ECDC TECHNICAL REPORT

Risk assessment guidelines for infectious diseases transmitted on aircraft (RAGIDA)

Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

January 2020

Introduction

The Middle East respiratory syndrome coronavirus (MERS-CoV) was first discovered in 2012 in a patient who died from severe respiratory disease [1]. Since then, and as of 16 January 2020, 2 521 cases have been reported worldwide, including 919 deaths (crude case fatality 36%). Most cases have been reported from the Arabian Peninsula (and around 84% specifically from Saudi Arabia), and all cases elsewhere had a travel history to the Arabian Peninsula or were a contact of someone who had a travel history to the region.

This virus belongs to the Coronaviridae family, which includes a large number of viruses widely distributed among mammals, birds, and fish [2]. In humans, they are the second most common cause of the common cold. MERS-CoV infections may be asymptomatic, cause mild respiratory illness, or cause severe or fatal lower respiratory tract infections. The typical symptoms include fever, cough, dyspnoea and gastrointestinal symptoms. Renal or pulmonary failure have been commonly described in fatal cases [3-5].

The diagnosis of the disease should be performed by using an initial screening test, followed by a confirmatory test. The standard screening test is reverse transcription PCR. The only available treatment is symptomatic care. There is still a lack of consensus on the optimal treatment of cases [6,7].

In 2007, the European Centre for Disease Prevention and Control (ECDC) initiated the RAGIDA project (Risk Assessment Guidelines for Infectious Diseases transmitted on Aircraft). This was in order to assist national public health authorities in the European Union in assessing the risks associated with the transmission of infectious agents on-board aircrafts, and to help in the decisions on the most appropriate, operationally feasible public health measures for containment (e.g. on whether to contact trace air passengers and crew in case of exposure).

The RAGIDA project combines evidence retrieved from the literature with expert knowledge. In 2009, the production of the series of guidance documents for assisting in the evaluation of risk for transmission was initiated for several infectious diseases [8,9].

The resulting disease-specific operational documents provide a range of viable options for decision-makers, particularly when faced with the choice of whether to contact trace air travellers and crew potentially exposed to infectious diseases during a flight.

This RAGIDA guidance is to assist public health authorities in decision making regarding contact tracing when a case of MERS-CoV is found to have been travelling on an aircraft. A literature review was performed from January to May 2019, after which an expert meeting was organised in November 2019 to discuss the scientific basis for public health measures. Participants of the expert panel were selected from public health experts with experience in the investigation and follow-up of cases and MERS-CoV experts, as well as experts from the aviation sector, the medical evacuation field, and representatives of ECDC and the World Health Organization. No conflicts of interest were declared by any of the participants.

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During the process of developing this guidance, a novel coronavirus has been identified as the cause of an outbreak in Wuhan, China (2019-nCoV). With the epidemiological and virological information available as of 20 January 2020, the approach proposed in this guidance could also be used for contact tracing of novel coronavirus cases associated with the 2019-nCoV outbreak in China or other novel coronavirus infections, until further evidence warrants a new review.

Literature review

A systematic literature review was carried out using four online databases (PubMed, Embase, Scopus and Global Index Medicus) and through a manual search of additional sources (news reports, notifications from countries, Google search, the Disease Outbreak News (DON) page of the World Health Organization, and the Early Warning and Response System (EWRS)) [10]. The initial search was carried out on the 18th of February 2019, with updates up to May 30th 2019. No limits were set regarding time coverage, language, type of study design, or publication status.

Of the 728 records retrieved, titles, abstracts and full texts were screened independently by two experts. Only records describing a case of MERS-CoV that travelled by aircraft during the symptomatic phase of the disease and who was confirmed with laboratory testing were considered. As a result, 47 records (18 peer-reviewed articles, nine EWRS notifications and 20 WHO DON reports) describing 21 cases of MERS who had travelled on aircraft were identified for inclusion in this review. For 15 of the 21 cases included, more than one source of information was identified. Two cases were mentioned in six different records, and nine records described more than one case.

The 21 cases identified boarded a total of 31 flights; eight cases boarded more than one plane during their travel. The majority of the cases were male (18/21), with ages ranging from 18 to 85 years (mean 55).

Over half of the cases were probably exposed in Saudi Arabia (country of flight origin), and other countries of probable exposure included Qatar, United Arab Emirates, Jordan, South Korea, Oman and Kuwait.

Exact flight durations were reported for only two cases, but were estimated for the remaining cases using an online mapping tool. The flight durations ranged from 1 hour and 20 minutes to 9 hours and 30 minutes. The HEPA filter function of the aircraft was not described in any of the records identified.

Out of the 47 records included in the review, 29 stated that contact tracing had been carried out on the case's flight, and of those, 18 described the investigation results. Contact tracing of the passengers and crew on board the aircraft was carried out for at least 17 cases and 24 flights. It was not mentioned if contact tracing had been carried out for the remaining four cases. The contact tracing investigations were aimed at passengers seated within either a distance of two seats all around the MERS-CoV case, two or three rows from the case, or included all passengers and crew. The time delay for initiating contact tracing after the flight ranged from less than one day (when the disease was suspected but not yet confirmed) to 28 days. The proportion of contacts successfully traced ranged from 35% to 100%, and the proportion of contacts followed for 14 days or more ranged from 15% to 100%. No secondary cases were reported among all traced passengers.

The most significant limitation was the scarce information in many of the records about the flights, contact tracing, and follow-up. The review aimed to gather the information available of all known MERS-CoV cases to have travelled by air, so records were not excluded based on the quality or quantity of the information given.

During the screening process, 16 records were found describing eight cases of MERS-CoV infection who had travelled by aircraft before symptom onset. For two of these cases, contact tracing of passengers on the flights was conducted. No secondary cases related to any of the eight confirmed cases of MERS who undertook flights have been reported.

The absence of any detected transmission event suggests a low probability of transmission. However, this does not preclude that the impact of one exported case could possibly be high, as we have learned from the MERS-CoV outbreak in the Republic of Korea in 2015 [11]. We further conclude that the quality of data collection and reporting about contact tracing and follow-up is limited, and that we are therefore uncertain whether mild or asymptomatic MERS-CoV could have occurred among the contacts.

Contact tracing

The assessment of possible transmission of MERS-CoV on an aircraft needs to be undertaken on a case-by-case basis. This individual risk assessment should take into account the index case classification, the symptoms and disease severity during the flight, and the timing of possible contact tracing in relation to the flight.

The proposed algorithm for contact tracing is outlined in Figure 1.

Objectives of MERS-CoV contact tracing

Contact tracing of passengers possibly exposed to MERS-CoV on-board an aircraft might have different objectives:

- to facilitate timely diagnosis and treatment as appropriate
- to implement timely control measures like isolation or quarantine as appropriate
- to provide preventive health advice to contacts
- to slow down spread upon introduction into a country/region
- to assess the epidemiologic situation
- to better understand the characteristics of the virus.

Operational challenges of MERS-CoV contact tracing

In addition to the limited evidence to assess the risk for MERS-CoV on-board aircraft found in the literature, the effectiveness of contact tracing measures remains unclear.

Several factors hamper contact tracing and effective public health measures:

- non-specific symptoms
- delayed case identification
- high incidence of other respiratory diseases clinically similar to mild MERS
- multiple modes of travel
- lag of decision for immediate action
- difficulties in obtaining passenger contact details in a timely manner
- extensive human and/or other resource needs.

Therefore, the feasibility and cost-benefit of contact tracing need to be carefully assessed. Once the passengers have disembarked, it is challenging to follow up possible contacts in a timely manner and to implement appropriate intervention. Effective contact tracing requires significant operational resources. The operational challenges and resource needs are also considered in the proposed algorithm for contact tracing.

Criteria to be considered in the risk assessment

Case classification

Contact tracing should be initiated upon confirmation of a MERS-CoV case, according to the WHO case definition (https://www.who.int/csr/disease/coronavirus_infections/case_definition/en/).

For a probable case, contact tracing can be considered depending on the epidemiological situation and available resources.

Symptoms, severity and infectiousness during flight

The infectiousness of the index case is likely associated with symptoms and disease severity. Therefore, decisions on contact tracing and other interventions should take into account this factor.

Mild or initial symptoms of MERS-CoV are low-grade fever, runny nose, sore throat, and muscle aches. Severe disease is characterised by progression of respiratory symptoms to cough, shortness of breath and acute respiratory distress syndrome, with a median of two days between hospitalisation and admission to the intensive care unit [12].

Severely ill patients may also present with symptoms outside the respiratory tract. Up to one third of severely ill patients have, apart from the respiratory symptoms, also gastrointestinal symptoms, such as nausea, vomiting, or diarrhoea. Acute kidney injury has also been reported in up to half of critically ill patients.

A case of MERS-CoV is assumed to be infectious only upon symptom onset and not prior to that. Shedding of viral RNA in respiratory secretions appears to be dependent on the severity of illness and has been documented up to 28 days following symptom onset [13,14]. The virus can also be isolated from infected, but non-symptomatic or mildly symptomatic individuals, however their role in transmission remains debatable.

Timing of contact tracing in relation to the flight

The mean incubation period for MERS-CoV is assumed to be on average five to six days (range 2-14). [12,15,16].

When contact tracing can be initiated **within 14 days after the flight**, a full *contact tracing and follow-up* can be performed *until 14 days after the flight*.

The identified contacts should be informed about the event, the symptoms and the need to consult a doctor when symptoms develop. The identified contacts should be encouraged to limit their contact with others, and be strongly discouraged to travel. If any of them develops symptoms, the person should be immediately isolated and multiple specimens should be collected under appropriate infection prevention and control procedures and according to relevant laboratory protocols [7].

When contact tracing can be initiated **between 14 and 28 days after the flight**, contacts may be contacted once to ask if symptoms have developed.

When **more than 28 days have passed since the flight**, no contact tracing should be initiated.

Extent of contact tracing

The existing evidence on MERS-CoV transmission supports a potential role for transmission through droplets, aerosols and direct contact [16]. The respective importance of these modes depends on the setting. The virus has also been isolated from body fluids such as urine, stools and vomitus making transmission via these routes also theoretically possible.

Several approaches to tracing contacts of MERS cases have been applied without yielding any cases thought to have been infected on-board aircraft; therefore contact tracing should focus on those at highest risk of infection [17].

Contact tracing efforts should focus on:

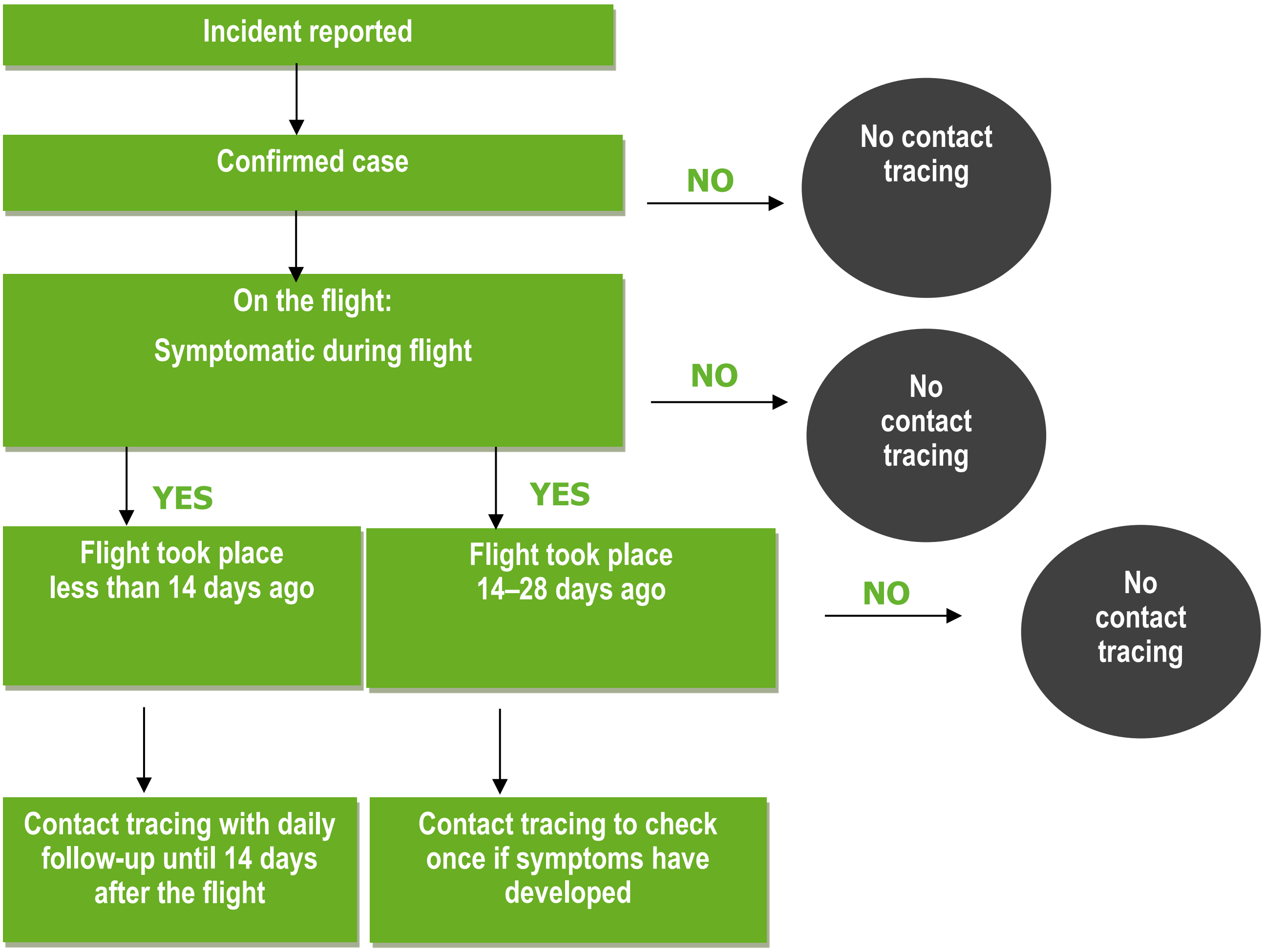
- passengers seated two seats in all directions around the index case AND
- crew members serving the section of the aircraft where the index case was seated AND
- persons who had close contact with the index case e.g. travel companions or persons providing care.

If severity of symptoms, secretions, diarrhoea, other symptoms, or movement of the case warrant more extensive contact tracing, larger portions of the aircraft or the entire section of the aircraft can be subject to contact tracing. This also applies if, during contact tracing, a secondary case is identified.

If a crew member is the index case, all passengers seated in the area served by the crew member during the flight should be regarded as contacts, as should the other members of the crew.

Algorithm for contact tracing

Figure 1. Algorithm for contact tracing for MERS cases who had been traveling on aircraft while symptomatic.



All cases diagnosed should immediately be reported by the national authorities to the Early Warning and Response System (EWRS) if identified in EU/EEA, and to WHO under the International Health Regulations (IHR) (2005).

Consulted experts

This report of the European Centre for Disease Prevention and Control (ECDC) was coordinated by Josep Jansa, Teija Korhonen, Pasi Penttinen, and Emmanuel Robesyn.

This document represents the consensus opinion of individual experts taking part in an Expert Meeting organised by ECDC and held 26 November 2019 in Stockholm, Sweden.

The experts that participated in the meeting (in alphabetical order): Francisco Alvarado-Ramy (US Centers for Disease Control and Prevention, United States), Talía Berruga Fernandez (Uppsala University, Sweden), Gavin Dabrera (Public Health England, United Kingdom), David SC Hui (Chinese University of Hong Kong, China), Bryan Kim (Korea Centers for Disease Control and Prevention, Republic of Korea), Jean-Claude Manuguerra (Institut Pasteur, France) Tanarak Plipat (Thailand Department of Disease Control, Thailand), Johan Skjäl (Finnish Transport and Communications Agency, Finland), Laurent Taymans (International SOS, Belgium), Maria Van Kerkhove (World Health Organisation, Switzerland)

In addition, the following expert provided comments during the review process of this document: Ninglan Wang, (World Health Organisation, France).

This document reflects the personal views of the experts in their individual capacity and it does not necessarily represent the view of their institutions.

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