World Health Organization

WHO R&D Blueprint

Informal consultation on prioritization of candidate therapeutic agents for use in novel coronavirus 2019 infection

Geneva, Switzerland, 24 January 2020

R&DBlueprint

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Appropriate WHO Confidentiality Undertakings were signed and submitted to WHO by all participating experts

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INTRODUCTION

Currently there are no therapeutic agents licensed and available for novel coronavirus 2019. At the time of the deliberations, one clinical trial was currently ongoing in China including with Lopinavir and Ritonavir. Another RCT is being planned to evaluate the safety and efficacy of Remdesevir. Chinese experts are considering a flexible design that could include additional study arms if pertinent.

In order to rapidly inform the further design and conduct of clinical trials in regions affected by nCoV, there is an urgent need to progress with the prioritisation of the investigational candidates most suitable for clinical trials. A preliminary review of the current pipeline of candidates for treatment of the nCoV, at different stages of development, was conducted based on available information provided. There are major gaps in knowledge around the new virus, in particular the extent of its susceptibility to the different therapeutic options considered, as none of these were developed specifically for nCoV. Nevertheless, it is important that a high level prioritization is made based on the limited information available and updated as further pertinent data emerges.

During the Ebola Public Health Emergency of 2014-2016 WHO further developed its ethical guidance on use of investigational/repurposed therapeutics during outbreaks. This guidance placed a major emphasis on prompt initiation of well designed, ethical clinical trials using the most promising therapeutic candidates available. In the context of the current outbreak of nCov, individual patients may be offered investigational therapeutics on an emergency basis outside clinical trials, as part of protocols for compassionate use or as part of randomized clinical trial. WHO's guidance "Managing Ethical Issues in Infectious Disease Outbreaks" states that compassionate use of unlicensed therapeutics, or Monitored Emergency Use of Unregistered Interventions, is only justified when clinical trials cannot be initiated immediately and where a set of defined ethical criteria are met (MEURI, https://www.who.int/emergencies/ebola/MEURI-Ebola.pdf).

Also important is the need to consider the potential operational challenges with the implementation of various trial designs and, with the administration and monitoring of different investigational therapeutic agents. The anticipation of such potential challenges is critical, so appropriate mitigation measures are implemented in advance, if pertinent.

Although there is incomplete information about several aspects related to the clinical evolution and severity of the disease and with respect to the safety and potential efficacy of available candidate therapeutics (the majority of which were designed or

considered to treat MERS-Cov and SARS), it is imperative to prioritise candidate therapeutics that could potentially reduce mortality and improve clinical disease.

This meeting was called to deliberate on potential therapeutic candidate that could be further evaluated in the current nCoV outbreak. The intention is to assess the evidence available for these candidates with regards to safety and efficacy and recommend those that should be advanced for clinical care through a compassionate protocol and/or evaluated in a clinical trial.

This expert consultation convened clinical care partners and experts in the field of randomized controlled trials (RCTs) for evaluating investigational therapeutics (in particular clinical experts, trialists, and statisticians).

OBJECTIVES OF THE CONSULTATION

The objectives of this consultation were:

1. To outline criteria that could inform the evidence-based selection of therapeutic agents for clinical trials;
2. To review and critically appraise the existing evidence regarding different investigational therapeutics agents;
3. To decide on the more promising candidate therapeutics - based on currently available evidence - that can be evaluated in humans infected with nCoV to reduce mortality and disease progression.

This Consultation presents an initial step towards the evaluation of candidate therapeutics against this novel Coronavirus. There are ongoing efforts to identify additional candidate therapeutics and to expand the body of evidence available on each of the candidates.

Agenda items

- Introduction and roll-call
- Assessment of potential conflicts of interest by the panel experts
- Update on current nCoV outbreak
- Update on therapeutics landscape
- Discussion on priorities
- Conclusions and next steps

EXPERT PANEL

Chairperson: Marco Cavaleri

Name	Position	Institutional Affiliation
Marco Cavaleri	Head of Anti-infectives and Vaccines.	European Medicines Agency, Amsterdam
Eric Pelfrene	Office of Anti-infectives and Vaccines, Human Medicines Evaluation Division	European Medicines Agency, Amsterdam
Sina Bavari	Independent Consultant	
John Marshall	Co-Director, Critical Illness and Injury Research Centre	St. Michael's Hospital, Toronto, Canada
Karl Erlandson	Interdisciplinary Scientist	Biomedical Advanced Research and Development Authority (BARDA)
Hilary Marston	Medical Officer and Policy Advisor	National Institute of Allergy and Infectious Diseases (NIAID)
Philip Coyne	Assistant Professor of Tropical Public Health	F. Edward Herbert School of Medicine, Uniformed Services University of the Health Sciences.
Josie Golding (standing in for Jeremy Farrar)	Epidemic Preparedness and Response Programme Officer	Wellcome, UK
Raymond Corrin	Special Access Program Advisor at Health Canada	University of Ottawa, Canada

Full list of invited experts but only those listed in the table above participated:
Raymond Corrin (Health Canada), Karl Erlandson (US HHS), Hilary Marston(US NIH), Philip Coyne(US PHS), Sina Bavari (Independent consultant), John Marshall (SMH Canada), Marco Cavaleri (EMA), Jeremy Farrar (Wellcome Trust), Markus Mueller(University of

Wien), Bin Du (Peking), Regine Lehnert (BfArM), Yaseen Arabi (Saudi Arabia); Yi Guan (Hong Kong); Wannian Liang (MOH China); Ross Upshur (University of Toronto)

WHO Secretariat: Alejandro Costa, Janet Diaz, Ana Maria Henao-Restrepo, Vasee Moorthy, Marie-Pierre Preziosi, Ximena Riveros Balta, Kolawole Salami, Siya Temu.

Assessment of conflicts of interest

WHO Declaration of Interest forms were completed and provided to WHO by all participating experts. Such DOIs were reviewed by the WHO Secretariat as par applicable WHO guidance. The following interests, if any, were declared: :

Name	Confidentiality Undertakings; Assessments of Conflicts of Interest
Marco Cavaleri	No conflict of interest declared
Eric Pelfrene	No conflict of interest declared
Sina Bavari	No conflict of interest declared
John Marshall	No conflict of interest declared
Karl Erlandson	No conflict of interest declared
Hilary Marston	No conflict of interest declared
Philip Coyne	No conflict of interest declared
Josie Golding (standing in for Jeremy Farrar)	No conflict of interest declared
Raymond Corrin	No conflict of interest declared

UPDATE ON CURRENT nCoV OUTBREAK

As of 24 January 2020, a total of 846 confirmed cases of a novel coronavirus (2019-nCov, hereafter referred to as nCoV) have been reported, of which 830 cases were reported from China. Other confirmed cases were reported outside of China in six countries (see https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200124-sitrep-4-2019-ncov.pdf?sfvrsn=9272d086_2). Of the 830 cases, 177 cases have been reported as severely ill and 25 deaths have been reported to date.

UPDATE ON CANDIDATE THERAPEUTICS

An overview of the types/classes of candidate therapeutics included in the deliberations and their stages of development is presented in the attached high-level summary table. The table includes monoclonal and polyclonal antibodies, as well as repurposed drugs including nucleoside analogues and protease inhibitors.

OVERVIEW OF THE DELIBERATIONS

Overall considerations

- A preliminary review of the current pipeline of candidates for treatment of the nCoV, at different stages of development, was conducted based on available information and notwithstanding the current gaps in knowledge around the new virus, in particular the extent of its susceptibility to the different therapeutic options considered, which were mainly investigated and/or developed for MERS-CoV.

- It was agreed that candidate therapeutics that are still in preclinical phase of evaluation should not be prioritized over more advanced candidates with available clinical safety and efficacy data, as the purpose would be to identify products that could be ready for testing at the earliest.

- Antibodies discovery platforms may be time consuming to develop (involving several months) and this should consider vis a vis the potentially rapid outbreak evolution. However, they may be effective and should be further explored.

- The route and complexity of administration should also be considered if large number of patients require treatment. For example, monoclonal antibodies would be delivered intravenously and in a complex format, this could be resource consuming.

Summary of points on various candidate therapeutics

- Among the different therapeutic options, Remdesivir was considered the most promising candidate based on the broad antiviral spectrum, the in vitro and in-vivo data available for coronaviruses and the extensive clinical safety database (in particular coming from the Ebola virus disease clinical trial and MEURI) in eastern Congo). Further, studies in mice using Remdesevir showed superior efficacy over Kaletra + IFNbeta. A clinical trial is being planned in China to evaluate the safety and efficacy of Remdesivir in association with optimized standard of care.

- Among the repurposed drugs, the investigation of the antiretroviral medicine (HIV protease inhibitors), lopinavir/ritonavir, either alone or in combination with IFNbeta1b, which is a combination currently investigated in the Kingdom of Saudi Arabia for the treatment of MERS-CoV (MIRACLE trial), was considered a suitable second option for rapid implementation in clinical trials. Preclinical data available and limited clinical experience in the context of MERS, would suggest that it could provide some degree of clinical benefit and would be worth investigating particularly in severe cases. Based on the investigation conducted in Saudi Arabia (with mortality at day 90 as the endpoint), a protocol assessing lopinavir/ritonavir as monotherapy, is being implemented in China, with clinical improvement by day 28 as the endpoint. Recruitment of this trial is close to completion. Interim analysis outcomes are anticipated shortly.

- It was reflected that monoclonal and polyclonal antibodies that are currently in early development are mainly targeting MERS. Based on current knowledge on the viral composition and homology with other coronaviruses, it might be anticipated that the likelihood that the current investigational immune-therapeutics will retain sufficient activity against the new virus might be low. However, since immune-therapies could play a significant role in the treatment of the nCoV, it is warranted to continue exploring the possibility to further develop medicines based on this approach specifically targeting the nCoV. Further preclinical studies are required to asses and validate emerging monoclonal antibodies before advancing them into clinical evaluation. There is ongoing work to ascertain if there is cross protection between available monoclonal antibodies and nCoV. Monoclonal antibodies could be promising and kept in view, but the focus currently should be on candidates that could be evaluated immediately.

- The use of convalescent sera could also be an option for consideration, but it remains to be defined if sufficient amounts of sera with high antibodies titres could be feasibly collected, using concentration and purification processes.

- Other agents in Phase I clinical development such as a TMPRSS-2 inhibitor might merit further discussion.

- Among the products that should not be prioritised, there was consensus that Ribavirin does not appear like a candidate worth further investigating, based on the available evidence. The experience with its evaluation in SARS in Canada in 2003 may have resulted in higher mortality than in other countries. It also reduced haemoglobin concentration- a side effect that is undesirable in patients with respiratory disorders.

- Immunosuppressants and immunostimulators (e.g. corticosteroids/steroids) were also identified as products to be deprioritised as there is not enough information when the treatment should be given, and they may possibly be harmful in the context of mild illness, although there is evidence of efficacy in the setting of severe illness. This again underlines the importance of differentiating between mild and severe disease.

- Chloroquine was also mentioned as product for which there is insufficient evidence to support its further investigation.

- It is useful to distinguish interventions that might be appropriate for patients with mild disease from those that could benefit patients with more severe disease. In general, the former will be ambulatory or managed on a hospital ward and face a low probability of death. The therapeutic priority is accelerating symptom resolution and in particular, reducing spread, and the appropriate class of agents are those directed at the virus. Patients at a higher risk of death are likely to be in an ICU or other monitored area and face a risk of death not simply from viral proliferation, but also from the organ dysfunction that results from the host response to infection. Effective treatment, therefore, needs to also address that support, and the biologic processes that lead to organ dysfunction.

- Non-antiviral products not on the list provided, such as statins, heparin and high dose vitamin C, were mentioned as products for which more discussion could be considered. Of note, further analysis of the CITRUS ALI study has shown the efficacy of high dose Vitamin C (50mg/kg/6hrs) in preventing mortality from acute lung injuries as compared to placebo. This should be considered for evaluation in nCoV.

- Finally, there are other products, not on the list provided, in early development and that would deserve to be discussed in a second stage. Information will be shared by and with the meeting participants.

- As WHO deliberates on the ideal clinical trial platform; a platform trial model that enables the evaluation of multiple/different interventions simultaneously and sequentially and is well-suited to the challenge at hand such as the REMAP-CAP trial - a platform trial in severe community-acquired pneumonia is up and running in Australia, New Zealand, Canada, the UK, and a dozen EU countries, and designed to be rapidly adapted to the needs of a pandemic should be examined. REMAP-CAP trial is, however, not currently recruiting in China, but the platform, or at least the model, is well worth exploring as a mechanism to launch studies quickly.

PROPOSED NEXT STEPS

It was agreed that in order to inform the decision making by the various countries that are reporting confirmed cases and be able to finalize the proposed global master protocol for this trial, WHO R&D Blueprint will communicate the initial deliberations of the expert panel as soon as possible.

The panel will be convened again as more evidence becomes available.

In the interim, WHO R&D Blueprint will continue to seek and gather additional evidence on all the candidates including but not limited to additional data on safety of Remdesivir including among 60-year-olds and above, effects and safety of convalescent plasma and invitro activity of Favipiravir against coronaviruses. Emergent data should be made available to the expert panel as it becomes available.

The panel was made aware that in parallel WHO R&D Blueprint is also convening an expert group to ascertain if there is cross protection of antibodies and antivirals.

WHO R&D Blueprint will gather as soon as possible more information about availability, manufacturing capability and emerging data on the prioritized therapeutics (especially Remdesivir and Lopinavir/Ritonavir) from individual companies.

Members of the expert panel were invited to share with the WHO R&D Blueprint any information on additional potential candidate therapeutics that should be considered.

WHO R&D Blueprint is coordinating a clinical trials experts group aiming to develop a master protocol for a RCT to evaluate efficacy of therapeutics against nCov. This expert group will be informed of the outcomes of this expert panel deliberations so that the RCT design can be modified accordingly.

The panel of experts agreed to reconvene in a week's time.

Note that above prioritization decisions are preliminary and may change as further information is provided to WHO.

APPENDIX

Overview of the types/classes of candidate therapeutics

Product type and candidate	Target disease	Description	Status of clinical development	Preliminary results
Monoclonal Abs				
80R mAB S3.1 m396	SARS	Human monoclonal antibodies	In vitro	inhibited different SARS-CoV subtypes Didn't neutralize GD03 strain
GD27 Gd33 MCA1 JC57-14 MERS-4 CDC2-C2 VHH-83, HCAb-83 CVHHs NbMs10 NbM10-Fc LCA60	MERS	HmAbs/ Fab-RBD HmAbs/ Fab-RBD HmAbs/ Fab-RBD Macaque mAbs/ Fab-RBD HmAbs/ Fab-RBD HmAbs/ Fab-RBD Dromedary VHHs Dromedary VHHs Dromedary VHHs Llama VHHs Llama VHHs Human survivors	In vitro and in vivo (Tg mice)	Most of mAbs can neutralize pseudotype or live MERS-CoV and some shown protection in animal models in vivo
REGN3048 and REGN3051 Antibody Cocktail	MERS	Fully (mAbs) against S protein of MERS-CoV	Double-blind, placebo-controlled Phase I study. Single ascending dose cohorts safety, 48 subjects. NCT03301090	No results posted
Polyclonal Abs				
AB-301	MERS	AB-301 is a purified human immune globulin G (hIgG) polyclonal antibody designed to specifically	Group sequential design with multiple interim analyses to determine futility or efficacy. Single 50mg/kg infusion of SAB-301 vs. placebo control	Single infusions of SAB-301 up to 50 mg/kg appear to be safe and well tolerated in healthy participants.

		bind to the MERS-CoV spike (S) protein	NCT02788188	
Convalescent plasma	MERS	convalescent plasma or hyperimmune Igs is often used for treatment of emerging infectious diseases	RCT, double blinded, single dose scalation phase II, >14 years- 160 subjects	Unknown
Drugs Nucleoside analogues				
GS-5734/Remdesivir	Ebola- MERS	Nucleoside analogue	In vitro HAE cells In vivo, mice and marmosets Phase 1 safety Ebola trial, phase II/III Phase 2: https://clinicaltrials.gov/ct2/show/NCT02818582 Phase 3: https://clinicaltrials.gov/ct2/show/NCT03719586	
BCX4430	Ebola	Nucleoside analogue	https://clinicaltrials.gov/ct2/show/NCT02319772https://clinicaltrials.gov/ct2/show/NCT03891420https://clinicaltrials.gov/ct2/show/NCT03800173	No results posted
Ribavirin+INF	HepC-Influenza	Nucleoside analogue	349 MERS patients, 144 (41.3%) patients received RBV/rIFN (RBV and/or rIFN-a2a, rIFN-a2b, or rIFN-β1a; none received rIFN-β1b). https://www.ncbi.nlm.nih.gov/pubmed/31925415	RBV and/or rIFN-a2a, rIFN-a2b, or rIFN-β1a) therapy was used in critically ill MERS patients but was not associated with reduction in 90-day mortality or in faster MERS-CoV RNA clearance
Drug Protease inhibitor				
Lopinavir/Ritonavir	HIV - MERS	Protease inhibitor	Retrospective comparative analysis (41/111)	Acute respiratory distress syndrome or death reduction from 28% to 2,4%

Lopinavir/Ritonavir/Ribavirin/IFNa	MERS	Protease inhibitor + Nucleoside analogue	Compassionate use: Korea (1) Greece (1)	Virological clearance and survival Viremia and viral NRA persist for 4 weeks, patient died
Lopinavir/Ritonavir + IFN-β1b	MERS	Protease inhibitor	Miracle: This is a placebo-controlled clinical trial to assess the feasibility, efficacy and safety of a combination of lopinavir/ritonavir and Interferon beta-1b in hospitalized patients with MERS https://clinicaltrials.gov/ct2/show/NCT02845843	Ongoing