Assays to accelerate vaccines development - WHO Network experience during COVID

WHO Assays WG

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R&DBlueprint
Powering research to prevent epidemics
To develop and standardize **assays** to support vaccine development

+360 experts from 26 countries and >130 entities were convened since Jan 2020

- Live deliberations on **assay design and performance**
- Researchers collaborating on **protocols** and access to reagents and proteins
- Researchers collaborating on developing international and secondary **serology standards**

**Improved interpretability** of immune responses and harmonization of results

**Enhanced access** to assay, proteins and reagents for **ALL** developers
Situation at the time of the first meeting, Jan 24, 2020

26 experts attended the meeting
Small number of nCoV viral sequences had been deposited in GSAID
One viral isolate cultured, only available in China
Vaccine candidates, immunoassays, mAbs, hyperimmune sera – MERS and SARS-CoV
Very limited SARS-CoV convalescent sera
Several labs were producing recombinant Spike protein – but not widely available
Labs were in the process of vaccinating lab animals to produce hyperimmune serum
Pre-existing Knowledge of coronaviruses was vital for rapid immunogen design and formulating key questions

- Structures of Spike proteins from MERS-CoV and SARS-CoV, including proline mutations needed to lock the protein in a pre-fusion conformation

- Nucleocapsid protein assays used to assess infection

- Assays needed to assess Th1 vs Th2 responses – VAERD some SARS-CoV vaccines

Pallens et al PNAS 2017, Wrapp et al Science 2020
Group members openly shared both positive and negative data, allowing for rapid progress and less duplication of effort

- Date were shared at group meetings, at WHO R&D Forums and at WHO consultations. [https://www.who.int/teams/blueprint/covid-19](https://www.who.int/teams/blueprint/covid-19)

- Data were rapidly uploaded and disseminated on pre-print servers

- Protocols were shared between members of the group and then widely to the scientific community
Rapid sharing of viruses was challenging; use of repositories was essential, as well as alternate technologies

- Issues with agreements, lockdowns, etc interfered with rapid sharing

- Pre-existing repositories were important and the WHO BioHub was established to serve this role in the future

- Alternate technologies that did not require live virus were employed for neutralization - recombinant viruses, Pseudoviruses, surrogate viruses
Cell culture derived viral mutation of the furin cleavage site was identified and a sub-group was formed to address this
SARS-CoV-2 Antibody Standards were generated and their appropriate use was demonstrated

International Standards: highest order calibrant - established by the WHO Expert Committee on Biological Standardization

- 21/346 – 2nd Int. Stan. – Oct. 2022
- 21/338 - 1st Int. Stan for VOCs

Secondary Standards: Regional or national reference material, calibrated to the IS

- Instructions for calibration [https://cdn.who.int/media/docs/default-source/biologicals/annex-2---who-guidelines-on-secondary-standards-for-antibody-testing---11-may-2022.pdf?sfvrsn=c0d1c8ce_1&download=true](https://cdn.who.int/media/docs/default-source/biologicals/annex-2---who-guidelines-on-secondary-standards-for-antibody-testing---11-may-2022.pdf?sfvrsn=c0d1c8ce_1&download=true)
Neutralizing antibodies were identified as a correlate of protection

Adoptive transfer of IgG in NHPs

https://www.nature.com/articles/s41586-020-03041-6

Neut vs protection from symptomatic disease

https://www.nature.com/articles/s41591-021-01377-8
T cell responses were associated with reduced disease severity and are conserved across variants.

Megapool (MP) approach to allow simultaneous testing of large numbers of epitopes. – SARS-CoV-2 MP shared with many groups.
The rise of variants showed the need for adaptable and agile systems to assess variants

- Various laboratories and consortia arose to assess the impacts of variants - Agility, ECDC, NIAID
  https://epi.tghn.org/covax-overview/enabling-sciences/agility_epi/#ref1
  https://www.niaid.nih.gov/research/sars-cov-2-assessment-viral-evolution-program#:~:text=SAVE%20provides%20a%20comprehensive%20real,%2Dor%20vaccine%20induced%20immunity

- WHO R&D Blueprint hosted multiple consultations on assessment of variants
  https://www.who.int/teams/blueprint/covid-19

- WHO Technical Advisory Group on viral evolution (TAG-VE) was formed to advise WHO on the impact of variants and provide recommendations on updates to the WHO classification of variants
  https://www.who.int/publications/m/item/terms-of-reference-for-the-technical-advisory-group-on-sars-cov-2-virus-evolution-(tag-ve)#:~:text=The%20recommendations%20of%20the%20TAG,Advisory%20Group%20of%20Experts%20on
Loss of protective immunity due to variants demonstrated the need for updated vaccines

- WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-VC) was formed to review evidence and assess implications of VOCs on vaccine performance – advise the WHO on whether updated vaccines may be needed [https://www.who.int/groups/technical-advisory-group-on-covid-19-vaccine-composition-(tag-co-vac)]

- The evident need for broader vaccines led to WHO consultations on sarbecovirus vaccines [https://www.who.int/teams/blueprint/covid-19]
Summary

- The WHO Assays working group was established to coordinate the development and standardization of immune assays to support vaccine development for COVID-19 and then for other WHO priority pathogens.
- Sharing of protocols, methods and results helped to advance the development of immunoassays.
- Use of virus and reagent repositories such as the WHO Bio-Hub allows for rapid sharing of materials to facilitate assay development.
- International antibody standards were established and their appropriate use was demonstrated.
- Data generated by members of the group showed the contributions of antibodies and T cells for protection.
- Systems for assessing the impact of variants were established and continue to monitor the ongoing evolution of SARS-CoV-2. Ongoing evolution will lead to a continued need for updated vaccines and highlight the need for broadly protective SARS-CoV-2 or sarbecovirus vaccines.
Thank you

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COVID-19 Assays Achievements

- Viruses and other key reagents available
- Sharing of protocols and methods
- Binding assays developed – multiple antigens and formats – ELISA and multiplex
- Neutralization assays available – wtVNA, psVNA, sVNA
- T cell assays established (AIM, ICS, ELISpot) and common peptide pools
- Assess contribution of Fc functional Ab responses
- Practices to ensure integrity of working stocks of SARS-CoV-2 described
- Duration of immunity assessed
- Assays were adapted to assess impact of variants
- Data influenced decisions to boost or reformulate vaccines