National Collaborating Centre for Infectious Diseases
Centre de collaboration nationale des maladies infectieuses

NCCID RAPID REVIEW

Middle East Respiratory Syndrome Coronavirus: Ten Questions and Answers for Canadian Public Health Decision-makers

July 18, 2013

Ten Questions:

1. What are the case definitions and guidelines for surveillance and reporting purposes?
2. What has been the estimated severity rate?
3. Who has been at increased risk for severe illness?
4. What has been the natural history of a typical case and the effectiveness of care and treatment?
5. What was the original source of exposure and modes of transmission of exposure?
6. What are the ongoing sources of exposure and modes of transmission of infection?
7. What is known about the "epidemic curve"?
8. What geographic spread has been observed?
9. What are the opportunities and challenges for immediate surveillance in Canada?
10. What are the opportunities and challenges for effective prevention and control strategies in Canada at this time?

1. What are the case definitions and guidelines for surveillance and reporting purposes?

World Health Organization (WHO)

The most current case definition from the WHO for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was published February 19, 2013 as follows:

A **confirmed case** was defined as a person with laboratory confirmation of infection MERS-CoV.

A **probable case** was defined as:

a. A person with an acute respiratory infection with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or Acute Respiratory Distress Syndrome (ARDS)); **AND**

b. No possibility of laboratory confirmation for MERS-CoV because either the patient or samples are not available for testing; **AND**

c. Close contact with a laboratory-confirmed case.

Close contact includes**:**

a. Anyone who provided care for the patient, including a health care worker or family member, or who had other similarly close physical contact;

b. Anyone who stayed at the same place (e.g. lived with, visited) as a probable or confirmed case while the case was symptomatic.

Public Health Agency of Canada (PHAC)

On May 28, 2013, (PHAC) posted an interim guidance document with respect to the investigation of potential MERS-CoV cases in Canada as follows:

A **case under investigation** is defined as

a. a person with an acute respiratory infection, which may include history of fever and cough, and indications of pulmonary parenchymal disease (e.g. pneumonia or ARDS), based on clinical or radiological evidence of consolidation

AND any of the following:

i. History of travel to, or residence in the Arabian Peninsula or neighbouring countries within 10 days before onset of illness;

ii. History of close contact with a person with acute respiratory illness of any degree who had a history of travel to or residence in the Arabian Peninsula or neighbouring countries within 10 days before onset of illness;

iii. Occurs as part of a cluster that occurs within a 10-day period, without regard to place of residence or history of travel, unless aetiology has been identified;

iv. Occurs in a health care worker who has been working in an environment where patients with severe acute respiratory infections are being cared for, particularly patients requiring intensive care, without regard to place of residence or history of travel, unless another aetiology has been identified;

v. Develops an unexpectedly severe clinical course despite appropriate treatment, even if another aetiology has been identified, if that alternate aetiology does not fully explain the presentation or clinical course of the patient.

OR

b. A person with an acute respiratory illness of any degree of severity who, within 10 days before onset of illness, had close contact with a confirmed or probable case of MERS-CoV infection, while the case was ill.

Close Contact criteria:

Anyone who provided care for the patient, including a health care worker or family member, or who had other similarly close physical contact; **OR**

(*editor's addition for clarity*) anyone who stayed at the same place (e.g. lived with, visited) as a probable or confirmed case while the case was ill.

Cluster criteria:
Two or more persons with onset of symptoms within the same 10-day period and who are associated with a specific setting, such as a classroom, workplace, household, extended family, hospital, other residential institution, military barracks or recreational camp.

A **confirmed case** is a person with laboratory confirmation of infection with MERS-CoV.

A **probable case** is

a. a person with an acute respiratory infection with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or ARDS); **AND**

b. no possibility of laboratory confirmation for MERS-CoV because either the patient or samples are not available for testing; **AND**

c. close contact with a laboratory-confirmed case.

***Comment**: There are a variety of national and international case definitions and indications for testing for MERS Co-V which may make it difficult to compare findings in different settings, especially if testing protocols and case classifications are not specified in a surveillance or other type of report. Some case definitions take into account severity of illness, especially for non-lab confirmed cases. Aside from categorization by death or survival, levels of severity such as need for hospitalization or intensive care are not clarified in most case definitions, especially confirmed cases. Similarly, if the reason for testing or the type and timing of testing is not specified in the case definitions, the result could be higher observed rates of cases in settings where asymptomatic contacts or mild cases are tested more frequently or a lower observed rate of cases in cohorts where testing was inadequate or too late to detect the virus. Without systematic testing based on guidelines and/or standards, it may be difficult to make valid estimates and comparisons of disease rates, severity rates and case-fatality rates. In other words, variations in denominators and numerators which are not clearly described can result in significant under- or over-estimation of incidence and severity.*

Canadian public health officials should consider the benefits of reviewing and clarifying case definitions including severity categories for confirmed and other categories of cases as well as testing protocols. These both could be used as a guide for more systematic testing and reporting that should result in more useful surveillance information in Canada and internationally.

2. What has been the estimated severity rate?

a. As of July 18, 2013, WHO has been informed of a world-wide total of 88 laboratory-confirmed cases of infection with MERS-CoV, including 45 deaths. The earliest documented onset of illness in reported cases is April, 2012.

b. The median age of all cases has been 56, but there were no reports or analyses found that sub-analysed cases by severity of illness or the reasons for and methods of testing.

***Comment:** It is not clear what tests were used, for what types of cases or contacts, at what point in time of the natural history of the disease, or what anatomical samples were obtained. Without that information, it is difficult to estimate the sensitivity of the test method and the rate of false negatives. False positives could also occur depending on the specificity of the test methods, including phenomena of "cross-reactivity" in serologic tests and contamination or other "errors" in PCR test kits and usage.*

There is incomplete information about denominators such as the total number and proportion of asymptomatic contacts and milder ILI cases that have been tested with an appropriate test at the appropriate time. Disproportionate testing of severe cases compared to milder cases would constitute a detection bias. This could happen because of test type validity (sensitivity and specificity), and frequency of testing of individuals or groups. Such factors could result in a bias towards identification of the MERS-CoV in the more severe cases. Thus, the case fatality rate of 45/88 ≈50% may be an over-estimate of the true severity rate of illness associated with infection by this virus. The development of a valid serologic test that can be used to confirm the presence of infection which has provoked an immune response should be helpful for more accurate assessment.

Comment continued:
From another perspective, it is quite likely that the total number of cases is a significant underestimate of the true burden of illness. One reason for this is the likely very high number of cases of severe acute respiratory illness that have not been tested for MERS-CoV throughout the world or have been tested with low yield or low sensitivity methods because of test timing and/or test quality.

A reasonably high level of concern and caution of public health officials is probably reasonable at this time based on current evidence of the potential for severe disease, the current limited ability to systematically estimate severity, the uncertainty about the ease of human to human transmission and the unclear but probable trend of increasing worldwide spread in other countries and places.

When one considers the endemic or background rate and total number of cases of severe acute respiratory illness (SARI) in which a specific causative organism is never identified, it is likely that the proportion of severe illnesses and deaths from SARI that have been attributable to MERS-CoV is relatively small compared to the objective true (un-measured) incidence.

3. Who has been at increased risk for severe illness?

Descriptions of the epidemiology of the cases that have been sub-specified and analysed by severity or death were not found for this *Rapid Review*. The age range has been 2-94 years, with a median of 56 years for all cases (mild, severe or fatal). Males have outnumbered females by a ratio of 5:1.

Comment: *There appears to be higher than usual prevalence of underlying medical conditions in cases and deaths, but in the absence of clear definitions or standards for "underlying medical conditions" and a control or comparison group, the evidence for this association in MERS-CoV is not yet well established.*

4. What has been the natural history of a typical case and the effectiveness of care and treatment?

a. The incubation has been estimated to range from 9-12 days. Based on a recent study on patients who have acquired MERS-CoV in a health care setting (Assiri *et al.* NJEM, June 19, 2013), the median incubation period was 5.2 days, and the serial interval (the time between the successive onset of symptoms in a chain of transmission) was 7.6 days. Among patients in whom the illness progressed, the median time from the onset of symptoms to ICU admission was 5 days [range 1 -10 days], the median time to the need for mechanical ventilation was 7 days [range 3-11 days], and the median time to death was 11 days [5-27 days].

b. Early signs and symptoms were most commonly those of an influenza-like illness. Severe illness has been characterized by severe "pneumonia". Most of the cases were hospitalized and treated with mechanical ventilation or other advanced respiratory support.

c. To date, no reports were found of a specific treatment for MERS-CoV. This is a similar situation to that of SARS-CoV in 2002-2003.

5. What was the original source of exposure and modes of transmission of exposure?

a. This MERS coronavirus was not associated with human disease prior to the first published case report from Saudi Arabia in September, 2012. It appears to be morphologically different from the virus associated with the SARS outbreak first reported in 2002.

Comment: MERS-CoV *has been described as most similar to a coronavirus associated with bats, but there has been little, if any reported evidence of an association at this time with exposure to bats or other animals. Reports of clusters of cases associated with exposure to family members, common dwelling places and health care suggest that at least some cases have been associated with observed human to human transmission from exposure to shared air space with an ill person. This is also supported by reports of "secondary cases" with onset of illness considered soon enough after exposure to shared air space with a "primary" case.*

6. What are the ongoing sources of exposure and modes of transmission of infection?

"[There have been] multiple clusters of cases in which human-to-human transmission has occurred. These clusters have been observed in health-care facilities, among family members and between co-workers. However, the mechanism by which transmission occurred in all of these cases, whether respiratory (e.g. coughing, sneezing) or direct physical contact with the patient or contamination of the environment by the patient, is unknown. Thus far, no sustained community transmission has been observed." (WHO, July 17)

http://www.who.int/csr/disease/coronavirus_infections/faq/en/index.html

Comment: *The pattern of case reports with sufficient analysis suggests that the source of exposure is human infection (with or without severe illness) and that the mode of transmission is likely direct and/or indirect airborne and/or droplet nuclei. Illness likely results when several factors are true:*

Comment continued:

i. *There is a source case: a colonized or infected person who may be well or ill and has a sufficient viral load in the respiratory tract;*

ii. *There is sharing of airspace with such a person by a susceptible person without adequate personal protection;*

iii. *For those who are exposed as described above, it appears from documents that have been made available so far that a minority have progressed to illness (usually within one or two weeks) and that those that have progressed (often rapidly) to severe illness have had underlying medical conditions that may have made them more susceptible to infection, severe infection, and/or poorer outcome of care and treatment.*

7. What is known about the "epidemic curve"?

The European Centre for Disease Prevention and Control (ECDC) posted a histogram and map with the following text on June 18, 2013:

"The majority of reported cases continue to be associated with severe disease (lower respiratory tract infection such as pneumonia and/or renal failure). The majority of cases with more detailed information have reported a history of underlying disease or immunosuppression. Five cases (8%) with unknown immune status have presented with mild influenza-like symptoms. Thirty-eight of the 64 cases are reported to have died, resulting in a case-fatality ratio of 59%."

http://www.ecdc.europa.eu/en/publications/Publications/MERS-CoV-novel-coronavirus-risk-assessment.pdf

Comment: *Despite the apparent increase in reported new cases of MERS -CoV during the months of April and May and the possible increased spread to European countries, it is too soon and the data are too limited and potentially biased to interpret whether this indicates a trend of spread or an increase of testing. It is also difficult at this point in time to predict the future course of this apparently novel coronavirus.*

8. What geographic spread has been observed?

As of July 17, 2013, nine countries have now reported cases of human infection with MERS-CoV. Cases have been reported in France, Germany, Italy, Jordan, Qatar, Saudi Arabia, Tunisia and the United Arab Emirates. All cases have had some connection (whether direct or indirect) with the Middle East. In France, Italy, Tunisia and the United Kingdom, limited local transmission has occurred in people who had not been to the Middle East but who had been in close contact with laboratory-confirmed or probable cases. (WHO, July 17)

http://www.who.int/csr/disease/coronavirus_infections/faq/en/index.html

9. What are the opportunities and challenges for immediate surveillance in Canada?

a. WHO has not advised special screening at points of entry.

b. General case definitions, diagnostic protocols, and public health reporting requirements for severe acute respiratory illness of unknown cause have been in place in Canada and many countries for several years, especially since SARS.

c. PCR tests have been developed for infection, depending on the source of the biological sample (i.e. nasopharyngeal swab vs lower respiratory tract). Access to tests and an awareness of the clinical pattern and geographical distribution of cases has enabled the development of case definitions that are specific to MERS-CoV and can be used for more specific surveillance purposes.

Comment: *Communication to remind appropriate hospital clinicians of routine protocols for SARIs, adjusted now for the specific approach for testing and reporting for MERS-CoV, combined with an appropriate level of systematic primary care surveillance, should facilitate the early recognition of the presence of the MERS-CoV and other new or old causes of SARIs in Canada. The development of a valid serologic test that can be used to confirm the presence of infection which has provoked an immune response should be helpful for more accurate assessment of current, recent and past infection.*

10. What are the opportunities and challenges for effective prevention and control strategies in Canada at this time?

At this point in time, neither WHO nor Canada have made any announcements to restrict travel or trade because of this potential emerging outbreak.

Comment: *In addition to the surveillance policies and protocols referred to in #9 above, there does not appear to be any data at this time to indicate that there should be a change to the current PHAC guidelines for infection control practices in community and health care settings which specify routine, contact or droplet, and airborne situations.*

There does not appear to be sufficient evidence at this time with respect to MERS-CoV to support a policy of restriction of travel or any other activities in the everyday settings of everyday life, including health care.

Evidence to date does not seem to indicate a need for significant government investment in specific vaccine development for the MERS-CoV influenza virus nor does evidence appear to be present at this time for enhanced use of antiviral medications in non-severe cases of influenza-like-illness.

The information here used for knowledge translation was obtained from web-posted reports by official organizations, namely WHO, the US Centers for Disease Control, the European Centre for Disease Prevention and Control, and the Public Health Agency of Canada. Comments are the opinion of Dr. Joel Kettner, Scientific Director, National Collaborating Centre for Infectious Diseases.

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