WHO EMRO | Middle East respiratory syndrome coronavirus: current knowledge and future consideratio

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Review

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المتلازمة التنفسية الشرق أوسطية لفيروس كورونا : المعلومات الحالية والاعتبارات المستقبلية

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: جرى استعراض لأدبيات المعلومات المتاحة للعامة من أجل تلخيص الفهم الحاليالخلاصة
والثغرات الموجودة في المعلومات المتعلقة بالمتلازمة التنفسية الشرق أوسطية لفيروس
كورونا، بما في ذلك منشؤها وانتقالها والإجراءات الفعالة لمكافحتها ومعالجتها . ولقد
كان هدفنا هو تحسين فهمنا للفيروس من ناحية الصحة العامة والتأثير على استجابة الصحة
العامة على الصعيد العالمي . فقد تم البحث في قواعد البيانات الرئيسية والتعرف على ما
نشر من الأبحاث والتقارير ذات الصلة خلال الأعوام 2012-2015. من بين الأبحاث والتقارير
المنشورة التي استُرجعت في البداية والتي بلغت 2520 اعتبرت 164 دراسة ذات صلة
بالموضوع . وتشير النتائج التي جُمعت إلى أنه لا يزال يتعين اكتشاف الكثير عن المتلازمة
التنفسية الشرق أوسطية لفيروس كورونا . إن الأدلة التي تولدت في مجال التصدّي لهذا
المرض الناشئ قد استرشدت - إلى حد كبير - بالدروس المستفادة من التصدي لأمراض أخرى
يسببها فيروس كورونا . إن تحسين الترصد والبحوثَ الوبائية وتطويرَ معالجات ولقاحات
جديدة أمورٌ لا بد منها، وينبغي الحفاظ على زخم المكاسب الأخيرة من حيث الفهم الأفضل
لأنماط المرض، حتى يتمكن المجتمع الدولي من الإجابة على الأسئلة حول هذا المرض
.

ABSTRACT A literature review of publically available information was undertaken to summarize current understanding and gaps in knowledge about Middle East respiratory syndrome coronavirus (MERS-CoV), including its origin, transmission, effective control measures and management. Major databases were searched and relevant published papers and reports during 2012–2015 were reviewed. Of the 2520 publications initially retrieved, 164 were deemed relevant. The collected results suggest that much remains to be discovered about MERS-CoV. Improved surveillance, epidemiological research and development of new therapies and

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vaccines are important, and the momentum of recent gains in terms of better understanding of disease patterns should be maintained to enable the global community to answer the remaining questions about this disease.

Coronavirus du syndrome respiratoire du Moyen-Orient : connaissances actuelles et perspectives

RÉSUMÉ Une analyse documentaire des informations publiques disponibles a été entreprise afin de passer en revue les connaissances et les lacunes actuelles sur le coronavirus du syndrome respiratoire du Moyen-Orient (MERS-CoV), notamment sur son origine, la transmission, les mesures de lutte efficaces et la prise en charge. Notre objectif est d'améliorer la compréhension du virus au plan de la santé publique, et d'agir sur l'intervention de santé publique internationale. Nous avons effectué des recherches dans les principales bases de données et avons examiné les articles et rapports publiés pertinents pour la période 2012-2015. Sur les 2 520 articles et rapports publiés initialement sélectionnés, 164 études ont été jugées pertinentes. Les résultats recueillis indiquent qu'il reste encore beaucoup à apprendre sur le MERS-CoV. Il est impératif d'améliorer la surveillance, de procéder à des recherches épidémiologiques et de mettre au point de nouveaux traitements et vaccins. De même, il est nécessaire de maintenir l'élan suscité par les récentes découvertes en matière de compréhension améliorée du tableau épidémiologique, afin de permettre à la communauté mondiale de répondre aux questions jusqu'à présent sans réponse à propos de cette maladie.

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Introduction

Middle East respiratory syndrome is a viral illness caused by a novel human coronavirus. Named Middle East respiratory syndrome coronavirus (MERS-CoV), it was first reported in Saudi Arabia in 2012 (1). As of 5 September 2015, 1554 laboratory-confirmed cases had been reported to World Health Organization (WHO) (2), with a high case fatality rate. At least 552 deaths have been reported thus far, accounting for over one third of all cases (Figure 1) (2). This rate is higher than that of severe acute respiratory syndrome coronavirus (SARS), estimated at 15%, and is strongly age- and sex-dependent (3).To date, 26 countries on four

continents (2,4) have been affected. Since the initial outbreak in 2012, MERS-CoV has not been a rapidly spreading global contagion, but (based on modelling exercises) the possibility remains that it will evolve to pandemic proportions. The source of the virus in sporadic cases remains unknown although bats and camels have been implicated (5). MERS-CoV often presents as a lower respiratory tract disease associated with fever, breathing difficulty and pneumonia that can progress to acute respiratory distress, cough, multi-organ failure and death (6). The incidence and mortality are sex- and age-dependent respectively (7,8), and management is a challenge owing to the lack of any proven effective therapy (9,10).

Much has been written in the past few years in terms of epidemiological patterns, gene sequencing, immunogenicity and the animal–human and human–human interfaces. Consequently, a myriad of literature has been produced, much of it providing evidence to answer questions about the origin, transmission, effective control measures and management of the disease.

We reviewed the publicly available literature and aggregated current data relevant to MERS-CoV to identify gaps in the knowledge in order to improve public health understanding of the virus and better shape the global public health response.

Methods

We searched the databases Medline, Embase Classic+Embase, Science Direct, Global Health, Cochrane database, WHO Library and Information Network for knowledge database (WHOLIS), the Index Medicus for the Eastern Mediterranean Region (IMEMR), the Stephen B Thacker CDC Library (CDC Library), the European Centre for Disease Prevention and Control (ECDC) and the National Institute for Clinical Excellence (NICE) databases on 19 April 2015 for “Middle East respiratory syndrome coronavirus” [MESH] OR “MERS-CoV” [keyword] OR “MERS” [keyword] for publications between 2012 and 2015. We retrieved 2520 papers, which were screened to result in 164 that were deemed relevant (Figure 2). Papers were included if they addressed MERS-CoV in any context. These were supplemented by iterative reviews of the reference lists of relevant published papers in addition to grey literature identified in WHO reports.

The following information was extracted and summarized: the origin and reservoir of the virus, epidemiology (clinical and demographic characteristics of the virus), exposure, transmission and risk factors for human infection, therapeutic options, effective infection control measures in health care facilities, seroprevalence in high-risk groups, appropriate serological diagnostic assays and effective public health control measures.

Results

Origin and reservoir of the virus

The putative candidate source of MERS-CoV is vespertilionid bats (11). Genetic material from specimens taken from MERS-CoV patients shows that MERS-CoV also has a close genetic relation with coronaviruses found in bats in southern China (12), South Africa (13), Europe (14,15), Thailand (16), Mexico (17), Ghana (15) and Saudi Arabia (18) as well as in other species, such as hedgehogs (19). Bats are thought to be the origin of a zoonotic infection transmitted to dromedary camels, and ultimately from camels to humans through close contact (20, 21). Camels have been acting as mixing vessels for viruses from different hosts (11,22), and they have been shown to have neutralizing antibodies against MERS-CoV (23–31). In camels testing positive for MERS-CoV, juvenile dromedary camels are often virus-positive, while older camels are more likely to be seropositive and virus-negative (25, 27,31–33). Serological studies have also indicated that camels can be the natural hosts of MERS-CoV infections, which were established long before the first human MERS-CoV cases were identified (26,28,34,35).

Epidemiology of MERS-CoV

Demographic characteristics

MERS-CoV was first reported in Saudi Arabia in September 2012 (1). The first infected human died of respiratory and renal failure (36); the virus was traced back to April 2012, when an outbreak of pneumonia resulting in two deaths occurred among health care workers in an intensive care unit in Jordan (37). To date, 26 countries on four continents have been affected. In the Middle East: Egypt, Islamic Republic of Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, United Arab Emirates and Yemen; in Africa: Algeria and Tunisia; in Europe: Austria, France, Germany, Greece, Italy, the Netherlands, Turkey and the United Kingdom; in Asia: China, the Republic of Korea, Malaysia, Philippines and Thailand; and in North America: the United States of America (2,4).

The initial predominance of male cases reported in earlier outbreaks has now levelled out to a more balanced sex distribution (7,8). A pattern of seasonal distribution seems to be emerging in the majority of cases (38): April 2012 (Jordan, Zarqa public health hospital) (39), April–May 2013 (Saudi Arabia, Al-Hasa outbreak) (8) and April–May 2014 (Jeddah and United Arab Emirates outbreaks) (40) (Figure 3). The incidence of cases in the spring raises the possibility of a seasonal cycle. This is possibly linked to the fact that camels give birth in the spring (March) (23, 32,41).

Clinical characteristics

The current WHO case definition (42) identifies probable cases as having febrile acute

respiratory illness with clinical, radiological or histopathological evidence of pulmonary parenchymal disease, cough, requirement for hospitalization with suspicion of lower respiratory tract involvement, history of direct contact with a probable or confirmed case, and history of residence or recent travel to a country where MERS-CoV is known to be circulating in dromedary camels or where human infections have recently occurred. This spectrum of signs warrants laboratory testing, where seroconversion in 2 samples by screening and a neutralization assay confirms a case. Although the initial cases of MERS-CoV were detected among patients admitted for severe pneumonia, individuals with mild or no symptoms have also been reported (2–4,44). Thus, WHO has highlighted the importance of also seeking out asymptomatic cases.

The clinical presentation of MERS-CoV infection can range from asymptomatic to very severe pneumonia with acute respiratory distress and multi-organ failure, resulting in death. The clinical course is more severe in immunocompromised patients (6), (although recent case reports indicate that some recover) (45,46), and in pregnant women, where infection has been shown to result in stillbirths. The clinical course is more likely to be mild in individuals without underlying medical conditions (7,47-49).

In its typical form, MERS-CoV infection presents as fever, cough, sore throat and myalgia, which can then be followed by dyspnoea that progresses rapidly to pneumonia, often requiring extracorporeal membrane oxygenation or other organ support. One-third of patients have gastrointestinal symptoms (1,6,7,36,39,50-52). Chest radiography and computed tomography findings are generally consistent with viral pneumonitis and acute respiratory distress syndrome (7,8,47,53–55), and laboratory findings include leukopenia, particularly lymphopenia (1,7,8,39,56).

The median time from symptom onset to hospitalization is 4 days (range 0–16), from symptom onset to admission to an intensive care unit is 5 days (range 1–15) and from symptom onset to death is 11.5 days (range 4–298) (44,50). The time spent in hospital, terminating in either discharge or death was relatively short (median, 7.0 days and 9.0 days, respectively) (44).

Viral characteristics and classification

Deep sequencing methods were used predominantly for genome analysis during the emergence of MERS-CoV (14,22). It is predicted that MERS-CoV encodes at least 10 open-reading frames bracketed by 5' and 3' untranslated regions (57,58). Structural proteins include the spike (S), envelope (E), membrane (M) and nucleocapsid (N) (59,60), and non-structural proteins include a papain-like protease (61-63), transmembrane domains, a 3C-like protease (61), an RNA-dependent RNA polymerase, a helicase and an exonuclease

(14,59,64,65).

Genomes collected from samples of MERS-CoV over the past 3 years show close genetic similarity (66): an alignment of 56 complete or near-complete genomes sampled between 2012 and 2014 differed by 0.00–0.38% (66) (Figure 4).

MERS-CoV belongs to a lineage C within the Betacornavirus found in both humans and camels that are different from other Betacoronavirus that have infected human such as SARS, and the endemic known human Betacoronavirus: OC43, HKU1, NL63, and 229E.

Pandemic potential

Estimations and modelling studies show that a pandemic is unlikely; however, concern remains (67). The estimate is based mainly on calculation of the basic reproduction number (R0) – the average number of infections caused by 1 infected individual in a fully susceptible population (68–71) – from publicly available data. The estimation from the modelling studies suggests that current data are consistent with 2 scenarios: “(i) a sustained epidemic in an animal reservoir with sporadic spillover into humans, and (ii) sustained human–human transmission causing a slowly growing human epidemic” (44). Incomplete case contact tracing, limited testing and clinically defined cases in the absence of laboratory confirmation might affect some R0 calculations and make it difficult to identify patterns in disease incidence.

Transmission and infection control

Although transmission originated from zoonotic events (1,20,37), clusters of human–human transmission of MERS-CoV are now well documented (30,36,38,55,72-82), predominantly among people in health care facilities and within households (3,7,8,22,30, 36,38,43,44,55,72–75,77,79–86). Consequently, human–human transmission of MERS-CoV has been defined as sporadic, intrafamilial and health care-associated. The current pattern of disease is a combination of repeated introduction of the virus from camels to people, resulting in limited, unsustained, human–human transmission (40,87).

MERS-CoV RNA has been identified in the milk, nasal secretions and faeces of camels (88). When MERS-CoV is introduced into camel, goat or cow milk, it can survive for prolonged periods (89); however, pasteurization removes its infectivity (90). Accordingly, the consumption of undercooked or raw animal products, including meat and milk, imposes a high risk. Animal products processed appropriately through proper cooking or pasteurization are safe for consumption but should be handled with care to avoid cross-contamination with uncooked foods

(91). In aerosol tests, MERS-CoV viability decreased by 89% at 70% relative humidity but by only 7% at 40% humidity (89,90). This can have implications in terms of optimal levels for room temperature/humidity control for detected cases to limit spread of the virus. Thus, as a general precaution, WHO recommends general hygiene measures, including regular hand-washing, especially after touching animals; avoiding touching the eyes, nose or mouth with the hands; and avoiding contact with sick animals, particularly for anyone visiting farms, markets, barns or other places where camels are present (87,91). Wearing protective gowns and gloves while handling animals is also recommended (91,92).

As many of the cases have occurred in health care settings (8,81,84,93), it is important that all health care workers practice appropriate infection control measures and apply standard precautions consistently (92) when taking care of patients who are suspected of having or have been confirmed as having MERS-CoV infection (36), especially contact precautions and eye protection. Application of droplet precautions is also required when caring for patients with symptoms of acute respiratory infection, and airborne infection isolation precautions should be applied if necessary (36).

Therapeutic options

In the absence of pathogen-specific interventions, treatment of hospitalized patients remains supportive. Treatment is directed at relieving symptoms and includes rest, fluid and analgesics, and mainly depends on the provision of organ support and management of complications (10,44,94). Broad-spectrum antimicrobial agents, antivirals (94–96), interferon-α2b (96) and antifungal agents have been known to be used to minimize the risk of co-infection with opportunistic pathogens (44). There have been some research advances in terms of development and registration of drugs for human use against emerging infectious agents (97,98); however, progress has been slow.

Promising treatment approaches currently emerging in the scientific literature (66) include the novel molecule K22, which targets viral replication without cellular toxicity (99). It targets viral MERS-CoV 3C protease (79) and the interface between the MERS-CoV receptor-binding domain (RBD) and the receptor by inhibiting the enzymatic function of dipeptidyl peptidase 4 (DPP4) (100). An experimental recombinant nanoparticle vaccine candidate has been produced (101) based on MERS-CoV S monoclonal antibodies directed towards the S protein, and this holds promise for use as a therapeutic and prophylactic agent (102–104). A further vaccine candidate has been shown to elicit antibodies in mice (105,106), and another is a conserved peptide that may provide the basis for an epitope-directed universal vaccine (107).

Molecular diagnostic assays

The viral genome was initially detected in human clinical samples with primers targeting highly conserved regions of the coronavirus genome (44); however, validated (108) real-time reverse transcriptase polymerase chain reaction (rtRT-PCR) assays are now recommended, as they been shown to be both sensitive and specific. Multiple assays are also widely used, i.e. those targeting a region upstream of the E gene or regions within open reading frame 1b (ORF 1b) (nsp14 protein) (108), ORF 1a (nsp6 protein) (109) and the nucleocapsid protein gene (4).

Discussion

A great deal of evidence has been generated in response to this emerging disease, guided mainly by lessons learnt from responses to other coronavirus diseases such as severe acute respiratory syndrome (SARS). Although much has become clearer with regard to MERS-CoV epidemiological patterns, gene sequencing, immunogenicity and animal–human and human–human interfaces, there is undoubtedly much more to be discovered about the operationality of the virus.

WHO, through the Global Alert and Response Disease Outbreak News releases and close proactive contact with the ministries of health of Member States, has so far managed to contain the disease and avoid pandemic spread. Challenges remain, however, owing to a lack of sufficiently detailed data on patient notifications and publications, resulting in a slowing down of evidence-based diagnostic support for outbreak investigations (110). For a more thorough understanding of the clinical significance and epidemiology of MERS-CoV, detailed data from sampling, laboratory analyses, and clinical and epidemiological studies are required to improve the quality of support during outbreaks.

Risk communication to the public is also important, especially among people who have contact with camels. Rapidly and comprehensively updated data case definitions and guidelines for investigations, research study protocols, travel advice, risk assessments and summary updates via purpose-built coronavirus-focused information portals have been instrumental in curbing MERS-CoV. The WHO has played a leading role in all of the above and recommends that such a system of data transparency and continuous updates adopted and linked at country level.

Public health authorities, clinicians and academic scientists must work even more closely together to discover and report relevant data to public health authorities through official channels (111). Global understanding of the epidemiology and treatment for MERS-CoV has improved since the novel outbreak in 2012; however, greater attention should be paid to more-effective prevention. Further emphasis should include upstream prevention through better

interdisciplinary collaboration and communication on all aspects of health care for humans, animals and the environment to improve capacity to identify potential pathogens before they become human threats and to prevent their emergence where possible (111). Some initiatives are showing promise: the One Health Initiative (112) approach, for example, provides a means for interdisciplinary collaboration and communication in all aspects of health care for humans, animals and the environment and could promote the alignment of priorities in global health.

Much remains unknown about MERS-CoV. Surveillance, epidemiological research and the development of new therapies and vaccines are important, and the momentum of recent gains should be maintained to enable the global community to answer the remaining questions about this disease. Below is a list of questions, which is by no means exhaustive, that remain unanswered based on the review of publicly available literature:

What is the natural host for MERS-CoV? And what are the mechanisms for animal–human and human–animal transmission

What is the route of transmission? And what is the best personal protective gear for use by frontline health care workers as well as those working exposed to camels and other potential reservoirs for the disease (animal–human interface)?

Does MERS-CoV infection generally result in a subclinical outcome, except in people with comorbidities? And does the high mortality rate primarily reflect infection of patients with substantial co-morbid conditions?

Are current serological tools sensitive enough to detect the immune response to mild or asymptomatic MERS-CoV infection?

Do differences in occupational and environmental circumstances provide a valid explanation for the initial dissimilarity in terms of disease affection? What is the prevalence of underlying disease in the two sexes?

Does MERS-CoV inhibit interferon induction by novel mechanisms not used by other

coronaviruses?

Does lack of recognition by innate host immune sensors result in high levels of virus in the lung and an imbalanced immune response?

What is the average duration of MERS-CoV shedding in infected humans, and does it differ with age, sex and occupation?

What other events occurring in the northern spring may influence the increase in human exposure to MERS-CoV?

Why does MERS-CoV continue to affect wide areas of Saudi Arabia but in such very low numbers? Do mass gatherings have an as yet unidentified role in the spread of the virus and its subsequent geographical distribution?

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