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Subject: CSWG Mtg Summary 12 Mar 2021: (1) RNA Harmonization Update, (2) Creating WHO Serology Int'l Std
Date: March 15, 2021 at 7:00 PM
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Coronavirus Standards Working Group Meeting Summary

Dear Colleagues —

Thanks to all for our meeting Friday 12 March — and especially thanks to those involved in the SARS-CoV-2 Viral RNA Harmonization Study, to May Chu and her team working to develop the anti-SARS-CoV-2 Serology Harmonization Study, and to Mark Page who presented a detailed description of the development of the anti-SARS-CoV-2 WHO International Standard (Mark's slides are here)!

I presented an update on logistics and deliveries of the Viral RNA study panels (my slides with details are here) -- thanks to all who worked with David Catoe to make it go as smoothly as it did. Sample panels were received at 13/14 labs intact and still frozen. We had to omit one of the inactivated virus samples from the panels (Zeptometrix, never received at JIMB), we had one sample with some packaging failures (Imperial College, rescued by David in outer packaging), and one panel shipment failure (box shipped with the wrong priority to NIB, on the slow boat, not received yet, likely thawed). We had good feedback and useful questions on the SOP, and we've updated and revised it.

Our meeting recording is here, and our website will be updated to include the slides and this meeting summary.

Following Friday's meeting, I've invited Neil Almond of NIBSC to present on the various panels that NIBSC are developing to support evaluation of diagnostic serology devices. Neil's presentation is scheduled for 26 March.

Some takeaways I had from Mark's presentation this week, and Heinz's last week...
The complexity of the results of the collaborative study Mark presented leads me to consider how best to frame the question of a "harmonized" standard panel against the

WHO IS (including making distinct a harmonization study from either simultaneous or following benchmarking studies...). **I am a naif when it comes to immunology and serological measurements (I welcome anyone to help further my understanding!).** Writing these notes below is helping me to frame some questions about possible study designs (more to follow!).

Wearing my metrology hat, I observe:

- We're measuring a suite of different sample properties
    - neutralizing titre, IgG, IgA, IgM...
- We're measuring these properties different ways
    - cell-based neutralizing assays, ELISA, Flow Cytometry, Inhibitory assays...
    - with different targets/specificity
- The properties are correlated though the biology
    - the correlation relationships have different relationships, time constants, and hysteresis
    - there are individual-individual effects
    - there are viral variant-variant effects

- Amongst the measurements...
    - it's clear that there are method-specific and 'measurand'-specific biases (a measurand is the entity intended to be measured, for instance neutralizing titre, IgG, IgA, IgM...)
        - "Method-specific" is to be expected when the underlying principles of the measurement methods vary so profoundly (from live-virus to lateral flow and everything in-between!) --
        - "Measurand-specific" because the measurands are really different, and the relationship of measurements of one property of a sample are only incidentally related to the other properties of that sample
    - comparison of samples should only be valid for a given measurand/property

- The relationships amongst measurements of samples will depend on both measurand and method
    - AND I'm considering the strong patient-patient effects observed in the INSTAND EQA results presented last week
        - with strong variation amongst multiple labs and methods measuring the individual patient samples
        - and strong variation amongst the individual patient samples
    - so will also depend on the individuals in the panel

I may be mistaken, but can see why challenges exist in harmonization and calibration.

It's not clear to me that a given measurement (measurand combined with method) should have the same calibration relationship across a sample panel as a different measurement. Consistent trends arise because of the biology, but I expect the scope of calibrations might be quite limited. This has important implications for design of a harmonization study. We have more to learn from NIBSC and others, I suspect!

I invite robust conversation!

Cheers and stay safe!
Marc

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