of death among MERS-infected patients, as well as assess the risk of required mechanical ventilation and intensive care unit (ICU) admission.

Method: Using Pubmed and Web-of-Science databases, a search was performed for studies of MERS. Articles reporting clinical outcomes of severe (confirmed) case-patients with MERS in the Kingdom of Saudi Arabia (KSA) were included. Specifically, studies that reviewed the risk of mechanical ventilation, ICU admission, and death were the focus of this study.

Results: Of 21 eligible articles, most focused on patients in ICUs; these had higher death rates. Five articles reported 100% of MERS case-patients admitted to ICU received mechanical ventilation. Twice as many males as females were reported.

Conclusion: Given the extensive complications and fatality rates associated with MERS, further research should provide a better understanding of transmission, its clinical course and association with severe manifestations and death. The initiation of well-designed research in the KSA Ministry of Health is important to improve preparedness and strategy planning. This could aid in building effective public health surveillance, evidence-based strategies and recommendations for MERS management and prevention.

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1. Introduction

a. Rationale

The Middle East respiratory syndrome (MERS) is a viral respiratory illness caused by a novel corona virus. A zoonotic virus, MERS is similar to SARS, which also affects the respiratory system. Infected patients present with fever, cough, and shortness of breath. Other symptoms (e.g., pneumonia, gastrointestinal illness) have been reported, but are not always present [1].

The number of laboratory-confirmed MERS case-patients reported to the World Health Organization (WHO) has reached 1,917; including 677 deaths [2]. It has a high mortality rate of 35%[8]. Cases and outbreaks of MERS have been in countries of the Arabian Peninsula, primarily in the Kingdom of Saudi Arabia (KSA) where most cases have been reported (>85%); the first case was reported September 2012. [1, 3]. This study focuses on KSA.

As a zoonotic virus, bats are the main host of MERS; many studies show they are an ideal reservoir [4]. A polymerase chain reaction (PCR) test on bat fecal samples in October of 2012 in Bisha, KSA was positive for MERS; results showed 100% nucleotide match to the MERS from a patient living in Bisha area[5]. However, scientists do not fully understand the transmission of MERS from animals to humans, and given the limited information on contact between bats and humans, it is challenging to prove that bats are the direct source of the virus[4].

Additionally, several serologic studies proved the link of MERS and dromedary camels. One found evidence linking MERS with dromedaries in two human cases of MERS in October of 2013; these were in a farm in Qatar, where camels had positive nasal swabs for MERS [4]. Furthermore, a previous study found that the number of case-patients with a positive serology for MERS was several times higher in those with regular camel contact than in the general

population. However, although bats and camels have been linked to MERS infection, there have also been MERS-infected case-patients with a negative history of exposure to sick animals or their products. [6, 7]

MERS can be severe enough to cause respiratory failure which then requires mechanical ventilation and support in an intensive care unit (ICU). Previous studies estimate multi-organ failure and death in 20% -- 40% of confirmed patients [9]. Underlying comorbidities and older age have been associated with life-threatening severe disease and death.[10] A recent study in KSA estimated the infection fatality ratio to be 22% (95%CI=18, 25) in the total population; 79% (95%CI=70, 86) among those ≥ 70 years of age [11].

The factors leading to severe illness and outcome among MERS patients are not well defined. As a newly emerging pathogen, there is a knowledge gap; therefore, more scientific research is needed. After reviewing published studies with different study designs and populations and differing results associated with MERS death, the profit of conducting a systematic review of published MERS articles became apparent. Therefore, this study reviews KSA MERS patient clinical prognoses and summarizes the risks of ICU admission and mortality. The review should aid public health better prepare and respond to MERS plus understand its outcomes and help outline the process of policy making.

b. Objectives

This systematic review aims to comprehensively summarize available data about the risk of ICU admissions and confirmed deaths associated with MERS in KSA. It compares these risks among studies, regardless of treatment. Conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12], it measures the risk of admission to ICU, mechanical ventilation and death, and compares those risks by gender

focusing on laboratory-confirmed case-patients with MERS and includes case reports and series, case-control and retrospective, observational studies, plus surveillance reports.

2. Methods

This study did not require IRB approval because it did not meet the definition of research with "human subjects" or "clinical investigation"; a letter of exemption was received from Emory University.

a. Eligibility criteria

Studies were selected according to this outline:

Study Design

All studies that measured risks of ICU admission and death were included. Reports published as conference abstracts, vaccination trials, editorials, letters, reviews and articles without abstracts were excluded.

Participants

Studies describing the complications and deaths in confirmed MERS cases of KSA nationals or residents ≥ 18 years of age were included.

Outcomes

Primary outcomes:

- Death
- ICU admission
- Mechanical ventilation

Outcomes were handled as dichotomous variables.

Setting

Studies based in the KSA are included. Studies based outside of KSA were excluded.

Language

Articles published in English between April 2012 and February 2017 were included. Articles published in Arabic or other languages were excluded.

b. Information sources

Published studies of MERS case-patients were retrieved from PubMed and Web of Science.

c. *Search strategy*

The search was restricted to the English language and human subjects.

The following search terms were used in to identify relevant published articles:

- "MERS" OR "middle east respiratory syndrome" OR "novel coronavirus"
- "Saudi Arabia" OR "SA" OR "KSA"
- "hospitalization" OR "intensive care" OR "ICU"
- "mortality" OR "critical" OR "death" OR "severe"

The reference lists of the articles included were explored for better saturation of the literature.

d. Study selection

Published studies were required to meet the following characteristics for eligibility of inclusion: (i) studies on confirmed cases of MERS regardless of case definition and (ii) studies reporting clinical outcomes of both surviving and deceased patients.

A systematic narrative synthesis of the results in the text and tables summarize the findings of

included studies. The narrative synthesis explains the relationship and findings within the included studies.

e. Data collection

The following data (if available) were extracted from each article: authors name, publication year, study design, proportions of MERS confirmed ICU admission, gender, patients undergoing mechanical ventilation and deceased patients.

f. Data synthesis and analysis

A formal meta-analysis was not performed. Therefore, the main outcomes extracted from eligible articles were summarized to describe the results of the study (i.e., the prevalence of ICU admission, mechanical ventilation, and death).

3. Results

a. Study selection

Among a total of 124 relevant articles were first identified through searching Pubmed and then nine additional articles were found through bibliography screening (totaling 133); 100 articles were excluded by screening abstracts and titles. After screening of duplicates, another 10 articles were excluded. This resulted in a total of 23 articles that were selected for full-text assessment. Of these, two were excluded for not meeting the inclusion criteria after the assessment, resulting in 21 eligible articles. All 21 articles were included in the qualitative synthesis of the systematic review. The flow diagram of the article search process and selection

is shown in Figure 1.

b. Study characteristics

Twenty-one studies were conducted in KSA from 2013 through 2016 among mixed populations in different regions and different hospitals. The definition of the syndrome was dependent on the author. Most articles defined a case as any patient with confirmed MERS

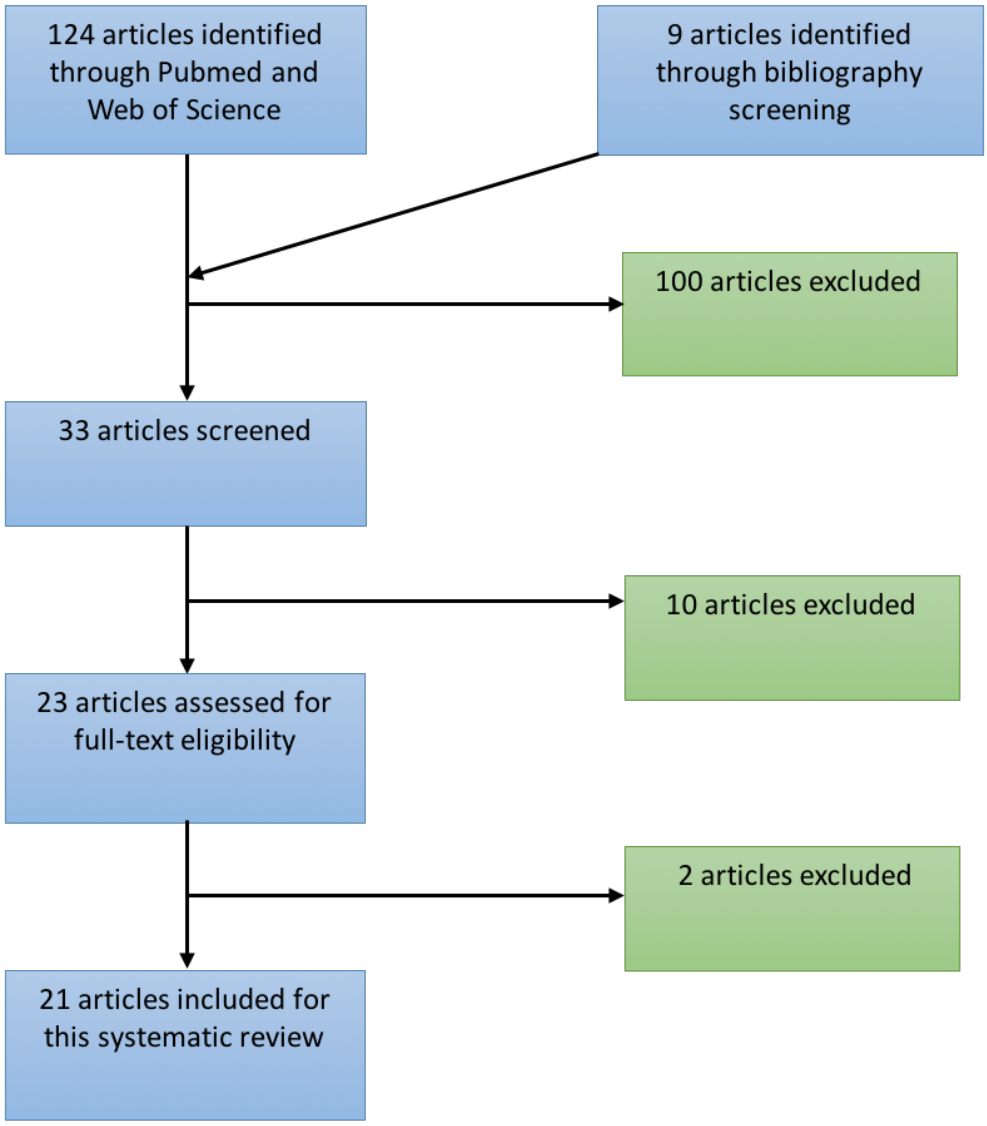

Figure. 1. Flow Diagram of Study Selection, MERS-CoV, Kingdom of Saudi Arabia, 2017

infection based on a positive real-time polymerase chain (PCR) reaction. Some authors added other characteristics to the case definition such as: fever (>38C), cough, shortness of breath (SOB), sore throat, and gastrointestinal manifestations. Variations in sample size were noticed depending on study design. Sample size in case reports and series ranged from 3 to 12 case-patients; larger samples were identified in studies with different designs, such as observational retrospective studies. The reviewed articles included:

- Thirteen retrospective studies; three described outbreaks in Riyadh and Eastern Province of KSA [13-25]
- One prospective study conducted in an ICU in Jeddah [26]
- Two case-control studies were conducted in tertiary hospitals in Riyadh and Eastern Province of KSA [27, 28]
- Four case reports in a series were conducted in Riyadh, Hafr Al Batin, and Al Ahsa cities and reported family, community, and healthcare-associated clusters [29-32]
- One surveillance study was conducted during March – May 2014 in Jeddah region of KSA [33]

Hospital outbreak and surveillance studies demonstrated smaller estimates for the risk of death than in ICU cases and retrospective studies. The proportions of ICU admission were available in 16 articles, while the proportions of mechanical ventilation were available in 14 articles (Table 1). The proportion of ICU admission ranged from 38.5% to 100%. The proportion of mechanical ventilation ranged from 19.6% to 100%. Only 16 articles reported proportions of gender, specifically males. Although male predominance of infection was observed in most studies, one article was an exception [28].

Table 1. Prevalence of MERS-CoV cases, ICU admission, mechanical ventilation and death in studies conducted in Saudi Arabia between 2013 – 2017.

Manuscript	Population (Confirmed MERS-CoV cases) N	Sex-Male N(%)	ICU admission N(%)	Mechanical ventilation N(%)	Death N(%)
Retrospective					
Assiri, Al-Tawfiq, et al., 2013	47	36	42 (89%)	34 (72%)	28 (60%)
Assiri, McGeer, et al., 2013	23	17 (74%)	18 (78%)	18 (78%)	15 (65%)
Omrani et al., 2014	44	32	44	41	34 (77%)
Saad et al., 2014	70	46 (65.7%)	49 (70%)	46 (65.7%)	42 (60%)
Das et al., 2015	15	11	12	12	9
Alsahafi & Cheng, 2016	939	624	NA	NA	425/924 (46%)
Sherbini et al., 2017	29	20 (69%)	NA	9	10 (34%)
Al Ghamdi et al., 2016	51	NA	19 (37.3%)	10 (19.6)	19
Khalid et al., 2016	14	NA	14 (100%)	14	9
Almekhlafi et al., 2016	31	NA	NA	27 (87.1%)	23 (74.2%)
Al-Dorzi et al., 2016	63	NA	63	(80.9%)	(63.4%)
Alraddadi et al., 2016	39	21	15 (38.5%)	12 (30.8%)	11(28%)
Aleanizy, Mohmed, Alqahtani, & El Hadi Mohamed, 2017	190	116(61.1%)	NA	NA	69 (36.3%)
Prospective					
Al-Hameed et al., 2016	8	6	8	7	5
Case-control					
Al-Tawfiq et al., 2014	17	11 (65%)	8(53%)	NA	76%
Mohd et al., 2016	80	48	15 (18.7%)	NA	8 (10%)
Case series					
Arabi et al., 2014	12	NA	12	NA	7 (58%)
Case report					
Memish, Zumla, Al-Hakeem, Al-Rabeeah, & Stephens, 2013	4	4	2	2	2
Omrani et al., 2013	3	3	2	2	2
Memish et al., 2014	12	6	NA	NA	5
Surveillance					
Feikin et al., 2015	102	76	36 (35.2%)	NA	41

4. *Discussion*

We reviewed the risk of ICU admission and death associated with MERS by systematically searching published articles from KSA. Most of the studies examined focused on patients in the ICU, where patients tend to have advanced stage of disease severity. This resulted in relatively higher estimates of mortality.

The risk of requiring mechanical ventilation was also reviewed. It was clear that the majority of ICU patients, if not all, needed respiratory support. For instance, of the sixteen articles reporting ICU admissions, 5 articles reported 100% of MERS patients admitted to ICU have received mechanical ventilation. This finding amplifies the severity of MERS and its association with respiratory failure and life threatening complications.

The results and estimates extracted from the articles varied depending on the study design. Apparently, retrospective cohort studies yielded in high risk estimates for severe disease and death which are relatively similar to the results of studies conducted in ICU settings. Meanwhile, estimate from studies conducted in hospital outbreaks and surveillance data were lower. These findings raise concerns of potential unmentioned biases associated with case diagnosis and detection.

Furthermore, males were found to be diagnosed with MERS in larger numbers than females, as reflected in the nearly doubled number of males observed in these studies. This may pertain to their lifestyle in Saudi Arabia (e.g. more exposure to infected camels, more interaction and contact with potentially infected individuals or likelihood of smoking habits). Nonetheless, both sexes shared the same clinical presentations.

Limitations

Considering the novelty of this virus and its attendant outcomes, limited information was evident. Therefore, one of the important limitations was lack of studies regarding the identification and understanding of the pathogenesis, infectivity and risk factors. In addition, there was limited information on MERS patients in different settings other than in hospitals. Failure to review grey literature (i.e., websites, governmental agencies) is another limitation in this study.

Conclusions

To respond to and end outbreaks of MERS, prevention of transmission from animal to humans is crucial. Given the extensive complications and fatality associated with MERS, further research should occur to better understand MERS transmission, its clinical course and its association with severe manifestations and death. The initiation of well-designed research programs in the MoH in KSA is important to improve the preparedness and strategic planning in such situations. This could aid in building effective surveillance, evidence-based strategies, and recommendations for MERS management and prevention. Constancy and dedication to current best practice of MERS management guidelines is encouraged among healthcare providers.

5. Funding

There were no external funds provided for this study.

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Appendices

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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