Variant vaccines:  
What is the state of R&D, do we need them, and who decides?

Member State Briefing – 3 February 2022  
Dr. Soumya Swaminathan
COVID-19 advisory group pathway to informed decisions

Strong, multidisciplinary mechanism of external experts for evidence-based decision making

**Aim:** Monitor & assess SARS-CoV-2 variants and evaluate their impact on countermeasures, including vaccines, therapeutics, diagnostics or effectiveness of public health and social measures.

**Virus**
- **Monitoring & surveillance**
  - TAG-Virus Evolution (VE)
    - determines where variants are circulating
    - Advises on VOI or VOC determination based on variants’ alteration in:
      - transmission or disease characteristics or
      - impact on vaccines, therapeutics, diagnostics or
      - effectiveness of public health and social measures

**Vaccine Products**
- **Research & evidence assessment**
  - Vax Research Expert Group
    - methods standardization for vaccine development and assessment
  - Vax Effectiveness WG
    - assesses and supports VE and impact studies
- **Regulatory TAG**
  - Advises on EUL of vaccines through evidence-based assessment
  - TAG-CO-VAC
    - determines if changes to vaccine composition are needed through evidence-based assessment

**Vaccine implementation**
- **Policy**
  - SAGE
    - recommends policies and strategies on vaccine use and immunization programmes through evidence-based assessment
Vaccine Effectiveness against Omicron:

- **Primary Series**
  - 5 studies with VE estimates 2+ weeks after primary series
  - Only 2 looking at hospitalization

- **Booster Dose**
  - 10 studies with VE estimates 1-2 weeks post booster dose*
  - Only 3 looking at hospitalization
  - 1 study evaluated VE in immunocompromised
    - 3 doses of Moderna VE=21.7 (0.0-45.0)
  - Almost all studies provide comparison of performance Delta to Omicron → Omicron VEff always lower than Delta

* (2 not graphed because they provide relative VE comparing 3 to 2 dose recipients, not unvaccinated)
How well do current vaccines work against Omicron? (1/2)

**Context of the vaccine performance evidence**

- **Lab studies** numerous and supportive, but their predictive link to performance limited
  - 51 neutralization studies show a 14–35 fold **reduction in neutralization**, much larger compared to other VOCs (improved with booster, but still lower than Delta)
  - 10 cellular immunity studies show that **T-cell immunity largely preserved against Omicron**
- **Veff data is limited** geographically and on the vaccines studied – plus methodological constraints, so no single study should be relied on alone
  - 22 real world studies with limited geographical/epidemiologic representation
    - Canada, Denmark, Qatar, South Africa, UK, USA (i.e. 1 country in Africa, 0 in South America, Asia)
  - Data is mainly from **mRNA vaccines**, or **mixed regimens**: No Veff studies to date from inactivated or protein vaccines
  - Evidence to address **wanning** over time is still too preliminary
  - Studies on **transmission**, a critical outcome, are very difficult to conduct – are largely inferred from studies of infection
How well do current vaccines work against Omicron? (2/2)

**Key take-aways are emerging from growing body of evidence**

- VEff remains **high** (following primary & booster) against the **severe disease** end of the spectrum, but....

- **Lower against Omicron** than Delta, for all outcomes, and....

- Greater reduction against **infection** than severe disease outcomes, but...

- **Boosters** make a substantial difference in vaccine performance against Omicron (though still below Delta)

Need to keep monitoring the situation to understand VEff of all the vaccines in use, to understand if there is true waning of the booster dose, and if the protection against hospitalization and severe outcomes remains sufficient.
Main conclusions

• Structural similarity between sarbecoviruses should enable development of a pan-sarbecovirus vaccine.

• Pan-sarbecovirus vaccines may have a better chance of blocking transmission and facilitating herd immunity, and are expected to be more durable.

• A variety of strategies may induce broader immune responses. These include different antigen presentation strategies as well as inclusion of additional antigens.

• Current vaccines, due to broadly acting responses, are working well against severe disease. Major benefit of next generation vaccines could be in reducing infection and transmission.

• Continued investment in R&D is critical. Equity and access are essential.

• While we deal with the pandemic, preparing platforms for the next variant or virus is key.
State of vaccine R&D and approaches to variants

Dr. Melanie Saville
3rd February 2022
‘Variant Vaccines’ – what is the state of R&D?

What approaches are being considered?

- Optimize use of current vaccines
  - Regimen/booster
  - Mix and match

- Variants of current vaccines
  - Strain change
  - Multivalent

- Next generation broad protection SARS-CoV 2
  - Protect against existing and future variants

- Universal Coronavirus
  - Broadly protective beta coronavirus
  - Pan coronavirus

Quick/simple

Slow/complex
Fold reductions in neutralizing antibodies by vaccine platform and variant

Neutralization data suggest large drop against Omicron for all vaccines
- Improves somewhat with booster dose
- More preserved cellular immunity

**Primary series (excludes boosters)**

**Booster doses**

[Link to neutralization plots](https://view-hub.org/sites/default/files/2022-01/Neutralization%20Plots_0.pdf)
[Link to neutralization plots](https://view-hub.org/sites/default/files/2022-01/Neutralization%20Plots_0.pdf)
More and more data becoming available: But what do they tell us?

Potential for improving cross-neutralization against Omicron with existing vaccines

- High
  - 2 dose + VOC nat. infection
  - 2 dose + VOC boost
  - Infection + 1 or 2 dose
  - Homol. 2 dose + heterol. boost
  - Heterologous 2 dose
  - Homologous 2 dose
  - Homologous 3 dose
  - Incompleted primary immunization (single dose)

Caveat
Limited data is currently available
Need to link with effectiveness data which remains limited
Omicron triggered new wave of variant specific vaccine development in addition to broadly protective vaccine development.

COVID-19 current vaccine development pipeline - Variants

- **31%** preclinical candidates targeting Omicron
- **24%** preclinical candidates targeting broadly protective

* Includes only broadly protective Betacoronavirus (BPBC) and broadly protective SARS-CoV-2 (BP-SARS-CoV-2) projects currently under assessment by CEPI.
Variant R&D activities in COVAX R&D portfolio and from most advanced licensed COVID-19 vaccines

- All CEPI’s COVID 19 partners are developing variant constructs
- >50% have manufactured variant clinical trial material
- Preclinical data on most variant vaccines

<table>
<thead>
<tr>
<th>Developer</th>
<th>Region</th>
<th>Tech</th>
<th>Variant activities and progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZ</td>
<td>UK</td>
<td>Adeno vector</td>
<td>Delta, others</td>
</tr>
<tr>
<td>Novavax</td>
<td>US</td>
<td>Protein</td>
<td>Beta, Omicron</td>
</tr>
<tr>
<td>Clover</td>
<td>China</td>
<td>Protein</td>
<td>Delta</td>
</tr>
<tr>
<td>BioE</td>
<td>India</td>
<td>Protein</td>
<td>Beta, Delta, Omicron</td>
</tr>
<tr>
<td>SK</td>
<td>S. Korea</td>
<td>Protein</td>
<td>Beta, SARS-CoV broadly protective</td>
</tr>
<tr>
<td>Zerun</td>
<td>China</td>
<td>Protein</td>
<td>Beta, Chimera</td>
</tr>
<tr>
<td>Gritstone</td>
<td>US</td>
<td>saRNA</td>
<td>Beta, Omicron</td>
</tr>
<tr>
<td>VBI</td>
<td>Canada</td>
<td>Viral vector</td>
<td>Beta</td>
</tr>
<tr>
<td>Pfizer/BioNTech</td>
<td>US</td>
<td>mRNA</td>
<td>Omicron: Phase II immuno trial</td>
</tr>
<tr>
<td>Moderna</td>
<td>US</td>
<td>mRNA</td>
<td>Omicron: Phase II</td>
</tr>
</tbody>
</table>

Non CEPI funded
Calls for broadly protective SARS-CoV-2/ Sarseco vaccines

**Perspective**
Universal Coronavirus Vaccines — An Urgent Need
David M. Morens, M.D., Jeffery K. Taubenberger, M.D., Ph.D., and Anthony S. Fauci, M.D.

**NIAD portfolio – plan to fund up to $43M**

<table>
<thead>
<tr>
<th>Developer</th>
<th>Region</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioNetAsia</td>
<td>Thailand</td>
<td>mRNA/VLP</td>
</tr>
<tr>
<td>SK Bio</td>
<td>S. Korea</td>
<td>Protein nano-particle</td>
</tr>
<tr>
<td>Zerun/ Walvax</td>
<td>China</td>
<td>Protein</td>
</tr>
<tr>
<td>Under DD</td>
<td></td>
<td>Protein vaccine</td>
</tr>
<tr>
<td>Seed funding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MigVax</td>
<td>Israel</td>
<td>Protein vaccine</td>
</tr>
<tr>
<td>VIDO</td>
<td>Canada</td>
<td>Protein vaccine</td>
</tr>
<tr>
<td>Affinivax</td>
<td>US</td>
<td>Protein on poly saccharide backbone</td>
</tr>
</tbody>
</table>

**CEPI portfolio – plan to fund up to $200M**

First CEPI partnerships for Broad coronavirus vaccines will be announced shortly

**University of Wisconsin, Madison**
Project Title: PanCorVac (Center for Pan-Coronavirus Vaccine Development)
Grant: 1 P01AI165077-01

**Brigham and Women’s Hospital, Boston**
Project Title: Discovering Durable Pan-Coronavirus Immunity
Grant: 1 P01AI165072-01

**Duke University, Durham, North Carolina**
Project Title: Design and Development of a Pan-Betacoronavirus Vaccine
Grant: 1 P01AI158571-01A1

**CEPI**
Call for Proposals:
Broadening protection against SARS-COV-2 and new broadly protective Betacoronavirus candidate vaccines

First CEPI partnerships for Broad coronavirus vaccines will be announced shortly
Regulatory requirements for variant vaccine

Population
First or second “boost” to homologous or heterologous primary series
(No prior Covid-19 infection)

Neutralizing antibody titres
Original virus
neut assay
Variant virus
neut assay

Guidelines (Feb 2021)

- Primary analysis
  - nAb GMT ₁ vs. ₃
  - Non-inferiority
  - The lower bound of the 95% CI around the GMT ratio ≥0.67

- Secondary Analysis
  - nAb GMT ₂ vs. ₃
  - Superiority
  - Lower bound of the 95% confidence interval around the GMT ratio >1

Note:
- Links to efficacy data but relevance of comparison back to original strain
- Comparison using different assays

Discussion at RAG (Dec 2021) and ICMRA (Jan 2022)

- Primary Analysis
  - nAb GMT ₂ vs. ₃
  - Superiority
- Descriptive
  - Neuts vs. other VoCs

Original vaccine “boost” arm

Variant vaccine “boost” arm

Original vaccine “boost” arm samples against original strain

Original vaccine “boost” arm samples against variant strain

Variant vaccine “boost” arm samples against variant strain
Regulatory considerations

Evolving environment in virus exposure and vaccine roll out raises additional regulatory questions for second generation vaccines

• What are the regulatory requirements for
  • New booster only vaccines?
  • New variant vaccines?
  • Chimeric vaccines (broadly protective)?
  • Multivalent vaccines?

Developers should continue to progress variant development programmes

• Generates experience for the developer
  ○ Platform experience – eventual elimination of clinical data requirements
  ○ Streamline and accelerate development – c.f. 100 days
Update on the Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC)

Information Session: COVID-19
03 February 2022
Evolution of SARS-CoV-2

Amino acid changes in the spike protein of VOC and VOI
Three potential scenarios used for planning

**Scenario N°1: 5th endemic coronavirus**

SARS-CoV-2 remains highly contagious but causes mild illness in the majority of cases. The virus can be grouped with the 4 other coronaviruses that circulate endemically. This scenario is not unrealistic, but it may take many years to be realized.

**Scenario N°2: “Flu-Like”**

The disease presents itself as recurring epidemics when the conditions of transmission are favorable (similar to seasonal influenza). Since the population has basic immunity, severe forms of the disease are observed only in people at risk. It will be important to continue to vaccinate at-risk groups and adopt preventive measures when transmission is high.

**Scenario 3: Ongoing pandemic through new VOCs**

A new variant emerges evading acquired immunity and resulting in a large number of cases. The health system is overloaded and therefore there are more deaths. The situation is very similar to what was experienced at the beginning of 2020 in many regions of the world.
Technical Advisory Group on COVID-19 Vaccine Composition

Functions of the TAG-CO-VAC

• Make recommendations to WHO on the methods to assess the impact of VOCs on vaccines

• Provide interpretation of available evidence on the effect of VOCs on vaccines, including but not limited to vaccine effectiveness

• Recommend to WHO, for each COVID-19 vaccine platform, adaptations (if any) needed so that vaccines continue to safely provide WHO-recommended levels of protection against VOCs.

Credits: Kanta Subbarao, TAG-CO-VAC Chair
Two-step decision making process

When would the TAG-CO-VAC recommend a change in vaccine composition?

1. CHANGE?
   What features of a newly emerged VOC prompt consideration of change in vaccine strain composition?

2. WHAT?
   What specific “strain” should be recommended in updated composition?

What information would be needed?

- Virologic, epidemiologic, clinical, antigenic VE data
- Do the data exist or does it need to be generated? If so, who can do this?
- Regional vs global data?

Credits: Kanta Subbarao, TAG-CO-VAC Chair
Key messages

• Indicates **protection against severe disease and death is more likely to be preserved** by current COVID-19 vaccines for the Omicron variant.

• Urges the world to **accelerate broader access to primary vaccination**, particularly for groups at greater risk.

• Stresses vaccination strategies based on repeated **booster doses** of the original vaccine composition is unlikely to be appropriate or sustainable.

• Calls for the development of COVID-19 vaccines that have high impact on prevention of **infection and transmission**.

• Specifies until such vaccines are available and as the virus continues to evolve, **the composition of current COVID-19 vaccines may need to be updated** to ensure WHO-recommended levels of protection.
Options to consider

- a **monovalent vaccine** that elicits an immune response against the predominant circulating variant(s), although this option faces the challenge of the rapid emergence of SARS-CoV-2 variants and the time needed to develop a modified or new vaccine;
- a **multivalent vaccine** containing antigens from different SARS-CoV-2 VOCs;
- a **pan SARS-CoV-2 vaccine**: a more sustainable long-term option that would effectively be variant-proof.

The TAG-CO-VAC is considering the strain composition of COVID-19 vaccines, and encourages vaccine developers to gather data on a small scale on the breadth and magnitude of immune response for monovalent and multivalent vaccines against VOCs – this data would then be considered in a broader decision-making framework on vaccine composition.
Thank You