ECDC/WHO Europe Joint virology working group

Second meeting: 24 February 2021, 14:00-16:00 CET

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European Medicines Agency point of view

- Presentation by [redacted] (EMA, NL):
  - Which evidence about the need to update? Assays showing lower cross-neutralisation against B1.351/P1 variant; but no correlate of protection defined so far, so difficult to judge only on seroneutralisation assay; importance of efficacy assays, like Novavax conducted in UK and South Africa at moment of variant circulation; reduced efficacy against B1.351 observed when considering mild disease; need of more data on severe disease as this is currently the primary goal of vaccination campaigns.
  - Discussion between all regulatory agencies to reach agreement on requirements for evaluating an update of vaccine; Reflection Paper to be published by EMA.
  - Requirements: no non-clinical data will be required; for clinical data: no large randomized trials but small studies to look at immune-bridging using two types of studies for non-inferiority analysis based on neutralising titers; 1) naïve patients: primary vaccination with variant vaccine compared to with parent vaccine; 2) previously vaccinated: single dose of variant vaccine (booster effect)
  - For now: only evaluation of update of existing platforms and comparison with homologous platform; can evolve in future; requirements can also evolve in future if correlate of protection is defined
- Discussion:
  - Question: Vaccine effectiveness of updated vaccines after natural infection vs prior vaccination?
  - Will need to be considered as more and more people will have had past infection.
  - Companies: currently, trying to understand booster effect after primary vaccine; soon, need to understand booster effect after natural infection.
  - Who should do these studies? Companies or public health institute?

Presentations on pseudovirus assays and microneutralisation

- [redacted] (RIVM, NL):
  - Previous work on stabilization of pre-fusion HIV1 env glycoprotein trimer.
  - Pseudoneutralisation assay using 293T-ACE2 cells and HIV1 backbone, with nanoluciferase as readout reporter: useful for data on neutralization resistance; speed in implementation when new variant; used for comparative mapping using a set of monoclonal antibodies; useful for risk assessment of new emerging mutations.

- 5.1.2e (SSI, Denmark):
  - Live virus microneutralisation assay: 3d; anti-nucleocapsid protein ELISA; normalisation against positive control included in each run.
  - Used with convalescent plasma/serum; post-vaccination; antigenicity comparison of variant vs early pandemic strain; competition format (using spike protein).

Discussion on virus neutralisation assays

- NIBSC makes international standards that will help harmonising the assays; aims at reporting in international units per millilitres rather than neutralisation titers, but not that straightforward.
- Different variants might have difference in growth/replication properties: difference in growth rate observed, so standard growth curves to be run on parallel? How to normalise the different virus response to make the performance of tests comparable?
- Question remains to whether neutralisation is a correlate of protection or can be use as an in-vitro surrogate of protection? If fold differences in neutralising titers to be used as trigger for update of vaccines, then need for accurate measuring.
- Pseudovirus assays or PRNT (plaque reduction assays) might be less sensitive to difference in growth rates of the different variants.
- Cells used in the different labs might influence the results? In UK: consensus to use Vero/hSLAM rather than Vero E6 to avoid introduction of furin cleavage site deletion after a few passages of the virus (although effect on assay is unknown).
- Harmonising/controlling for the cells could be starting point in stardardising materials.
- Use of competition assays for antigenic characterisation seems promising.
- Expression of results using international standard: still the goal to express in international units, but for the moment, difficult when using different variants in the assays; harmonization with international standards is good for both live virus and pseudovirus assays when using similar sequence of the spike.

Discussion on pseudovirus assays

- Spike protein can be easily manipulated to study substitutions.
- Several backbones used by experts: HIV/lentivirus, VSV; different readout: luciferase, GFP.
- High throughput; good correlation with PRNT

Discussion on other types of assays (incl. surrogate neutralisation assays)

- Might be a problem if only focusing on RBD.
- Development of in-house assays: need to consider issues with conformation (incl. monomer vs trimer).
- Binding assays like Luminex: correlation with neutralisation is not always good.
- Expert raised question whether conformational microarrays could be useful for antigenic characterisation.

Discussion on choice of substitutions to study

- Could be based on: in known antigenic site or/and epidemiological changes?
- Monitoring of glycans (loss or addition of glycosylation sites)? Not much done

Discussion on reporting into TESSy

[redacted] (IRVM, NL)'s perspective in context of future ECDC contract to offer virus characterisation opportunity to EU/EEA countries

- How to report the results to requesting country is not yet clearly defined
- Variants thought to be included: B1.1.7; B1.351; B1.1.7 with E484K; P1; P2; E484K in different backbones (currently identified in 8 different backbones in NL); B1.525 with E484K and L888F
- Requires having matching sera: currently collected in another project
- Could be difficult to define which variants to report in TESSy

Discussion on training

No time to discuss this point – to be included in another meeting of the VCWG

Closing remarks

If experts would like to share protocols, they can use the EZCollab COVID-19 protocol sharing group: https://ezcollab.who.int/euroflu/flulab/covid19_protocols

Request for VCWG members for wishes for next meeting (topics) and for suggestions for presentations

Feedback also welcome from VCWG members on format of meeting, way the VCWG should work and frequency.