COVID-19 Evidence Accelerator Collaborative

Diagnostics Evidence Accelerator #45

Thursday, *March 17, 2022, 12-1 PM ET*

Call Summary

Introduction to Diagnostics Evidence Accelerator Meeting #45

This week's Diagnostics Evidence Accelerator meeting consisted of 2 presentation:

1. Totality of Evidence for the Evaluation of Repurposed Therapeutics for COVID-19 (Névine Zariffa, NMD Group and Jaap Mandema, Certara)
2. Genomic Surveillance for SARS-CoV-2 Variants (Molly Steele and Philip Shirk, CDC)

Totality of Evidence for the Evaluation of Repurposed Therapeutics for COVID-19 (Névine Zariffa, NMD Group and Jaap Mandema, Certara)

International COVID-19 Data Alliance (ICODA) unites international health research data to enable discoveries that benefit everyone, everywhere, by reducing the harm of COVID-19 and enable an efficient data response to future pandemics and other health challenges. The presentation focused on how real-world studies (RWS) and randomized controlled trials (RCT) are both necessary tools to understand the impact of the COVID-19 pandemic. Figure 1 lists the strengths and limitations of RWS and RCTs discussed during the presentation

	RWS	RCTs
strengths	• First to report • Described the course of the disease • Relevant to clinical experience • Broad patient population • Subgroups can be interrogated • Can be conducted before and after key RCT readouts	• Can be powered/designed explicitly for specific hypotheses • Addresses both known and unknown confounders through randomization • Endpoints are clear • Start of treatment is same in both groups • Follow up duration is explicit • Good degree of standardisation • Can be aggregated through established Meta-analysis techniques
limitations	• Unknown confounders can never be addressed • Known confounders can be addressed to some degree • Exposure to treatment is often unclear • Follow up window may be problematic • Some endpoints are not captured directly • Some important covariates may not be available • To date, no aggregation has been conducted	• Delayed Start • Logistically more burdensome on staff engaged with patient care • Limited to data collected • Must be able to recruit • Many trials were single-blind or open-label • Many smaller/under-powered trials conducted

Figure 1: Strengths and limitations of real-world studies and randomized controlled trials.

In addition to the strengths and limitations listed above, there is a sizable time delay between reporting of observations studies and randomized controlled trial results. In the initial months of the pandemic, information comes from observational studies. It is not until after month 12 of the pandemic where RCTs contribute approximately 50% of all studies reported. In order to be prepared for future pandemics, there are multiple elements that need to be taken into consideration. One of those elements is evaluating repurposed drugs. The public health community needs to be able to use all relevant study results to be rigorous and quick in their evaluation of repurposed drugs to prioritize drugs to be included in platform studies and drugs to be deployed to patients based on data collected.

The presentation focused on two research questions:

1. Are the results the same in RWS and RTCs?
2. Can RWS and RCT be combined to accelerate the evaluation of repurposed drugs?

The data collected was compiled in a database called COVID-19 clinical outcome database (CODEx). This database

- Is continually updated
- Provides summary level data from treatment and vaccine studies
- Includes all study design details, patient characteristics, and biomarker, efficacy, and safety outcomes and analyses
- Includes standardization of endpoint units, clinical terms, and statistical calculations for quick exploration and initial statistical analysis of data across studies

There were five drug classes that were looked at in this study. They are anti-IL6 (tocilizumab, sarilumab), corticosteroids (all), antivirals (remdesivir, lopinavir/ritonavir, umifenovir, and favipiravir), anti-malarial drugs and convalescent plasma. The primary endpoint of interest was death. The results of the exploratory analysis outcome RWS vs RCTs random effects meta-analysis showed that the difference is significantly larger between study heterogeneity for non-randomized vs. randomized studies across all treatment classes. Additionally, there is an overestimation of treatment effect for non-randomized real-world studies vs. randomized controlled studies for Anti IL-6, antivirals, and plasma therapy. There was a trend toward overestimation for antimalarials and there was no impact detected for corticosteroids.

There is currently no covariate explanation for the observed RWS/RCT differences or the RWS heterogeneity in estimated OR of death using multivariate analyses. There were factors included for possible effect on treatment effect, RWS/RCT differences and heterogeneity. These factors are propensity score (PS) vs. a multivariate analysis vs. crude means (no adjustment) applied; baseline disease severity (level of oxygen requirement); study blinding of RCTs; sample size; and preprint vs. peer-reviewed publications. Additionally, the study location of Asia, Latin America, or Middle East vs. EU/North America (shown on Age, sex, other patient factors) could have possible effect on treatment effect. The factors included for possible effect on treatment effect, RWS/RCT differences and heterogeneity are propensity score (PS) vs. a multivariate analysis vs. crude means (no adjustment) applied. The results also showed that the crude mean is impacted by both confounding and immortal time bias. Propensity Score adjustment eliminates the negative bias due to confounding with only the positive bias due to immortal time remaining. Therefore, immortal time would be another source of bias.

Additionally, the team looked at how information is accumulating over time on different treatments such as Hydroxychloroquine, Anti-IL6, and Plasma Therapies. In their analysis, they designated anything above 1 as a worse outcome and anything below 1 as a better outcome. Their reference was standard of

care and the data was weighted by degree of heterogeneity. For Hydroxychloroquine, the results showed that there were a high number of RWS resulting in a high confidence interval at the beginning of the pandemic. However, when the RCT come in, the confidence interval decreased even as the patient population increased. For Anti-IL6, there was a greater amount of uncertainty in confidence at the beginning, however the certainty sat below 1. Once the RCT were introduced, the confidence interval became tighter and the certainty was closer to 1 leading FDA to grant an EUA to Anti-IL6 due to lower mortality rates. Plasma therapies showed the similar results of lower mortality, however, once the NIH RCT came out, the result did not show lower mortality.

In conclusion, RWS as a group have much more heterogeneity than RCTs. Additionally, RWS appear to exaggerate the treatment effect relative to RCT estimates in all drug classes except steroids. There is no single variable that explains the differential effect between RCTs and RWS or the heterogeneity. There is no impact of baseline disease severity, study blinding (for RCTs), sample size, publication status, geographic region, age, sex, and other patient attributes. Finally, despite these differences between RCTs and RWS we may be able to develop a reasonable strategy to coordinate the information from both study types to drive clinical insights earlier in the pandemic. In the future, the research team will continue to analyze

- Improving the design, conduct and reporting of RWS would facilitate aggregate analyses.
- The temporal nature of the pandemic and macro-level covariates has yet to be considered fully in aggregate analyses.
- Other ICODA projects are concerned with evolving standard of care, application to MICE to this setting and Bayesian multivariate meta-analyses.
- These approaches could be deployed to other diseases and settings. Notably, COVID19 vaccines studies are/will be available for interrogation in CODEx.

Question and Answer:

- How can we connect the therapeutics lens to the RWE diagnostics lens?
    - It gets a lot complex when we begin to integrate diagnostics. Issues such as conducting know confounder matching.
- In the work of ICODA, how do you see this work going? Are there questions that we cannot answer for diagnostics using the duplicate trial design?
    - There is a lot more foundational work that needs to be done in the diagnostics space before conducting comparative inference. Repurposed drugs have a unique feature where there has been an increased learning.

Genomic Surveillance for SARS-CoV-2 Variants (Molly Steele and Philip Shirk, CDC)

CDC has three sources of genomic surveillance data. The first one is National SARS-CoV-2 Strain Surveillance (NS3). This is a partnership with state public health laboratories and APHL. It contains approximately 3,000 random specimens per month, including additional priority specimens (novel variants, infections in vaccinated people). The second source is Contract Sequencing Data. This is a partnership with commercial diagnostic laboratories and conducts >10,000 sequences per week. The third source is Tagged Metadata from Sequence Repositories. Data from this leads to CDC guidance for surveillance sequences in GISAID/GenBank. State/local health departments, universities, and non-federally contracted diagnostic labs tag sequence metadata in public repositories. Figure 2 shows the data workflow.

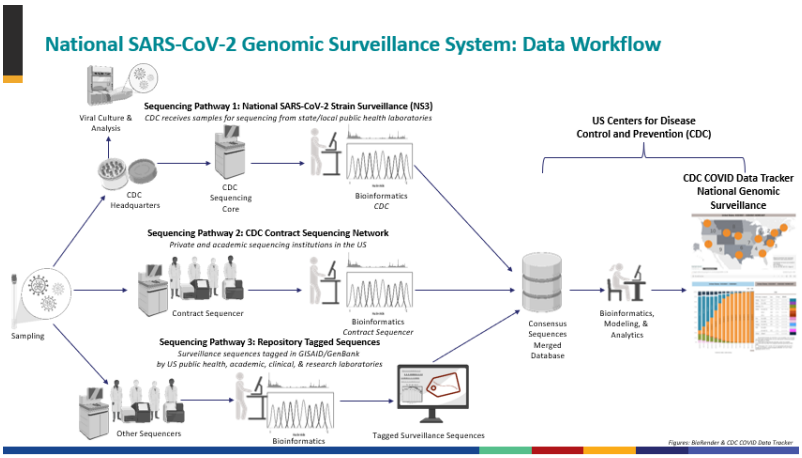

Figure 2: Data Workflow

Figure 3 shows the weekly timeline for surveillance.

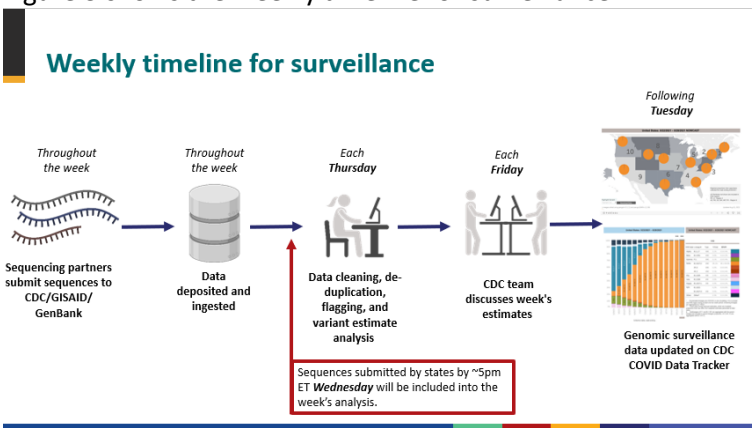

Figure 3: Weekly Timeline for Surveillance

With the different sources of data, they were able to increase the temporal and geographic variability in sequencing volume. There were challenges that emerged in this work. Table 1 shows the challenges that the research team experienced and solutions that they had adopted.

Challenges	Solutions
Sequenced specimens may not be representative over temporally or geographically	Weighting strategy using complex survey design
Time from specimen collection to posting of sequence data (2-3 weeks)	Multinomial regression model to "nowcast" estimates of proportions to present time
Uncertainty in estimating proportions	Model-based 95% confidence intervals for variant proportions

Table 1: Weighting and nowcasting to estimate variant proportions challenges and solutions.

For their complex survey design, the primary sampling unit (PSU) was source for sequence data (i.e., laboratories). The strata were state and week (i.e., temporal and geographic sequencing variability). The weights accounted for the probability that a specimen from an individual test was positive for SARS-CoV-2 by RT-PCR and a specimen from a positive RT-PCR test was sequenced. The time frame was a survey design only generates estimates of variant proportions for time periods with sufficient sequence data. For their multinomial regression model was a regression model

with multiple categories (variants) as dependent variable. This generated weighted proportions estimates for the most recent 2 weeks. There are two models, National and HHS regional models, used with week and week + region as predictors. The national model predicts variant every week. The regional model predicts variant every week and the region. Table 2 shows the variant proportion estimates and data timelines. These can be found on their COVID-19 tracker.

Estimate	Geographic Level(s)	Weeks Included in Estimate	Time Lag (Weeks)	CDT Example for the week ending 3/12
Nowcast	• National • Region	21	0, 1	Estimates for weeks ending 3/5 and 3/12
Weighted Proportions*	• National • Region	1	2+	Estimates for week ending 2/26 and earlier
	• Jurisdiction	4	3	Estimates for **4 weeks** ending 2/19

***Flags applied to analysis if National Center for Health Statistics (NCHS) Data Presentation Standards for Proportions are not met:** https://www.cdc.gov/nchs/data/series/sr_02/sr02_175.pdf
COVID Data Tracker, Variant Proportion Estimates: https://covid.cdc.gov/covid-data-tracker/#variant-proportions

Table 2: Variant proportion estimates and data timelines.

Nowcast predictions and weighted estimates for Omicron

There are very little sequence data is available within one week of collection. However, sequencing totals continue to increase over time. For Omicron's proportion has rapidly increased in the United States. The national weighted estimates at different reporting weeks have similar point estimates and narrow 95% confidence intervals (CI). Omicron went from 1% to 50% in 2 weeks, Delta went up in approximately 7 weeks, and Alpha went up in 12 weeks. The reason why Omicron sequences went up quickly was due to the labs submitting Omicron sequences faster compared to other sequences. However, all Nowcast predictions within 1 week of weighted variant share.

In order to future proof Nowcast predictions, we must focus on data quality. We must get timely submissions (by Wednesday), have geographic representation, improve genome completeness and coverage of spike, and adopt resilient sequencing approaches to future proof new variants. Additionally, it is important to recognize uncertainty in the estimate's confidence and prediction intervals and NCHS data quality flags. In conclusion, sequencing takes time; weighted variant proportions estimates are stable; and Nowcast estimates for variants with rapidly changing proportions are sensitive to bias in data availability. There can be bias in reporting speed can only be determined retrospectively.

Next Steps

- Continue making data connections through the Evidence Accelerator and through www.EvidenceAccelerator.org.

Next Meeting: Thursday, April 21, 2022 12-1 pm ET