Summary report on the

Consultative meeting to determine the public health research agenda on MERS-CoV

WHO-EM/CSR/093/E

Riyadh, Saudi Arabia
2–3 March 2014

World Health Organization
Regional Office for the Eastern Mediterranean

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Document WHO-EM/CSR/093/E/06.15

Contents

1. Introduction

Middle East respiratory syndrome coronavirus (MERS-CoV) emerged as a novel virus which was first identified in Saudi Arabia in 2012 causing severe acute respiratory disease in a handful of patients. Since then, hundreds of cases have been reported, principally in the countries of Middle East, and between July 2012 and March 2014, laboratory-confirmed cases of MERS-CoV have been reported from 11 of the countries in the World Health Organization (WHO) Eastern Mediterranean Region.

Since the emergence of this virus, human infections, primarily acquired in the community, continued to increase and a significant number of cases have occurred in hospital settings as a result of secondary transmission. Despite the increasing evidence that the virus might have been circulating in camels, there were a number of critical knowledge gaps in regard to how the virus is transmitted from animals to humans, its route of transmission and the specific types of exposure that result in infection. One of the recommendations of the 2005 International Health Regulations (IHR) emergency committee to the countries reporting laboratory-confirmed cases was to continue their efforts to determine the origin and transmission route of the virus and how humans get the infection from close contact with animals.

A consultative meeting to determine the public health research agenda on MERS-CoV was organized by the WHO Regional Office for the Eastern Mediterranean during 15–16 December 2013 in Cairo, Egypt. That meeting was attended by participants from all the countries in the Region affected by the MERS-CoV outbreak. One of the major recommendations from the meeting was that all countries affected by the outbreak would participate in a multicountry case–control study, coordinated by WHO to address the critical knowledge gaps

surrounding the transmission route of the virus and the specific exposure that results in human infection.

As a follow-up to the December 2013 meeting, another consultative meeting was held in Riyadh, Saudi Arabia, from 2 to 3 March 2014, organized by the WHO Regional Office for the Eastern Mediterranean and hosted by the Ministry of Health of Saudi Arabia. The main objective of this meeting was to finalize the protocol for a case–control study to assess potential risk factors related to human illness caused by MERS-CoV) and the related study questionnaire.

A message from Dr Ala Alwan, WHO Regional Director for the Eastern Mediterranean, was read to the meeting in which he acknowledged the contribution of Saudi Arabia in expanding global scientific knowledge and public health understanding of the possible source of MERS-CoV. While no sustained person-to-person transmission of the virus had yet been found, he stressed that the threats from this novel virus to global health continue to be real and persistent. Although evidence is accumulating that camels may be widely infected, more than three-quarters of laboratory-confirmed human cases reported to WHO do not have a history of direct contact with camels or other animals. It is critical that the route of transmission and the exposures that result in human infection should be further studied.

In the previous consultative meeting on MERS-CoV, held in December 2013 in Cairo, all affected countries in the WHO Eastern Mediterranean Region agreed to participate in case–control studies to help find out more about the route of MERS-CoV infection. This follow-up meeting aimed to finalize the research implementation plan with standardized data collection and analysis in all the affected

countries. A successful conclusion would send a broad signal that all involved were committed to combining their efforts to combat this novel virus.

Dr Ziad Memish, Deputy Minister for Preventive Medicine at the Ministry of Health in Saudi Arabia, welcomed participants to the meeting, and reminded them that it was almost two years since the first case of MERS-CoV infection had been diagnosed and that the extent of the disease had turned out to be much greater than originally thought.

As a prelude to the discussion on the case–control study, a summary of events leading up to the present meeting was given. The first few cases of MERS-CoV appeared in Jordan and Saudi Arabia during the period March–June 2012. In January 2013, the first technical consultation on MERS-CoV, organized by WHO Regional Office for Eastern Mediterranean, took place in Cairo to pool the latest scientific knowledge and to determine the knowledge gaps that needed to be addressed. Subsequently a supplement on the novel coronavirus was published in the Eastern Mediterranean Health Journal (EMHJ) outlining what was known about MERS-CoV at that time. The articles in that supplement systematically covered epidemiology, field investigation, mass gatherings, research gaps, risk communication and preparedness.

The intercountry meeting on MERS-CoV held in Cairo in June 2013 was an opportunity to share the available scientific information on the virus and to discuss transmission and practical steps to contain the spread. The meeting, which particularly focused on MERS-CoV surveillance, case management, infection control, laboratory diagnosis and the IHR, contributed significantly to improving public health

preparedness for preventing the spread of MERS-CoV infection across the countries of the Region. The main recommendations of the meeting were:

- to increase detection through enhanced surveillance and testing (by investigating every new case to determine the exposures that resulted in infection, the likely route of transmission, and the extent to which transmission is occurring);
- to share complete epidemiological, clinical and laboratory data with WHO on all confirmed and probable cases of MERS-CoV infection in accordance with the IHR;
- to develop, and participate in further development of, diagnostic assays through international networking with technical agencies, sharing of materials and resources, and participation in studies;
- to ensure international cooperation and collaboration, as envisaged by the IHR, to address the primary recommendations rapidly and to support Member States' capacities for preparedness and response.

In the technical consultative meeting on 15–16 December 2013 in Cairo, a public health research agenda on MERS-CoV was drafted. It was felt that a case–control study was necessary to understand the risk factors for MERS infection in order to prevent future infections, and affected Member States agreed to participate in a multicountry study supported by WHO and other international health agencies. WHO undertook to provide a draft protocol for the study to facilitate internal national discussions in preparation for a further meeting to discuss and finalize the research protocol and the implementation plan for the study.

At the December 2013 meeting, it was further agreed that serological studies represented a complementary approach to determining the

extent and severity of MERS-CoV infection in the countries of the Region. Participants felt that serological research should ideally be conducted within a multinational study, but that it could also be done individually by Member States. It is vital, however, for affected countries and WHO to work together to create a standardized panel of sera for comparing serological assays, and the study protocols will need to include the conditions under which the serum panel may be used, the roles of laboratories and investigators, and a standardized testing algorithm. WHO agreed to provide an overview paper and draft protocol to each affected country for discussion and approval.

It was further pointed out that the Food and Agriculture Organization (FAO) of the United Nations and the World Organisation for Animal Health (OIE) had agreed to support the implementation of animal studies by identifying reference laboratories for animal serological testing, identifying laboratories to conduct experimental studies, and providing guidance on the duration of quarantine for laboratory-confirmed MERS-CoV infections in camels.

There was considerable discussion of the role of camels in spreading the virus. From the data already gathered, there is a growing suspicion that camels may become reinfected. So far, over 95% of adult camels tested were seropositive for MERS-CoV. Since it seemed strange that Arabian camels were infecting humans but camels elsewhere were not, the view was expressed that there may well be human cases of MERS-CoV in other regions. It was further reported that the cases of camel transmission to humans which had been reviewed seemed to involve “intimate” transmission and very close contact. Actually, there are probably multiple routes of exposure, and there may be some link to the environment around the camels.

2. Summary of discussions

The meeting started with a discussion on the draft study protocol developed by WHO for conducting a case–control study to assess potential risk factors related to human illness caused by MERS-CoV, with a view to finalizing the protocol and the study questionnaire. A summary of the main discussion points centred around the components of the draft protocol is outlined below.

Study design

The aim of the study is to investigate behaviours and risk factors associated with MERS-CoV. Even though only a minority of cases have reported direct contact with camels or other animals, there is no other obvious exposure. It appears that camels do play an important role in transmission of the virus, although the precise route of transmission is unclear. Consequently, the study will require details of exposures that have occurred in human cases and in a group of non-infected persons for comparison. It will aim to find out what sort of exposures lead to human infection and what sort of exposures occurred in MERS-CoV cases that did not occur in non-diseased individuals.

The initial steps in preparing this kind of study include the development of a case definition and the selection of cases to be included. It is also important to identify the population that the cases come from. Once the cases are selected, the control group has to be selected from the same population (or population subgroup) in order to provide the frequency of exposure in the population where the cases have been found. The controls should be representative of the population from which the cases arise; they should not have the

disease but they would be eligible to be selected as a case if they did have it. Controls should be randomly selected, perhaps from similar neighbourhoods, from persons in the same hospital, or from persons with a similar disease; they may be friends of the cases, or they may be selected in another way. As an example, when controls are selected from among hospital patients, the important feature would be the catchment group of the hospital rather than the hospital itself.

There was discussion on possible bias in this type of observational study. Selection bias affects the way cases or controls are selected and may occur if exposure among those selected is not similar to exposure among those eligible. Information bias affects the classification of the diseased and the non-diseased, and therefore influences how exposure is measured. Recall bias is especially likely in the control group; for instance, many people may find it difficult to answer accurately a question about what type of food they ate during a specific period in the past. Some case–control studies use two control groups to try to avoid these kinds of biases. The meeting participants were shown how estimates and odds ratios are calculated in case–control studies.

A question was raised as to whether to include old cases, however, the older the case, the more difficult it would be for controls to recall details of what they were doing prior to the onset of illness in the case. There were also discussions about countries that had only a few cases and would thus find it difficult not to deal with all cases. It was agreed that a small number of cases was acceptable and that there could be up to four controls per case. As to whether to include deceased cases in the survey, it was noted that there were precedents for this which involved interviewing proxies but the information gathered would not be as good as that from an interview with a patient. However, proxies might need to be involved if the patient was on a ventilator.

The strengths of case–control studies include: they can be carried out quickly and inexpensively, they are appropriate for studying rare diseases, they examine multiple factors, and they are suitable for diseases with a long incubation period. It was pointed out that for MERS-CoV there is no viable alternative study design. It is still not known how primary cases become infected and there is insufficient knowledge on which to base preventive public health measures. A detailed exposure history is needed (and therefore detailed questions to identify the likelihood of exposure), as is a comparison group with a similar background.

Selection of cases and controls

It was decided that primary cases would be selected from individuals infected with MERS-CoV from nonhuman sources, while controls would be similar individuals who had not been previously infected. Exposures would be activities, contacts and things consumed in the period just before becoming infected, while the measure of risk would be the likelihood that a case has had a specific exposure compared to the likelihood that a control has had the exposure. The multinational approach would increase the power of the study by increasing the numbers involved, and would demonstrate consistency of findings across countries.

It was stressed that cases should not be selected on the basis of animal exposure (since animal-to-human transmission is not yet proven) but rather on the basis of not having human-to-human transmission. The task was simplified by the fact that most confirmed cases were adults and were able to give informed consent (though proxies could be used if the case was deceased or too sick to respond). A case should be excluded if there was known exposure to a human case before the

onset of symptoms (unless there was subsequent transmission to other humans). Other exclusions should be health care workers (because of the possibility of unrecognized exposure), exposure more than one or two months earlier (in order to avoid problems with recall), and travellers who acquired the infection in another country (since finding controls with the same experience would be too difficult).

There was discussion of whether including only cases that occurred up to one or two months prior to the study was reasonable The focus of the investigation would be the two weeks prior to the infection being reported, which would make recall easier than in a case identified a long time before. There was general agreement not to include older cases, although cases where the patient had survived could be very helpful. It was also agreed not to include “probable” cases (i.e. those not confirmed). As far as possible, cases included would be prospective rather than retrospective. While there was some concern about possible variants of the virus, it was noted that the same serotype had appeared in all cases so far.

It was decided that controls (up to four for each case) would be randomly selected from the same area as the case among near neighbours of the same age and sex. Hospital controls would be anyone of the same age and sex hospitalized in the same hospital as the case for any reason.

Two types of controls were proposed – one group based on hospital patients and the other based on area of residence. There was concern that family or community controls could lead to overmatching, and therefore the second (hospital) group was proposed. This raised a number of issues about the choice of control groups. For instance, if cases and controls are matched by area of residence, then it is not

possible to check area of residence as a risk factor. In addition, one drawback in choosing people from the same area is that the neighbours are likely to be of the same socioeconomic status and likely to do similar things and eat similar food.

Several of the participants felt that controls from the area of residence would be sufficient, while others recommended not asking questions in hospitals, pointing out that some cases were in private hospitals and permission might well be refused. Nevertheless, an argument was made in favour of hospital controls since a large proportion of cases had pre-existing illnesses, and therefore a control population could be chosen from persons with pre-existing illnesses.

After further discussion, participants agreed that all countries should use a group of controls based on area of residence, and if countries wished to use two groups of controls, the hospital-based group could be used as well. If all countries used the neighbourhood controls, the data from different countries could be harmonized in one database and would be meaningful. If any country also used hospital controls, this would be an added benefit and would improve that country's data.

Since each country would be asked to pilot the questionnaire agreed in the meeting, it was felt that each should do the randomization for its pilot testing. It was further agreed that a clear definitions of terms should be provided before the survey started.

Serological testing

It was pointed out that serological testing alone is not sufficient for confirming MERS-CoV; the neutralizing assay was described as the gold standard for confirmation but not for ruling out a positive case.

The purpose of serology in the proposed case–control study was to exclude from the controls anyone who may have been infected, so that such persons were not misclassified. It is also possible that cases may be misclassified, with a secondary case being wrongly identified as a primary case. Serology testing can help to clarify this. While a fully validated serological test is not necessary and there are several assays to choose from, it is necessary to use a standardized testing system in all countries if serological testing was proposed in the study.

Several types of assay were available but the study would require testing to be standardized, with the same assay used in all participating countries. All the cases would have already been confirmed by serology but it was proposed that controls should be tested to rule out previous mild MERS infection. Some persons selected as controls might be willing to answer the questions but unwilling to provide a blood sample, in which case they could not be used in the study. After discussion of the difficulties in obtaining blood samples from people who were not ill, it was agreed that serology should be dropped as a requirement for controls. In terms of the case–control process, it was not absolutely necessary to exclude persons who might previously have had unknown mild MERS.

Saudi Arabia offered to do all the testing for the study, including the testing for other countries.

Investigation of exposures

Three types of exposure would be investigated, food, animals and the environment, and human (as a control for other exposures), with the aim of identifying underlying risk factors that may predispose to infection. Questions should be limited to those which are useful and

can be analysed. The period of interest would be the two weeks prior to illness (it would be essential for both cases and controls to be asked about the same time period) and usual behaviours (especially for fatal cases where details of activities are not known).

Both cases and controls should be asked a standardized specific set of questions about exposures and underlying medical conditions as well as suspected target exposures (especially camels) and indirect routes of exposure such as food. The odds of exposure should be calculated for each group.

Participants felt that translation into Arabic would be essential and that in some situations other languages – Hindi, Nepalese, Urdu – would be necessary. It was proposed to test the questionnaire on a sample before launching the full study. Questions about alcohol use would be inappropriate in some countries though acceptable in others; questions about marriage (number of wives), religion and ethnicity were all acceptable. It was agreed that questions about animals other than camels should also be included.

Study questionnaire

There was concern that the draft survey questionnaire seemed to be very detailed. Experience with a simple questionnaire had shown that families either did not know or could not recall much of the information required, or they were annoyed about being asked about sensitive issues. Several participants said that it was difficult to obtain sensitive information, noting that some better-educated people had helped but others had completely refused to respond to personal questions.

Participants worked in groups to review the draft research protocol. They then reconvened in plenary and each group summarized its views on the questionnaire. Proposals were made regarding the initial general questions and also on those relating to exposures and the background of the persons being interviewed. It was proposed that the number of questions should be reduced and some should be made more appropriate to the culture and customs of the Region. The drafting team noted the proposals in order to revise the questionnaire accordingly.

Management, implementation and publication of the study

The success of the study would depend on a set of common standards and questions in all countries. It was suggested that an oversight committee should be established to advise on analysis and interpretation, with a single regional coordinator to organize training, data management, etc. However, there was a clear feeling that an international oversight committee was not needed since, although the studies would be identical in different countries, each country would conduct its own study and would be responsible to its own authorities.

Participants were informed that the draft protocol prepared for discussion was already undergoing ethical review at WHO. Involvement in the multinational study would require that the research project in each country should be submitted to the appropriate authorities in that country for ethical review. The questions were not especially sensitive; no children would be involved, and no medical procedures would be carried out except possibly taking blood samples.

It was agreed that, once translated into Arabic (and other appropriate languages), the questionnaire would be pilot-tested before the study

itself began. It would be useful to have assistance from WHO experts in formulating and developing the implementation plans in some countries. It was felt that extensive pilot-testing would not be necessary as the design of the study had been assiduous; piloting could take place among members of the community. The participants stated that they would be ready to begin the study soon after receiving the Arabic translation of the finalized questionnaire and following clearance from their national authorities.

The participants representing affected countries committed themselves to working together, coordinating their studies, calling on experts to assist where necessary, and endeavouring to facilitate the sharing of data and the publication of the study.

The report on the multinational study should be a joint publication with joint authorship from the countries conducting the study, and with no primary authors. Each country would, however, own its own data and could publish its own findings. WHO would provide support for data analysis and interpretation so as to translate the findings into a set of public health recommendations for the general public.

3. Next steps

The participants and experts were thanked for their active involvement in the meeting and for their contributions to the finalization of the questionnaire and the study protocol. It was noted that the case–control study on MERS-CoV would be the first international collaborative multicountry study ever conducted on an emerging infectious disease.

The following action points were noted.

- For uniformity and consistency, the multicountry international case–control study on MERS-CoV would be conducted in all the affected countries using the protocol developed by WHO and finalized in the meeting.
- WHO would finalize the study protocol and study questionnaires based on the discussions and recommendations suggested in the meeting by the end of March 2014.
- WHO would circulate the final protocol to all the countries along with the Arabic translation of the study questionnaire for ethical clearance by the competent authorities of the respective countries.
- The study questionnaire would be pilot tested on a limited scale in Saudi Arabia, and WHO would provide technical assistance to countries which needed it for either pilot testing or implementing the study.
- The affected countries would coordinate their work, share experiences and assist each other in training the interviewers, conducting data analysis, etc.
- Saudi Arabia would begin the study as soon as ethical clearance on the study protocol was granted.
- WHO would coordinate with the countries, upon request, to facilitate data pooling and merging of datasets from all affected countries into one uniform multicountry set of data and conducting further analysis of these datasets together with the countries for better interpretation and meaningful generation of information.

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