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WHO consultation on MERS-CoV therapeutics and vaccine evaluation

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Meeting report

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On November 30 2018, the WHO R&D Blueprint and Global Program on MERS convened a group of experts to discuss methodological issues and agree *a priori* on principles in the design, conduct and analysis of Phase2b/Phase 3 clinical trials to evaluate Middle East respiratory syndrome coronavirus (MERS-CoV) therapeutics and vaccines, based on key epidemiological considerations and driven by treatment and vaccine needs from a public health perspective. The group of experts included national representatives from countries affected by MERS-CoV, experts in MERS-CoV virology and epidemiology as well as members of the R&D Blueprint working group on clinical trial design. Post-exposure prophylaxis evaluation was not addressed within the scope of the workshop.

Epidemiological considerations

This section does not intend to summarize all the current knowledge on MERS-CoV clinical manifestations and epidemiology but intends to provide main epidemiological considerations for the design of clinical trials for MERS-CoV therapeutics and vaccines evaluation, based on the group discussions.

From 2012 until the end of November 2018, a total of 2274 laboratory-confirmed cases of MERS-CoV infections were reported from 27 countries with 817 associated deaths (case–fatality rate: 35.9%). Globally, MERS-CoV transmission in humans is sporadic and highly heterogeneous. The majority of MERS-CoV infections have been reported from the Arabian Peninsula, notably from the Kingdom of Saudi Arabia (KSA), with large regional heterogeneities in transmission. Furthermore, exported MERS cases have been observed in North America, Europe and Asia. In particular, a MERS case who travelled in 2015 to South Korea seeded a significant nosocomial outbreak causing 186 cases and 38 deaths. Of note, the last exported case to South Korea in September 2018 did not result in further human-to-human transmission due to rapid and comprehensive actions taken by Korean health authorities.

Transmission occurs between infected dromedaries and humans with potential subsequent human-to-human transmission most notably in health care facilities. Results of contract tracing suggest evidence of mild or asymptomatic transmission in health care settings among health care workers and possibly among individuals in contact with camels. Nevertheless, the majority of human-to-human transmission was observed to be acquired in larger outbreaks in healthcare facilities. The largest nosocomial outbreak was a multi-hospital outbreak in Jeddah and Riyadh resulting in more than 550 cases in six weeks in the Spring of 2014. Specifically within health care facilities, outbreaks have occurred in emergency departments, renal dialysis units and intensive care units (ICUs).

Globally, human-to-human MERS-CoV transmission has been less observed since 2016 thanks to significant changes in control efforts by the Ministries of Health and hospitals of affected countries, although the threat of large nosocomial clusters remains, especially in unprepared countries. Under the WHO Global Program on MERS, countries at-risk of MERS-CoV outbreaks have improved their ability to detect, respond to and control MERS-CoV outbreaks. For instance, In 2017, the KSA tested almost 700 000 samples, Qatar tested about 100 000 samples, and Kuwait tested about 14 000 samples for MERS-CoV. Contact tracing is now systematically performed in the event of an identified patient, which allows for the rapid detection of milder secondary cases, notably among healthcare workers. Furthermore, health systems of affected countries have been profoundly redesigned to improve triage procedures, testing and initiate treatment of confirmed MERS-CoV infections at the earliest opportunity.

The clinical spectrum associated with MERS-CoV infection is extremely variable. Approximately 20% of reported cases are asymptomatic or have mild respiratory symptoms and about 45% of recognized MERS cases are severe or fatal, and require ventilatory support and management in intensive care. Severe patients typically present with laboratory abnormalities (e.g. elevated AST, ALT, creatinine; leukopenia and thrombocytopenia), hypoxemia, and are at higher risk of developing acute kidney injury, multi-organ dysfunction and death. The overall crude mortality rate is 35.5% (number of reported

deaths/number of reported cases to WHO) but varies substantially. The risk of severe disease and death is significantly higher among males and those with underlying conditions such as hypertension, renal failure, diabetes and immunosuppression. Mortality among hospitalized patients can reach as high as 70%.

A cohort study of critically ill patients from several hospitals in KSA revealed that it took on average 5 days from onset of symptoms to come to an emergency department at the hospital, an additional 2 days to be transferred to an ICU, and one more day to undergo intubation. The late presentation of MERS patients has been challenging for existing therapeutic trials. In addition, the cohort study revealed that although most of the deaths occurred within 28 days of symptom onset, deaths continued to occur until 60 days, and more rarely until 90 days.

In order to better inform the design of therapeutics and vaccine trial, experts recognized that epidemiological and knowledge gaps remain. Experts underscore the need for sero-prevalence and modelling studies in order to better understand transmission patterns and to anticipate where new MERS cases from spill over events and where amplification in unprepared health care facilities and potentially households could occur.

Furthermore, meta-analysis of currently available and ongoing clinical studies is needed to better understand the wide clinical spectrum and to derive a prognostic model for mortality. Lastly, studies are needed to better understand the risk of spill-over events at the interface between camels and humans (these are currently planned or ongoing in a number of countries across Africa, the Middle East and South Asia).

Considerations on MERS-CoV diagnostics

Diagnostics development and evaluation for MERS-CoV were mainly conducted in the context of detecting human cases and confirming infection, as well as for surveillance in camels. Currently, nucleic acid tests are systematically used at point of care in support of clinical triage of patients with respiratory diseases and to confirm MERS outbreaks, while rapid diagnostic tests can be used in a more decentralized way to screen the virus in camel herds, in an effort to prevent transmission for camels to humans. Efforts are underway to ensure that currently available – used under emergency authorization - and investigational diagnostics fit the purpose of vaccine and therapeutic clinical trials with the right sensitivity and specificity, particularly in support of participant enrollment, baseline serological measurements and trial endpoint measurements. A Target Product Profile for MERS diagnostics needed from a public health perspective is under development and it is essential to integrate the vaccine and therapeutics trial needs, including the targeted endpoints, into the process in order to guide the development of new diagnostics and capitalize on the use of available ones.

Quantitative molecular assays could be used to assess viral load of MERS-CoV to confirm cases and to assess viral replication in patients and potentially responses to antiviral treatments. Careful evaluation must be done to assess the performance and quality of such assays in measuring differences in viral loads. Rapid antigen detection tests (e.g. lateral flow assay) could be used to inform preliminary participant inclusion to be subsequently validated with a more informative test in the trial reference laboratory. In vaccine trials, serological assays could be used to determine the effect of serostatus on vaccine efficacy and safety, as well humoral responses to vaccine. Serologic assays might be used to inform inclusion/exclusion criteria, as well as to prospectively understand where to conduct vaccine trials through the conduct of seroprevalence studies. Finally, serological assays could be used to establish immunological correlates of risk and/or protection.

Clinical trials to evaluate the safety and efficacy of MERS therapeutics

Overview of investigational therapeutics

This section does not intend to provide the full overview of therapeutics candidates developed to treat MERS patients but intends to highlight the main characteristics of the most advanced agents that could be considered for efficacy trials and to illustrate the rationale for ongoing clinical trials.

There is currently no specific licensed therapeutic to treat MERS patients. Standard of care refers to supportive procedures used in ICUs for managing patients with severe acute respiratory infection (SARI). Several antiviral and biological agents are under investigation for MERS-CoV in various clinical phases.

Based on the SARS experience, convalescent plasma derived from recovered MERS patients was explored as a treatment option for MERS patients. However, it was observed that only a limited number of MERS patients seroconvert and, among them, very few patients generate high and long-lasting antibodies titers against MERS-CoV, which raises serious doubts on the efficacy and feasibility of this approach.

In vitro studies have shown that combination of ribavirin (RBV) with different interferon (IFN) types inhibit MERS-CoV in Vero Cells. In a rhesus macaque model, high doses of RBV/ IFN-α2b administered within 8 hours post challenge showed partial efficacy in reducing clinical symptoms and viral loads. Later time points were not tested, in part because of the limitations of the model and despite the recognition that MERS patients present relatively later in their disease course under real conditions. Based on those preliminary data, RBV in combination with several IFN types (IFN-α2b, IFN-α2a, IFN-β1a) were widely used to treat MERS patients. However, a retrospective cohort study showed no effect on mortality or viral load reduction between those treated and untreated, after adjusting for time from onset of symptoms to treatment initiation and other covariates. It has been recognized that RBV concentrations required to inhibit MERS-CoV need to be far higher than what can be clinically acceptable in humans. IFN-β1b, used to treat multiple sclerosis, has shown to display higher level of inhibition than other type of IFN, but this approach has not been tested in MERS patients.

Animal studies have suggested that lopinavir/ritonavir, licensed for HIV treatment and previously used in treating SARS patients with unknown efficacy, have shown some level of inhibition of MERS-CoV. In a marmoset lethal challenge model, lopinavir/ritonavir alone or IFN-β1b alone compared to control have shown significant improvements in mortality and clinical manifestations, as well as lung viral load reductions. A placebo-controlled, randomized phase 2b/3 clinical trial (the MIRACLE trial, ClinicalTrials.gov, ID: NCT02845843), currently implemented in KSA, aims to assess the efficacy of the combination of lopinavir/ritonavir with IFN-β1b in treating hospitalized MERS patients. As of end of November 2018, the MIRACLE trial has enrolled 36 patients over two years across 10 participating centres, which highlights the difficulties of recruiting participants and hospitals and logistical challenges in a MERS treatment trial. To address some of these difficulties, trial investigators have established a mobile team to facilitate the consent of patients, IRB approval of new hospitals and training of healthcare workers on-site. A first interim analysis will be conducted early 2019 to assess the efficacy or futility of the combination therapy and will allow for sample size recalculation. Lastly, the group noted the existence of a triple therapy protocol in South Korea, designed to assess the efficacy of lopinavir/ritonavir, RBV and IFN-β1b in combination, although no data have emerged from this protocol.

Based on promising results from a mice model, a Phase 1 clinical trial of SAB-301, a human polyclonal antibody product developed on a transchromosomic bovine system, has shown to be safe and well-tolerated in humans, with a half-life of 28 days in healthy patients after a single infusion of 50 mg/kg. A Phase 2 clinical trial – called AIMS - is under consideration and review by KSA national authorities.

Several anti-S monoclonal antibodies are under development and have shown neutralizing activities in vitro and in vivo efficacy in transgenic mice and rhesus macaques models. So far, only REGN3048+REGN305, a cocktail of two monoclonal antibodies, has advanced to a Phase 1 clinical trial.

Remdesivir, a broad-spectrum antiviral nucleotide agent, has shown to inhibit MERS-CoV in vitro and to reduce disease burden in a murine model at doses administered 24 hours post-challenge and likely to be achievable intravenously in humans. Remdesivir has shown superiority in clinical and virological outcomes over lopinavir/ritonavir with IFN-β1b in this model. Intravenous remdesivir has completed a Phase 1 clinical trial and is currently being evaluated both for the treatment of acute Ebola virus disease and for the viral clearance from the semen of Ebola survivors.

For the treatment of MERS-CoV, it was recognized that a combination therapy may be attractive, particularly the combination of an antiviral with an antibody. However, while the biological plausibility of positive synergies for combination therapy could be assessed *in vitro*, it was noted that it is essential to obtain non-interference data in animal studies to obtain some indication of the potential added benefit of combination therapy, and lack of an unexpected harmful interaction, before moving to clinical trials. Furthermore, therapeutic evaluation and combination therapy evaluation is hampered by the lack of adequate and standardized MERS animal models and their predictive value in recapitulating MERS disease in humans. A better understanding of MERS investigational treatments and combination therapies could be leveraged from the development of more robust animal models.

Overview of trial design methodological elements

Epidemiological considerations and preliminary lessons learned from ongoing MERS clinical trials in KSA have identified challenges for the design, conduct and analysis of clinical trials to evaluate MERS therapeutics.

The limited and sporadic nature of MERS cases requiring hospitalization and difficulties in enrolling patients in current trials underscores the need for a multi-site, multi-outbreak, Master Protocol whereby various stakeholders would operate under a single protocol generalizable to all countries where MERS-CoV can potentially be circulating in an effort to generate systematically collected evidence. Furthermore, engaging stakeholders under a Master Protocol would potentially increase chances of answering research questions deemed to be the most relevant from the widest public health perspective and would also serve as a framework to transparently select the most appropriate therapeutic candidates for evaluation.

1. Target population – **all symptomatic hospitalized MERS confirmed patients**

Given the favourable risk-benefit profile of treating MERS with the potential candidate therapeutics and the challenges in recruiting MERS patients early, notably highlighted in the MIRACLE trial, experts underscored the need for an inclusive recruitment strategy, in the context of the research question that needs to be answered. All symptomatic hospitalized MERS confirmed patients should be recruited in the trial based on objective criteria of disease severity, also recognizing that treatment effect may be higher in this target population compared with assessing treatment effect in critically ill patients only. Laboratory confirmed patients who are asymptomatic but “hospitalized” as part of isolation/quarantine procedures, would be preferably excluded from the trial. It was also reflected that exclusion/Inclusion criteria in the context of treatment of severe disease could be kept as general as possible, as done in the currently ongoing study to treat Ebola patients with use of similar agents.

2. **Primary endpoint**

Option 1 – Day-60 mortality from the time that the first dose is given
Option 2 – Co-primary endpoint: Day-60 mortality + persistent organ dysfunction**.**
where the false positive error would be shared between the analyses of these two endpoints.

Given the high mortality of hospitalized MERS patients, it was agreed that a mortality endpoint should be considered for its clinical and public health relevance. Day 60 mortality was chosen over Day 28 mortality, because, although most of the deaths occur before Day 28, it has been observed that a significant number of patients are still at high risk of death among hospitalized patients from Day 28 until Day 60, and that it is essential to learn whether or not the intervention is able to prevent death among those patients and to avoid any misinterpretation that could arise from looking at Day-28 mortality only. Lastly, the choice of Day 60 mortality increases the trial power by potentially capturing more events.

It was also noted, that a composite endpoint (e.g. mortality combined with morbidity) would increase the power of the trial and would be relevant for the sub-population of non-critically-ill hospitalised patients. However, it was also noted that a co-primary endpoint would decrease interpretability of the results, due the composite nature and because measurements of morbidity endpoints are subjected to variability in definition and classification. Nevertheless, on the basis on including all hospitalized patients into the trial, Option 2 was equally considered as Option 1. This would call for definition of objective and standardised criteria to define organ dysfunction, and an assessment of the incidence of each component of the proposed co-primary endpoint in existing observational datasets.

Persistence and quantity of viral RNA shedding measured by date from first dose until RT-PCR negative was suggested as a secondary endpoint. In therapeutic trials, viral load has potentially three distinct uses. As with any other covariates, viral load could be a prognostic factor, i.e. baseline viral load may be indicative of the risk of mortality in patients and randomization should be stratified for it. As any other covariates, viral load could also be an effect modifier, i.e. one may observe more treatment effect on someone with higher or lower viral load. Finally, viral load could be assessed as a surrogate endpoint, i.e. the treatment effect on viral load captures the nature of the effect on the primary endpoint. So far, data on viral load and viral shedding in MERS patients is very limited and preliminary evidence suggests that viral load may not be the most important prognostic factor or a reliable surrogate outcome for mortality or other clinical endpoints.

3. Randomization – **individually-randomized** within each hospital

Given the very limited and widespread number of MERS cases, randomization at the individual level was preferred. The need for randomization was widely accepted to generate reliable evidence and enhance interpretability of results, especially given the large heterogeneity in clinical spectrum and to account for differences in standard of care across sites, as well as to balance additional unknown covariates. Randomization could be stratified by relevant prognostic factors (e.g. whether or not patient requires mechanical ventilation).

Randomization at the individual level was preferred over cluster randomization in this setting, because cluster randomization would substantially increase the study sample size and complicate data interpretation, especially given the heterogeneity across sites, and it has been agreed that the focus of the potential clinical trial should remain on direct treatment effects only. Lastly, it is not clear whether randomization at the cluster level would increase enrolment rate at a given site.

4. Comparator – **Standard of care arm**

Participants agreed that there is still equipoise around the use of investigational therapeutics in treating MERS patients, and therefore standard of care was deemed to provide an acceptable comparator. In addition, a standard of care arm would enhance trial interpretability. WHO is working with affected countries to implement technical guidance on MERS case management. Nevertheless, it was recognized that variations in care exist across sites and that a too stringent definition of standard-of-care may interfere with the training and practices of healthcare workers in new sites and affect patient enrolment. However, it was noted that imbalance in case management would be balanced by individual randomization within each site and stratification by site. Finally, placebo should be used in the comparator arm whenever possible and investigators should be blinded to the study data.

Trial designs - Factorial design (option 1) and two-arms design (option 2)

Two major options were discussed by the group and the decision to choose between the two options mainly should be driven by our understanding of the biological plausibility of the benefit of a potential combination therapy between an antiviral and an antibody product, recognized as a potentially attractive approach to treat MERS patients. It was also made clear that any new trial should not jeopardize the conduct of an existing trial.

Option 1 – Factorial Design – Drug A : Drug B : Drug A + Drug B : standard of care.
Drug A is expected to be a monoclonal or polyclonal antibody product
Drug B is expected to be an antiviral product

Option 2 – Two-arms Design – Drug C : standard of care.
Drug C is expected to be any of the investigational therapeutic

If it is biologically plausible that the mechanisms of action of Drug A and Drug B are complementary (i.e. to an individual who is given Drug A, the addition of Drug B still carries its benefit) and that toxicity would not preclude the combined use of Drug A and Drug B, a factorial design (option 1) was recognized to be the trial design of choice. This design has the potential to answer multiple primary questions, including some insights about potential interaction, in a much more efficient way than by doing separate trials answering one research question at a time. In a trial using a factorial design to study drugs A and B, the collective effect of Drug A would be measured by pooling the effect of Drug A compared with standard of care with the effect of Drug A + Drug B compared with Drug B only. Similar inference can be made for Drug B. An analysis to see whether there is an interaction effect could also be performed, but the power to detect an interaction will usually be low. A factorial design in principle requires the same sample size as a single two-arm trial, though a small increase in sample size to account for the testing of 2 hypotheses would be needed. However, if a positive synergy between the drugs were anticipated (i.e. Drug A carries more benefit in the presence of Drug B than when given alone), a factorial design might require even fewer patients than a standard two-arm approach. On the other hand, if there are negative synergies or no additive effect (i.e. Drug A carries less or no benefit, or more harm in the presence of Drug B), this factorial design approach will be underpowered and could lead to an inconclusive outcome. If such interaction is expected, a two-arm randomized trial (option 2), giving priority to the drug determined to be most promising, should be considered instead of a factorial design.

In both settings, secondary analyses would aim to assess the persistence of viral shedding, measured by date from first dose until PCR negative and perform subgroup analyses based on covariates of interest (e.g. mechanical ventilation requirement, ICU).

Data Monitoring Strategy

It was agreed that study data would not be released unless the trial was stopped for efficacy or futility, under close DSMB oversight, or by reaching its targeted number of patients or endpoints, to preserve the integrity of the trial and to prevent any prejudgment. Interim analyses to assess efficacy or futility can be timed to occur at after reaching a targeted amount of events. Assuming that roughly 100-200 cases per year are enrolled in the trial, option 1 or option 2 may take around 2-4 years to complete.

Clinical trials to evaluate the safety and efficacy of MERS vaccines

The group of experts was also asked to provide recommendations on clinical trials for human MERS only. Dromedary camel MERS vaccines were not in the scope of the workshop (though are in development). It was recognized by the group that the proposed recommendations on MERS vaccine trial design are preliminary, mainly because of epidemiological gaps, and will be revised as new evidence emerges.

Overview of investigational MERS-CoV human vaccines

This section does not intend to provide the full overview of vaccines candidates developed to prevent MERS-related burden of disease but rather to highlight the main characteristics of the most advanced agents that could be considered for efficacy trials and to illustrate the motivation behind current vaccine design.

There are currently no licensed MERS vaccines. Several candidate vaccines were reviewed during the IVI-WHO Joint Symposium for MERS-CoV vaccine development in June 2018. All current vaccine design approaches target the full-length spike (S) protein, with a wide variety of platforms ranging from live-attenuated, inactivated, protein-based (e.g. VLP), and viral-vectored (e.g. MVA, measles, adeno) approaches. Three candidate vaccines (2 viral-vectored and 1 DNA vaccine) have undergone initial dose-related tolerability and immunogenicity studies.

Based on animal data, it is recognized that both humoral and cellular immune responses, mainly induced by the S and the nucleocapsid (N) proteins, are required for full protection against MERS. In particular, passive immune transfer studies have illustrated the key role in protection of neutralizing antibodies that are primarily directed against the receptor binding domain (RBD) of the S protein. T-cell response has been observed in all MERS survivors, whether they had a mild or severe disease, whereas antibody response has been observed much more inconsistently over time. Also, reinfection with MERS has been observed but has not been clearly documented, which further raises concerns on the potential duration of immunity induced by natural infection or a MERS vaccine. Finally, there is no established immunologic correlate of protection.

MERS vaccine development is also associated with important safety concerns on the risk of disease enhancement. Originally described with SARS inactivated vaccines, pulmonary Th2-immunopathology, associated with eosinophilic infiltration and increased pro-inflammatory cytokines in the lung, has been observed after immunization with an inactivated MERS vaccine followed by a wild-type MERS-CoV challenge in a transgenic mice model. While the vaccine protected against infectious virus replication, it was associated with immunopathology. Similar changes were observed in a SARS murine model after immunization with various S vaccine constructs and virus challenge. These safety concerns have highlighted the need for careful safety studies and may provide an argument to design MERS vaccines targeting more discrete portions of the spike protein.

Overview of trial design methodological elements

The design of vaccine trials for MERS is even more challenged by the current epidemiology than the design of therapeutic trials, mainly because it is difficult to identify a target population and site in which enough transmission will occur and because sample sizes required to reach conclusive evidence are large. About half of observed transmission occurred in community setting, and the other half has been observed in health care settings.

Like for therapeutic trials, the group underscored the need for a Master Protocol that would be flexible to address both a preventive and a reactive setting, i.e. in response to an outbreak. Under a Master Protocol, one would aim to capture sporadic transmission events in specific population at-risk of MERS infection, typically in the Arabian Peninsula, as well as transmission occurring in nosocomial outbreaks in any country where an outbreak may arise. Likewise, engaging stakeholders under a Master Protocol would potentially increase chances of answering research questions deemed to be the most relevant from the widest public health perspective and would also serve as a framework to transparently select the most appropriate vaccine candidates for evaluation.

In a reactive setting, i.e. in response to an outbreak, it was noted that if identified early, MERS outbreaks in health care settings are typically of short duration, typically one month, which challenges the conduct of a vaccine trial in this setting. Furthermore, vaccine evaluation in such settings would require a vaccine that gives protection rapidly, ideally after the first dose. Given the short duration of nosocomial outbreaks, it was further noted that passive immunization might play a more appropriate role than active immunization.

Participants discussed the study endpoints and study population with respect to the broader use of a MERS vaccine, expected from a public health perspective.

1. **Primary endpoint**

Option 1 – Laboratory-confirmed acute clinical MERS illness
Option 2 – Co-primary endpoints: laboratory-confirmed acute clinical MERS illness and mortality, where the false positive error would be shared between the analyses of these two endpoints.

Participants recognized that a MERS vaccine that would nearly eliminate the risk of laboratory-confirmed acute clinical MERS illness would almost assuredly meaningfully reduce the risk for major morbidity or mortality, leading also to significantly less pressure on health systems. This reasoning contributed to support of Option 1. In Option 1, mortality would be a critical secondary endpoint. In this design, a trial with 62 primary endpoint events and a 5% false positive error rate would have 90% power to rule out a hazard ratio of 0.7 when the true hazard ratio was 0.3. Positivity at 2-sided p=.10 would occur with an estimated hazard ratio 0.45 and at the traditional 2-sided p=0.05 would occur with an estimated hazard ratio 0.41, the latter corresponding to estimated vaccine efficacy of 59%.

For a primary endpoint of mortality, it would be appropriate to design a study attempting to rule out the simple null hypothesis of no benefit. This lower bar for a mortality endpoint allows it to be included as a co-primary endpoint (option 2) with little to no loss of efficiency, and in fact potentially substantial gains in efficiency for vaccines that have beneficial effects on both the risk of acute clinical MERS illness and also on the risk of mortality.

It cannot be excluded that a vaccine could reduce the probability of acute clinical illness without having a large effect on mortality. For example, if a trial of a MERS vaccine were to yield statistically positive results by Option 1, with estimated vaccine efficacy in the range of a 55% to 60% reduction in acute clinical MERS illness, and if mortality in the control group would be expected to be approximately 40%, it cannot be assumed that such a vaccine would be preventing 55 to 60% of the deaths, since the vaccine

could be selectively preventing anywhere from very few to most of the cases that would have had high mortality risk. Similarly, a vaccine with 55 to 60% vaccine efficacy regarding laboratory-confirmed acute clinical MERS illness could have anywhere from little effect to a profound effect on mortality. Given that mortality risk in MERS illness is so high, including mortality as a co-primary endpoint (Option 2) is appealing due to the clinically compelling importance of obtaining definitive evidence about effects on mortality.

To illustrate the important increase in sensitivity of Option 2, suppose a clinical trial's 2.5% false positive error rate would be shared equally between ruling out the hypothesis of 30% vaccine efficacy regarding the endpoint, 'laboratory-confirmed acute clinical MERS illness' and ruling out the hypothesis of no effect on the endpoint, 'mortality'; further, suppose the trial with a 2:1 randomization between the vaccine and placebo arms has 62 participants having laboratory-confirmed acute clinical MERS illness and has an estimated 50% vaccine efficacy on that endpoint, and yet also has 40% mortality in the control arm and an estimated reduction in mortality risk of at least 70%, (a plausible scenario); in that setting, the trial would yield a negative conclusion about vaccine efficacy when using Option 1 and yet would yield the positive conclusion of a statistically significant effect on mortality when using Option 2.

The table in Appendix 1 gives power calculations for an additional set of simulations. The seventh column of the table shows the statistical power to rule out that Vaccine Efficacy is less than or equal to 30% (equivalent to a relative risk of 70% or higher) under option 1, based on only the relative incidence of acute clinical MERS illness, assuming a two-sided type 1 error rate of .05. The last column, also in bold, gives the statistical power to reject either the null hypothesis that vaccine efficacy is ≤ 30% for MERS illness or the null hypothesis that vaccine efficacy is ≤ 0 for mortality, option 2, assuming a two-sided type 1 error rate of .025 for each comparison. While not meant to represent all possible scenarios of interest, for all scenarios examined here the statistical power is either the same or higher for option 2 as for option 1.

It was agreed that more in depth discussion is needed about the relative merits of these two options, enlightened by further simulations and statistical calculations under various scenarios regarding sample sizes of trials and numbers of participants having laboratory-confirmed acute clinical MERS illness events, mortality rates, true levels of vaccine efficacy for effects on these two endpoints, and, for Option 2, regarding approaches for sharing the false positive error rates between the two analyses and regarding a range of null hypotheses for the mortality endpoint, (such as ruling out no effect or, instead, requiring stronger evidence that also rules out small effects on mortality).

It also was noted that a case definition of 'laboratory-confirmed acute clinical MERS illness' must be defined and needs to be standardized across countries that would operate under the Master Protocol.

Infection and potential for preventing transmission was also discussed as a potential primary endpoint, especially given the existence of asymptomatic transmission that could lead to severe disease and death. However, it was recognized that preventing transmission for an acute respiratory disease like MERS sets a bar very high for a vaccine in general, and in particular for MERS vaccines, with the risk of eliminating vaccines that would otherwise prevent disease and death. Nevertheless, it is critical that preventing infection in sputum should be studied as a secondary endpoint.
Mild and subacute illnesses, as well as immunological correlates of risk and of protection, were also suggested as secondary endpoints. For the latter, relevant samples need to be collected at baseline and some days – to be defined – after administration of the vaccine.

2. **Target population** – **Healthy adults and children**, excluding pregnant and lactating women, immunodeficient persons, and infants

The proposed target population discussed was preliminary and will be refined as our understanding of how people exposure to MERS evolves, in order to enrol the most appropriate population at-risk of MERS infection and disease, where transmission events are likely to occur. Furthermore, the definition of an appropriate study population for a MERS vaccine is challenged by the fact that the people that may potentially benefit the most from a MERS vaccine, from a clinical perspective, are people with co-morbid conditions and with varying degrees of immunosuppression.

Given the way MERS transmits from dromedary camels to humans and from humans to humans, an occupational-based target population would be appropriate.

In hospitals likely to be affected by a nosocomial outbreak, healthcare workers could represent an appropriate study population with respect to a vaccine. However, healthy healthcare workers typically have asymptomatic or mild MERS disease, which decreases the relevance of studying this population. It was further noted that a population more at-risk of an acute MERS disease would benefit more of a potential effective vaccine. In this regard, haemodyalized patients could be a potential target population, with potential strong acceptability depending on how the benefit is perceived. However, haemodyalized patients are not a healthy population, are likely immunosuppressed with implications for reduced vaccine-induced immunity, and may have potential need for higher vaccine dose and adjuvants. Therefore, careful safety and immunogenicity studies must be performed before considering this population for an efficacy trial.

In a community setting, camel workers could represent an appropriate study population. However, as for healthcare workers, camel workers are more likely to be asymptomatic or have mild MERS disease, which decreases the relevance of studying this population with respect to a vaccine. Household contacts or people in contact with people exposed to camels and that are likely to develop MERS disease could form a more appropriate target population in this setting. However, defining such population and locations in practice needs to be informed by epidemiological studies to assess whether transmission is likely to occur in this population. Finally, acceptance of the study by a community-based target population needs to be linked with a careful community engagement strategy.
Overall, it was noted that a clear understanding of attack rates in potential target populations are needed in order to assess the feasibility of conducting a trial in those populations.

3. **Randomization and comparator – 2:1 individual randomization placebo-controlled** within sites

Under the Master Protocol, the trial structure should allow new sites in affected areas to be added and within each site, participants would be individually randomized to receive either the vaccine or a placebo with a 2:1 randomization schedule, in order also to learn more about the vaccine safety profile.
The measure of vaccine efficacy would result from the combined incidence rate with respect to the primary endpoint across all sites.

Multiple vaccines could also be tested against a single placebo arm with as many hypothesis tests, comparing each vaccine against the placebo arm.
Finally, participants and investigators must remain blinded.

Data Monitoring Strategy

It was agreed that study data would not be released unless the trial was stopped, for efficacy or futility, under close DSMB oversight, or by reaching its targeted number of endpoints, to preserve the integrity of the trial and to prevent any prejudgment. Interim analyses to assess efficacy or futility can be timed to occur at after reaching a targeted amount of events.

Next Steps

1. Sero-prevalence and modelling studies to understand and anticipate better where MERS-CoV transmission may occur.
Serological studies, including longitudinal studies, must be conducted in MERS-CoV exposed population (e.g. camel workers and their family contacts, haemodyalized patients) in order to better define the vaccine trial population, derive attack rates, and to identify sites to conduct a vaccine, therapeutic, and post-exposure prophylaxis trial. Longitudinal studies in camels and at the animal human interface should also be conducted to better understand the spill-over transmission events. Such studies could be complemented by the use of mathematical models that would simulate the spread of MERS disease given current understanding of transmission patterns and control measures. Currently, several longitudinal studies in dromedaries is ongoing in several countries in Africa and the Middle East and several sero-epidemiological studies of occupationally exposure camel workers are planned or ongoing in Africa, the Middle East and South Asia.

2. Meta-analysis and retrospective cohort studies to better understand clinical progression of MERS disease and prognostic factors.
Meta-analysis and retrospective cohort studies of all currently available clinical and virologic data on MERS patients should be analyzed across countries in order to identify and define prognostic factors for therapeutic trials. Prospective, systematic monitoring of all future cases using WHO-approved instruments and sample collection for virology (on-site or to central laboratory) should be initiated as soon as possible.

3. Refine animal models to evaluate investigational agents and combination therapy before testing in humans, recognizing that current models have significant weaknesses in terms of reflecting and mimicking human disease.

4. Establish a collaborative and transparent framework for selecting candidate therapeutics and vaccines to be tested in efficacy trials.
Building upon existing MERS expert networks, WHO, under the WHO R&D Blueprint and the MERS Global Technical lead will convene independent working groups will be formed - one for treatments, one for vaccines - to establish a framework for selecting the most promising candidates to be tested in efficacy trials as well as in combination therapy. The group will be charged to define criteria for candidate selection, and to review and assess all the available evidence on each candidate.

5. Write a protocol for both MERS-CoV therapeutic and vaccine evaluation based on the preliminary recommendations outlined in this document.

Appendix A

Table 1: Sample power calculations to compare Option 1 (primary endpoint of MERS infection only) with Option 2 (co-primary endpoints of MERS infection and mortality) for a vaccine trial

All calculations based on 10,000 simulations/row, n=400 in placebo and n=800 in treatment arm; normal approximation to log(RR); rule out VE<30% for acute, VE=0% for mortality; all mortality among ill people

Probability of MERS illness		**VE, MERS illness**	**Probability of mortality (among ill)**		**VE, mortality**	**Power for Option 1: illness only***	**Power for Option 2: either illness or mortality****
Trt	**Ctrl**		**Trt**	**Ctrl**			
.1	.07	30%	.4	.4	0%	**.025**	**.14**
.1	.07	30%	.4	.3	25%	**.025**	**.36**
.1	.07	30%	.4	.2	50%	**.025**	**.70**
.1	.05	50%	.4	.4	0%	**.34**	**.46**
.1	.05	50%	.4	.3	25%	**.34**	**.67**
.1	.05	50%	.4	.2	50%	**.34**	**.87**
.1	.03	70%	.4	.4	0%	**.93**	**.93**
.1	.03	70%	.4	.3	25%	**.93**	**.96**
.1	.03	70%	.4	.2	50%	**.93**	**.98**

* “illness only” at two-sided α=.05 (rule out 30% VE)
** illness at two-sided α=.05; mortality at 2-sided α=.05

Abbreviations: Ctrl, control; Trt, treatment; VE, vaccine efficacy

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