



WHO R&D Blueprint **novel Coronavirus**

**Outline of designs for experimental vaccines
and therapeutics**

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to prevent epidemics



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Objectives of the call

- To provide a high-level summary of the epidemiological data regarding the nCoV infections in Asia
- To discuss the key elements of trial design for experimental vaccines and therapeutics for a novel coronavirus
- To agree on critical next steps to provide guidance in this area of work.

Overview of the epidemiological situation

China

Chinese authorities have reported a novel coronavirus (nCoV) in Wuhan, China. 41 cases were identified through the pneumonia national surveillance and confirmed for nCoV through sequencing and PCR testing. Most (unknown proportion) of the cases are linked to a seafood market which also sells live animals. Investigations are ongoing to determine the source and extent of infection.

Six sequences of the nCoV were released through GISAID. The sequences display overall 50-70% homology with SARS-CoV and the nCoV Spike, the potential target for vaccine antigen, displays about 67% homology with the SARS Spike protein. Preliminary phylogenetic analysis, also combining non publicly available sequences, suggest there is a common source to the infections, although the extent of the source remains uncertain.

Among the 41 confirmed cases, all are adults and have been hospitalized and isolated. 7 were reported to be severe, and there is 1 reported death. 7 have been discharged (CFR ~ 1/7). The full clinical picture is not known.



Chinese authorities are conducting in depth investigations and have reported that to date there is no clear human-to-human transmission but that the possibility cannot be ruled out, notably as a clustering event in a family was reported. No case was reported among healthcare workers.

Thailand

One case was confirmed in Bangkok, Thailand (a woman, resident of Wuhan who travelled to Bangkok for tourism). The case was detected through a thermal scanning system at the international airport. Preliminary investigation suggests she is not linked to the seafood market but would have visited other live animals markets in Wuhan.

Overview of WHO actions to date

WHO has activated the Incident Management System at the 3 levels of the organization and continues to monitor the situation closely and, together with its partners, is ready to provide technical support to China to investigate and respond to this outbreak. WHO does not recommend any specific measures for travelers.

WHO clinical team is working on a standard of care, associated with clinical characterization protocol, for clinical management of nCoV patients, and in preparation for planning for treatment trials.

Regarding experimental vaccines and therapeutics, the R&D Blueprint team with support from various partners is preparing a landscape analysis of the products in the pipeline that could be used against nCoV.

Moreover, a framework for prioritization of therapeutics is being adjusted to guide decisions regarding novel Coronaviruses and candidates to move forward for clinical evaluation.

Critical evidence that would be required to inform decisions on trial designs

The invited experts noted that the additional information on the following epidemiological and clinical characteristics of the outbreak would be critical:

- source and extent of outbreak
- nCoV reservoir and intermediate hosts
- extent of human-to-human transmission
- precision on CFR



- risk factors for infection and disease severity
- degree of homology with other coronaviruses and access to actual sequence material
- evolutionary potential relevant to changes in epidemiology and vaccine/treatment development
- safety profile of investigational products under consideration

Virologic, clinical, epidemiological and environmental investigations are underway to remove some of the uncertainties of the points above.

Potential trial designs

Notwithstanding the unknowns cited above, the experts were invited to consider potential designs under the assumptions that this was a nCoV, which transmits human to human via the respiratory route. An additional assumption was that the evidence to support a phase 2/3 clinical trial authorization was available.

It was noted that for the above scenario to be realistic one may need to assume that a mutation in the virus may occur to facilitate the establishment of human to human transmission,

Deliberations regarding evaluation of experimental vaccines against a nCoV

It was noted that the optimal approach will be the use of a master protocol, as part of a multicentric trial.

In addition, the participants noted that the “decision support tool for clinical trials” ([link](#)) could help structure this kind of deliberations.

It was also underlined that before a Phase 2/3 clinical trial is implemented there are a number of key steps that need to be addressed including proof of concept and preliminary safety data. These steps should be given high importance because their relevance not only for this novel Coronavirus but also for other viruses (e.g. MERS-CoV).

It was noted that this and other deliberations are contributing to define the stepping-stones and processes to prepare for the emergence of Disease X and also contribute to an evolving process to improve the approaches used.

Using as starting point the trial designs deliberations for MERS Cov vaccines, the following conclusions were made.



Target population

Healthy adults and children were proposed as target populations. Potential priorities populations may include health care workers (HCWs) and animal market workers and the close contacts of a confirmed case (ring vaccination).

Decisions on inclusion of pregnant and lactating women, immunodeficient people, small infants should be informed by a risk and benefit analysis. It was noted that a mutation of the virus or change in the epidemiology was necessary to make this event a more serious threat and under that scenario we would not want to exclude from the study these special populations.

Final decisions would depend on additional understanding of the epidemiology and clinical characteristics of the disease. For example, a better understanding of the source of infection, extent of exposure and other risk factors for infection and disease severity.

Participants also noted that the vaccine safety profile of each candidate vaccine and understanding of any potential genetic mutations of the virus would help inform decisions.

Endpoints

Lab-confirmed acute clinical illness or Lab-confirmed acute clinical illness and mortality were proposed as initial endpoints. This may increase the power of the trial.

However, participants noted that on the basis of information available, the case fatality rate (CFR) is approximately ($\sim 1/8$) with broad confidence intervals and 7/41 cases have been reported as severe. Hence improved understanding of CFR and disease severity would inform final decisions and mortality should therefore not be dismissed as an endpoint for a trial.

Although there are advantages on having mortality as an endpoint, the above information is critical.

Randomization

Individual randomization was proposed with a placebo/control arm.

Deliberations included observations on the benefits of implementing individual randomization within a ring structure (cluster randomized). The potential operational advantages of ring vaccination were discussed. If individual



randomization within rings is not operationally possible, then group randomization could be considered.

Regarding the use of a placebo arm, a delayed arm approached in a reactive vaccination scenario was proposed

Participants noted that decisions should be guided by information on safety profile of each candidate ("can the vaccine be more harmful than beneficial?")

Deliberations regarding evaluation of experimental therapeutics against a nCoV

It was noted that the optimal approach will be the use of a master protocol, as part of a multicentric trial.

It was also underlined that before a Phase2/3 clinical trial is implemented there are a number of key steps that need to be addressed including proof of concept and preliminary safety data. These steps should be given high importance because their relevance not only for this novel Coronavirus but also for other viruses (e.g. MERS-CoV).

It was noted that this and other deliberations are contributing to define the stepping-stones and processes to prepare for the emergence of Disease X and also contribute to an evolving process to improve the approaches used.

Using as starting point the trial designs deliberations for MERS Cov therapeutics, the following conclusions were made.

Target population

All symptomatic hospitalized nCoV confirmed patients were proposed as target populations.

This definition will be adjusted once we know better the clinical spectrum of the disease, including disease severity and CFR.

Decisions on inclusion of pregnant and lactating women, immunodeficient people, small infants should be informed by a risk and benefit analysis.

Final decisions would depend on additional understanding of the epidemiology and clinical characteristics of the disease as well as toxicity profile of the drugs.



Endpoints

A composite primary based on a mortality endpoint + a measure of clinical improvement (to be defined) was suggested given that preliminary data suggest that CFR and occurrence of severe disease would be sufficiently low to look for complementary events.

Final decisions would depend on additional understanding of disease severity and CFR.

Randomization

Individual randomization was proposed with a placebo/control arm.

Double-blinding was preferred especially as the number of enrolled patients is expected to be low and as the primary endpoint may contain a “soft” endpoint that may be sensitive to clinical judgment in various populations, recognizing the operational difficulties in implementing a placebo arm depending on the drug administration and regimen.

Efforts are ongoing to define and implement one standard of optimized supportive care, also associated with a unique clinical characterization protocol.



Proposed next steps

- Participants noted that it is important to continue to encourage and seek the perspective of researchers in the countries that have reported cases.
- WHO is preparing a landscape analysis of the vaccine and therapeutic investigational candidates that could be used against nCoV and will work on a evidence-based framework to transparently select most promising/advanced therapeutics and vaccines candidates to move forward for clinical evaluation.
- WHO will convene a meeting asap to discuss all critical steps that are required (e.g proof-of-concept, preliminary safety data, regulatory expectations) ahead of planning for efficacy trials as well as key epidemiological and clinical aspects that we must learn and that will help enlighten vaccine and treatment development.
- WHO will share updates on the epidemiological situation and the outcomes of the vaccines and therapeutics landscape analysis with the group.