Research priorities related to the Omicron variant

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Seconded to WHO

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Emergency meeting of the COVID-19 Assays and Animal Models expert working groups on Omicron variant

- The WHO R&D Blueprint Working Groups on COVID-19 Assays and Animal Models are two expert groups consisting of more than 600 global scientists with expertise in assays and animal models of viral diseases that have been meeting weekly since Feb. 2020 to discuss advances, to foster collaborations and to share, resources, reagents and research outcomes to avoid duplication of effort.

- More than 450 scientists participated in the meeting of Monday 29 November 2021 to discuss the Omicron variant

https://www.who.int/publications/m/item/assays-animal-models---outline-of-research-priorities-related-to-the-omicron-variant
Key Research Priorities

1- Ability of post-vaccination and convalescent sera to neutralize omicron.
2- Ability of current vaccines to prevent mild and/or severe disease
3- Ability of current therapeutic approaches, including monoclonal antibody therapy, protease inhibitors and nucleoside analogs to retain efficacy against the omicron VOC.

Planned *in vitro* and *in vivo* studies and availability of key reagents have been captured in a SARS-CoV-2 Omicron variant assays and animal models study tracker available on the WHO R&D Blueprint site [https://www.who.int/teams/blueprint/covid-19](https://www.who.int/teams/blueprint/covid-19)
Virus neutralization

Objective: Assess the neutralization titers against the omicron VOC in convalescent individuals, vaccinated and boosted individuals.

Challenges: For live virus assays, the major bottleneck is availability of Omicron virus isolates, which is limited by the time to propagate sufficient quantities of virus, generate full genome sequences, obtain export/import permits and transport internationally in the context of flight bans being imposed by multiple countries. For pseudovirus neutralization assays, delays may include restrictions in shipping of sera and generation and access to recombinant viruses.

Current efforts: AHRI is growing the virus and planning to share. Several other labs are growing independent isolates (UK-HSA and KU-Leuven). All groups can share viruses using the WHO-BioHub as a facilitator (https://www.who.int/initiatives/who-biohub) or other biorepositories (BEI, EVAg, NIBSC). Category 3 laboratories are needed for live virus propagation and storage.
Serology, T cells and Therapeutic Assessments

Binding Antibody
ACE2 Binding Inhibition
Fc-Effector functions

Challenges: Omicron Spike and RBD proteins and sera

T-cells: Cross-reactive T cells are likely essential to prevent severe disease.

Challenges: T cell assays are not easy to standardize. However, previous comparative data on variants exist.

Anitviral and mAbs: in vitro assessments of monoclonal antibody therapy, protease inhibitors and nucleoside analogs to ascertain whether they retain efficacy against the Omicron variant

Challenges: availability of Omicron virus isolates and other reagents
Animal models overview

**Upper respiratory tract**
- Humans
- Non-human primates
- Hamsters
- Cats
- Ferrets
- Wild-type mice N501Y

**Lower respiratory tract**
- Humans
- Non-human primates
- Hamsters
- Mice
- Ferrets

**Other organs**
- SARS-CoV-2 replication
- Humans
- Non-human primates
- Hamsters
- Mice
- Ferrets

**Clinical signs and pneumonia**
- Humans
- Hamsters
- Ferrets
- Non-human primates

**Vaccine-associated enhanced respiratory disease (VAERD) and antibody-dependent enhancement (ADE)**
- Humans: no reports
- Mice: inflammatory response and hepatitis in some
- Hamsters: mild pathology, low neutralizing antibodies and Th2 response in some
- *In vitro*: signs of ADE

**Ancestral strain infection and protection from VOC challenge**
- Humans
- Hamsters
- Non-human primates
- Mice

**Age**
- Hamsters
- K18-hACE mice
- Ferrets
- Non-human primates

**Obesity/diet**
- K18-hACE mice
- Hamsters

**Sex**
- Humans
- K18-hACE mice N501Y
- Wild-type mice N501Y

**Transmission and infectivity**
- VOC vs. ancestral strain
Animal models: VOC Research

**SARS-CoV-2 variants of concern (VOC)**
- alpha VOC (B.1.1.7)
- beta VOC (B.1.351)
- gamma VOC (B.1.1.28.1 / P.1)
- delta VOC (B.1.617.2)

**Non-human primates**
- infection of lower respiratory tract
- equal virulence
- B.1 immunisation is protective
- virus replication ↓
- break-throughs p.v. ↑

**K18-hACE2 mice**
- B.1 immunisation is protective transmission ↑
- infectivity ↑
- disease progression ↑
- viral fitness ↑

**Wild-type mice**
- transmission ↑
- no significant clinical symptoms
- mild lesions in nasal turbinates
- viral replication in nasal turbinates

**Hamsters**
- infection of lower respiratory tract
- equal virulence
- B.1 immunisation is protective transmission ↑
- pro-inflammatory cytokines ↑
- viral shedding after challenge

**Ferrets**
- ↑ transmission
Animal models: Omicron research priorities

1- Pathogenesis: In comparison with other VOCs
2- Cross-protection: Via passive transfer studies, vaccination+challenge studies and/or rechallenge studies
3- Transmission: Competition transmission studies have been conducted for other VOCs in hamsters, ferrets and cats
4- Drug resistance studies: mAb therapy, protease inhibitors and nucleoside analogs
5- If reformulated vaccines are needed: Vaccination+challenge studies (hamsters and NHPs), immunogenicity in mice.

Anticipated challenges: Access to viral stocks, omicron convalescent sera, vaccines and therapeutics
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