World Health Organization

WHO R&D Blueprint

novel Coronavirus

Prospects for evaluating cross-reactivity of nCoV with SARS-CoV

January 24, 2020,Geneva, Switzerland

WHO reference number WHO/HEO/R&D Blueprint (nCoV)/2020.3

R&DBlueprint

Powering research
to prevent epidemics

Table of Contents

Participants

Members of the R&D Blueprint Cross-Reactivity expert group

R. Baric, P. Bogner, C. Bréchot, M. Carroll, C. Clark, P. Daszak, W. Dowling, C. Florence, W. Florence, E. de Wit, V. Gerdts, R. Gomez Roman, B. Graham, B. Haagmans, J.O. Kim, M. Koopmans, G. Mattiuzzo, K. Modjarrod, V. Munster, M. Page, A. Shurtleff, E. Stemmy, J. Tree, L. Wang, V. Vasan, L. Wolfraim,

WHO Secretariat

A.J. Costa, A.M. Henao Restrepo, P. Gsell, A.X. Riveros Balta

Objectives of the call

- To discuss the theoretical potential for cross-reactivity between nCoV and SARS based on available sequence/modelling data
- To obtain an overview of the status of development/availability of critical materials and reagents needed to formally evaluate cross-reactivity between nCoV and SARS in the laboratory
- To discuss the key elements of experimental design for evaluating cross-reactivity
- To agree on critical next steps to provide guidance in this area of work.

Assessing the potential for cross-reactivity of nCoV with other coronaviruses

A number of vaccine candidates and antibody-based therapeutic candidates against SARS CoV and MERS CoV are in various stages of development. If there is found to be substantial cross-reactivity between nCoV and any other known coronavirus for which immuno-prophylactics and/or -therapeutics are already under development, it may be quicker to repurpose these medical countermeasures (MCMs) for use against nCoV than to develop new MCMs from scratch. The experts were therefore asked to comment on the potential of cross-reactivity based on available data – both the limited laboratory data that has been published by the Wuhan Institute of Virology and any available sequence and modelling data.

Data published from the Wuhan Institute of Virology

Unfortunately, Dr. Zheng-Li Shi from the Wuhan Institute of Virology, the lead investigator on the initial report of the nCoV isolated from 5 patients in Wuhan, China (Zhou et al, 2020), was unable to join this initial consultation but has been in touch with the Blueprint Team and will join subsequent calls.

The other experts on the call noted that the cross-neutralization data provided in this initial publication was limited to testing a horse anti-SARS CoV hyperimmune serum for neutralizing activity against the isolated nCoV. The investigators reported a neutralizing titer of >1:80 and apparently did not test further dilutions. However, it was noted during the call that this serum can be used to effectively neutralize SARS-CoV at titers of 1:100,000 or more. Therefore, it has very potent neutralizing activity against SARS but the limit of neutralization against nCoV has yet to be determined. Strong cross-reactivity has not yet been demonstrated.

Predictions based on sequencing and modelling data

Several sequences have been deposited to GISAID and the number is growing every day, showing increasing diversity among the newest isolates. The data submitted to GISAID are annotated with information on the platform used and a version number to allow for tracking updates. Ideally, submitted sequence data should also include clinical data on the patient from whom the sequence was obtained.

Current homology data indicates the nCoV has roughly 80% homology to SARS-CoV. However, the experts noted that the homology is significantly lower in critical regions, such as those involved in receptor binding and those known to be epitopes for neutralization. They also were skeptical to drawing strong conclusions before any structural data were available, and advised that laboratory confirmation was needed for any tentative conclusions made based on sequence and modelling data.

It was also noted that sequence data do not indicate substantial homology between nCoV and MERS, or with other known coronaviruses of veterinary importance for which veterinary MCMs have been developed.

Reagents needed for evaluating cross-reactivity in the laboratory

The WHO Blueprint team strongly encourages all countries to share relevant materials under a Materials Transfer Agreement that is acceptable to all parties. They have been developing guidelines and a generic MTA to facilitate sharing of materials relevant for development of diagnostics, vaccines, and therapeutics. This is available on demand.

Virus isolates

Dr. Zheng-Li Shi's laboratory is successfully growing virus isolated from patients in Wuhan, China. They have published their culture methods in their initial report (Zhou et al, 2020). It is not yet clear how or when (if at all) this virus will be made available for distribution.

The US CDC is also growing virus isolated from a patient in the United States. While the Chinese scientists do not report any difficulties growing their virus isolate, scientists from the US CDC report that their virus isolate is quite slow-growing, hampering efforts to grow up a large batch to make available for distribution.

For the time being, there are no other known sources of virus isolates, but this may change as new cases are reported in other countries.

Recombinant viruses

Ralph Baric from University of North Carolina, Chapel Hill, reported that his group is in the process of producing recombinant virus expressing nCoV Spike protein. The constructs are made and the transfections will be done imminently. When the recombinant viruses are available, they will be deposited with BEI to make them widely available. Miles Carroll from Public Health England reported that they are also working on producing recombinant virus in collaboration with scientists at the University of Liverpool.

Recombinant Spike protein

Barney Graham from NIAID reports that they are making a subunit protein for nCoV Spike protein. Vasan Vasan from CSIRO reports that they are also poised to develop a recombinant protein if needed. Bart Haagmans from Erasmus Medical Center reports that they are currently expressing recombinant S protein and validating an ELISA assay.

Hyperimmune serum/monoclonal antibodies

The experts agreed that a panel of SARS hyperimmune sera from convalescent patients will be useful for properly evaluating cross-reactivity between SARS and the nCoV. This has been identified as a gap. Barney Graham's group does have a panel of SARS-reactive human monoclonal antibodies.

Scientists in countries with reported cases of nCoV are trying to get ethical approval to obtain blood from convalescent patients. In the meantime, several groups are immunizing animals (e.g., with recombinant protein or DNA) to obtain hyperimmune serum against nCoV.

Proposed next steps

- nCoV virus isolate is urgently needed to properly address the question of cross-reactivity. The US CDC is willing to share an isolate but these efforts are hampered by the slow-growing nature of their isolate under the culture conditions being used. Investigators from the Wuhan Institute for Virology are encouraged to engage with US CDC scientists to see if they can assist in optimizing culture conditions.
- Several groups are on the cusp of having cross-reactivity data obtained from 1) recombinant nCoV virus or 2) recombinant nCoV protein tested against SARS hyperimmune serum (from animals or humans) or SARS-reactive monoclonal antibodies. Data should be shared as quickly as possible once it becomes available.
- A panel of high-titer sera from human SARS survivors would be a very useful tool, Also, nCoV hyperimmune serum as well as sera and B cells from nCoV survivors will also be very useful. Efforts should be made to source these for distribution.
- Identify other participants for future calls who are generating these types of materials.