Template for inclusion of SARS-CoV-2 vaccine booster in surveillance studies

Purpose:
Provide a common study template that could be used within SeroNet and beyond for the serosurveillance of individuals, including cancer/immunocompromised patients, receiving a SARS-CoV-2 vaccine booster. The template could be applicable to prospective interventional trials when investigators have access to vaccines for experimental use, or for observational studies where individuals receive vaccines as they become available in the community.

Dependent upon the needs of the study, this template provides guidance about recommended timepoints and sample types to collect post-boost for longitudinal evaluation of the immune response and to facilitate meta-analysis of the data.

Population can include:
- Immunocompromised individuals due to a cancer diagnosis or the effects from their treatment
  - Newly diagnosed cancer patients
  - Patients currently undergoing treatment for cancer, including chemotherapy, radiation therapy, immunotherapy, targeted therapy, or combinations of therapies
- Individuals with a history of cancer/cancer survivors
- Individuals with autoimmune diseases that are immunosuppressed
- Other immunocompromised individuals
- General population

This document is intended to be agnostic as to which booster individuals receive and will provide recommendations for:
- Specimen selection and collection
  - Timepoints for boost and collection
  - Specimen types
  - Specimen collection protocols
  - Key determinants to be considered
- Assays
  - Type
  - Benchmarking/standardizing
  - Standard protocols where available
- Data collection and common data elements (CDEs)

Design Considerations:
- Vaccine responses can be influenced by a number of factors and conditions
  - Age, prior SARS-CoV-2 infection, BMI, other infections, and co-morbidities
  - Time since first SARS-CoV-2 vaccine regimen, and the interval between the initial prime/boost series.
  - Cancer and autoimmune disease and their treatments could affect immunocompetence and therefore vaccination/boost responses.
  - Individuals with cancer are a complex and extremely diverse population and there are a multitude of considerations, including approaches to capturing the appropriate clinical information regarding an individual's cancer type, subtype, stage, treatments/regimen (chemotherapy, radiation therapy, immunotherapy, surgery), time since diagnosis, timing of therapy, etc.
  - Individuals with autoimmune diseases could experience flareups or other adverse reactions following vaccination.
- Recommendations for when specimens should be collected for optimal tracking of the vaccine boost induced immune response.
  - Inclusion of additional sampling timepoints following a documented infection (positive PCR) after boost.
  - Investigators should aim to collect timepoints within a narrow window, not more than 10-days from the scheduled timepoint to facilitate meta-analysis.
- Detailed collection of demographics and non-cancer related clinical data such as performance status, chronic diseases and specific therapies, co-morbidities, tobacco history (particularly lung cancer), alcohol history, other medications, etc.
- Collection of quality-of-life considerations and patient reported outcomes.

Scientific and Clinical Questions
- Homologous versus heterologous boost strategies. It is important to capture information about the initial vaccine type and regimen as vaccines may have a different mechanism of action that could impact the immune response.
- Changes in incidence of adverse events (vaccine or cancer related).

Timeline and specimen collection

Boost

D0   1M   3M   6M   12M   18M

Figure 1. *Recommended timepoints for the collection of biospecimens following SARS-CoV-2 booster vaccination. The timepoints indicate the recommended minimal timepoints for specimen collection to measure the immune response post-boost.*

Figure 1 shows the minimum recommended sample collection timepoints for studying the effect of a vaccine boost. Baseline serology assessment is critical for testing the ability of a (homologous or heterologous) vaccine boost to illicit a measurable serology response. The D0 timepoint is intended to establish a baseline and samples should be collected prior to the boost. This sample collection can occur on the same day as the vaccination, or up to one week before a planned boost. For long-term immune assessment it is recommended to include a timepoint at 12- and 18-months post-boost. For near-term assessment of whether a vaccine boost is successful in inducing an immune response an interim analysis at 3 months post-boost is recommended.

Samples should be collected as close to the indicated timepoint as possible and within a 10-day window. It is also recommended to collect a nasal swab at the time other specimens are collected for monitoring for breakthrough infection and viral shedding.

Table 1. *Recommended collection timepoints per specimen type. PB denotes post-boost timing. The timepoints with an X denote the minimum recommended specimen collection per timepoint. Other sample types within the table are recommended for additional collections based on study aims.*

Sample Type	D0 (Baseline)	1M (PB)	3M (PB)	6M (PB)	12M (PB)	18M (PB)
Serum	X	X	X	X	X	X
Plasma						
PBMC	X	X	X	X	X	X
DBS						
Saliva						
Nasal Swab	X	X	X	X	X	X

Table 2. *Minimum recommended assays per timepoint following vaccination. X denotes the minimum recommended assays per timepoint. Other sample collection timepoints within the table are recommended for additional assays depending on study aims.*

Sample Type	D0 (Baseline)	1M (PB)	3M (PB)	6M (PB)	12M (PB)	18M (PB)
Serology (IgG LBA)						X
Neutralization Assay	X	X	X	X	X	X
T Cell Assay	X	X	X	X	X	X

Sample Preparation and Assay Types
It is recommended to harmonize study collection protocols and to use assays that have been well characterized and validated. Below is a list of recommended assay types and protocols as available at the time of document completion. Sample collection/preparation protocols are dependent upon the assay type.

- Serum biospecimen processing
- Plasma biospecimen processing
- PBMC isolation and cryopreservation
- **Serology (LBA):** To distinguish natural infection from vaccine induced immunity we recommend performing an IgG LBA against both the Spike (natural infection and vaccine-mediated) and N (natural infection) proteins.
    - It is recommended to use an FDA EUA semi-quantitative or quantitative assay that is calibrated against the National SARS-CoV-2 Serology Standard and report all findings in international units (IUs).
- **Serology (neutralization assay):** To determine the presence and magnitude of functional, neutralizing SARS-CoV-2 antibodies as well as correlation with ligand binding assay results.
- **Immune cell assessments:** Disease related abnormalities and treatments for cancer and autoimmune disease can impact immune cell populations/ immunocompetence and potentially affect the response to vaccination. Therefore, especially a baseline immune assessment will be critical for the correlation of immune kinetics to immune status.
    - Assay types can include Complete Blood Count (CBC), flow-cytometry and CyTOF.
- **T cell assays:**
    - **ELISpot**: Quantitative assay that measures cytokines released from antigen stimulated T cells.
    - **Intracellular cytokine staining (ICS):** Flowcytometry-based assay that allows for simultaneous cellular phenotyping and single cell cytokine detection used to assess T cell responses.
    - **Activation Induced Marker (AIM) Assay:** Detection of antigen specific T cells.
- **SARS-CoV-2 diagnostic test**: PCR-based assay to detect viral RNA.
    - If a breakthrough infection is noted additional follow-up may be required

Common Data Elements

To facilitate metanalyses SeroNet recommends the use of a [minimum set of common data elements (CDEs)](#). Some data elements are recommended to be collected at each timepoint/encounter if feasible, others can be collected following consent at the beginning of the study. CDEs are roughly divided by:

- o Demographics
- o SARS-CoV-2 vaccine (and infection) history
- o Clinical characteristics
- o Patient reported outcomes
- o Assay results