Using online patient, clinician and caregiver conversations, domain name analytics, and random domain intercept opinion data to assess contraindication between monoclonal antibody treatments and SARS-CoV-2 vaccinations across the world in real-time

A. Context of possibilities for adverse interactions between monoclonal antibody treatments and COVID-19 vaccines

Roughly 75 percent of any community needs to be vaccinated against SARS-CoV-2 in order to reach herd immunity and to stop the pandemic. Yet vaccine hesitancy persists, based on many factors, one of which is hearing about negative reactions to the vaccine. There are legitimate questions about the possibility of adverse reactions in patients receiving monoclonal antibody treatment (mABs, also referred to as moAbs) for various cardiovascular, respiratory, hematologic, and autoimmune diseases as well as for cancers, and for infections such as the virus itself [1]. Over 50 different mAbs have already been approved for clinical use or are currently under development. There are also a dozen or more differently constituted vaccines against this virus in use or about to be in use across the globe. These vaccines include mRNA vaccines that do not use a lipid-based nanoparticle (LNP) carrier system (e.g., the Pfizer/BioNTech and Moderna vaccines), inactivated vaccines (e.g., the PicoVacc/CoronaVac vaccine), non-replicating viral vector vaccines (e.g., the University of Oxford/ AstraZeneca vaccine), and protein-based vaccines (e.g., Novavax).

The fear is that some vaccines can enhance inflammatory responses capable of aggravating symptoms of the original disease being treated with mABs. Aggravated symptoms include hypersensitivities, anaphylaxis and urticaria or other severe cutaneous reactions, but also cytopenias, vasculitis, pulmonary events, and liver injury. Canadian guidelines suggest that children under 18 with autoimmune disease (currently treated with mAbs) delay their vaccinations [2,3]. Guidelines in different regions of the world will, of course, differ.

Adverse events do occur with biologic agents, particularly mAbs, and they can be exacerbated by vaccines [4]. The combination of mAbs and vaccines can, theoretically, cause severe reactions. Because mAbs are large proteins, because they have a complicated structure, and because structure varies when recombinant gene technology is used in cell lines, these drugs are sometimes seen as foreign bodies by the immune system of the host. Drug/antibody immune complexes are known, at times, to produce negative consequences [5]. Vaccines may add to the problem [6]. There is a clinical need to be able to predict reactions to the mAb-vaccine combination and to develop reliable safety biomarkers [7]. This may be especially important in children [8].

There are currently individuals across the world taking mAbs who are receiving, or are in line to receive, a vaccine for Covid-19. A minority of this group may experience unwanted effects. Predicting who these people may be requires real-time data to help clinicians, regulators and public health agencies anticipate those at risk of adverse events and provide guidance on an appropriate evidence-based clinical response. Researchers need these data in order to determine the causes of adverse reactions. It is important to ensure that all patient groups clinically eligible for a Covid-19 vaccine receive it safely. This is vital for the patients themselves and also for the general population who, hearing about negative reactions, may decide against vaccination. In order to gather real-time information on the true risks of Covid-19 vaccines for diverse patient populations, it is insufficient to rely on the few case reports published in medical journals by clinicians treating SARS-CoV-2. Far more reports written by patients, caregivers and clinicians about drug interaction risks are retrievable online in a global, confidential, reliable and rapid manner.

Public health policy is most often developed on the basis of local data [9] or practice guidelines. Sources of information for policy makers are government websites, personal contacts, public health professionals, and politicians. Policy has traditionally not relied on results of research studies. It is time for global research initiatives such as the development of “safety signal” screening for drug-drug interactions that do not depend on complicated algorithms and that can accurately inform public health policy [10].

B. Formulating a hypothesis to decrease the frequency of unwanted effects

While some recommendations exist for vaccinations against SARS-CoV-2 in patients on biologics such as mAbs, they tend to be limited to specific diseases, specific types of vaccines and specific age ranges of patients. In order to formulate a hypothesis about the interactive risks between Covid-19 vaccines and mAbs, we propose the use of

a combination of three Web-based data-gathering approaches, and in a synthesis of these methods, in order to gather rapid and global data about age, sex, reproductive status, ethnicity and the disease for which mAbs are being prescribed. In the process of accessing these online data systematically, we can learn, in real-time, about individuals' reported experience with vaccines, and about important variables such as the duration and frequency of their mAb treatment. We are interested in the role of immunity in the reactions that take place and expect to find differences in age (specifically, children and the elderly most at risk), sex (women more at risk), and reproductive status (pregnant women more at risk). Equipped with these data, we will be able to not only predict who is most at risk, but also to determine the timeline post-vaccination at which adverse events are most likely to occur and the regions of the world that are most at risk.

In order to gather the most reliable online data to articulate a sound hypothesis, we will triangulate data from a number of Web-based sources to systematically gather online reports by: (i) clinicians, (ii) patients, (iii) caregivers and, (iv) stakeholders with knowledge of Covid-19, mAbs and the diseases for which they are used. This latter group in (iv) consists of knowledgeable clinicians, researchers as well as informal caregivers. To the extent that all these groups in (i-iv) participate regularly in knowledge-seeking and knowledge-production online, their statements, activities, questions and opinions online will be compared and analyzed in order to detect new and rapidly evolving information on the safety of SARS-CoV-2 vaccine-disease-treatment interaction (hereinafter, "interaction").

C. Research: Measuring Collinearity among three online signals to assess interaction risk

The data-gathering method that will inform the development of a hypothesis includes a mix of rapid Web-based data collection tools. Although each approach has been used for different purposes in the past, none have assessed drug interactions, and there has been no instance of these tools being merged to bring reliable evidence to light, evidence that can confirm or disconfirm a hypothesis about drug or vaccine safety.

We consider each data-gathering tool as a signal of potential interaction. If all three signals converge on a consistent finding – e.g., the interaction produces differential effects across age, sex, reproductive status, or geographic region – then we will have created evidence that warrants further testing in a clinical environment. To ensure that the safety data extracted from different online signals are as comparable as possible, a standardized approach of data synthesis is required, described below.

The current situation is an opportunity to develop a new approach to understanding how new drugs interact with environmental exposures such as vaccines. The same method can be applied to examining how drugs interact, for instance, with toxins, infectious agents, dietary changes, physical activity, psychological stress, inflammation, climate change, or radioactivity. New, inclusive approaches are needed to explore the effects on health of experiences in the real world [9]. Importantly, information from many different sources increases confidence in the data that are collected. The results are valuable when numerous data points converge; they are also valuable when they diverge because of differing perspectives on the same issue. Usually in clinical medicine, self-reports, and even expert opinions are not given the status of "evidence." And yet, for complex interactions, randomized clinical trials of two alternatives may not suffice. The rollout of the Covid-19 vaccines is a natural experiment with a highly significant potential for uncovering unsuspected interactions. Having global systems in place to learn rapidly from such an experiment should, we believe, yield important results. It can expand the number of people who safely receive a Covid-19 vaccine, and the number of people who acquire confidence in vaccines in general.

Although standard clinical trials and post-marketing surveillance have improved in terms of inclusivity, a number of long-standing structural and social factors still pose problems for many whose voices need to be heard. Drug safety risks may be underestimated and or mis-estimated for subgroups of the global population. Using Web-based tools provides an opportunity to mitigate some of the responsible factors. For example, problems in access to care, particularly access to academic centres likely to conduct trials, are a barrier to inclusivity [10]. Using Web-based tools that are accessible to the patient or caregiver at any location helps reduce this barrier. Likewise, if trust in the healthcare system or in medical research is at issue, Web-based tools that do not require enrollment into a study or attendance at a healthcare institution permit normally silent voices to be heard. Web-based tools disintermediate the healthcare system and the formal research process.

Signal 1: Scanning patient, clinician and caregiver forums for interaction reports

Web scraping refers to an automated action, which deploys natural language algorithms seeking out reported online content in close proximity to keywords [11] that contain the words "mAbs," "vaccine" and "Covid" or variants of these words. Open-source blogs written by self-identified patients, caregivers and clinicians can be searched in many languages, and be thereafter filtered to identify evidence of interaction. The search strategy uses language strings that denote active mAbs usage, such as "I'm on [name of mAb]…." or "I have been on [mAb] for ….", or "I've started [mAb]…", or "the [mAb] is giving me/ my patient/ my daughter or causing me/ my patient/ my son…", or "I am trying [mAb]…" or "…[mAb] gives me/ my patient/ my daughter/ my daughter….." in proximity to words denoting vaccination for Covid-19 (e.g., a "shot," "vaccine," or "jab"). After capturing the relevant Web-based content of mAb usage and vaccination and a description of an ensuing event (i.e., sickness, reaction, response, result), a report synthesis approach is deployed – identical for Signal 1, Signal 2 and Signal 3 (hereinafter, "synthesis approach"). Reports are synthesized into an ontology of risk categories that include both physical and psychological risks attributed to the vaccination. Three clinicians experienced in mAb treatment independently evaluate the reports, looking for immediate effects such as allergic phenomena, or later effects surfacing many days post-vaccination. Reactions that are reported may or may not turn out to be actual reactions to the vaccine but, even if unjustly attributed to the vaccine, they are still important because they speak to people's fears. All risk reports observed by patient, caregiver, or clinician are important to analyze.

Signal 2: Scanning domain name content for interaction reports

A systematic, real-time Web-based data-gathering method [12] can deploy a 'crawler' technology that identifies all domains (i.e., websites) that contain the generic or brand name of mAbs, in many languages. In some cases, domains that contain the brand name or generic name will not be registered and therefore will have no online content. In some cases, the domain names will be for sale or 'under construction'. In other cases, the domain name will have interaction content that can be geo-located to a region of the world. In order to obtain actual risk reports of observed or experienced interaction with a vaccine, the same synthesis approach is used as described above, with three clinicians evaluating the content posted on the domains.

Signal 3: Real-time random domain intercept opinion data for interaction reports

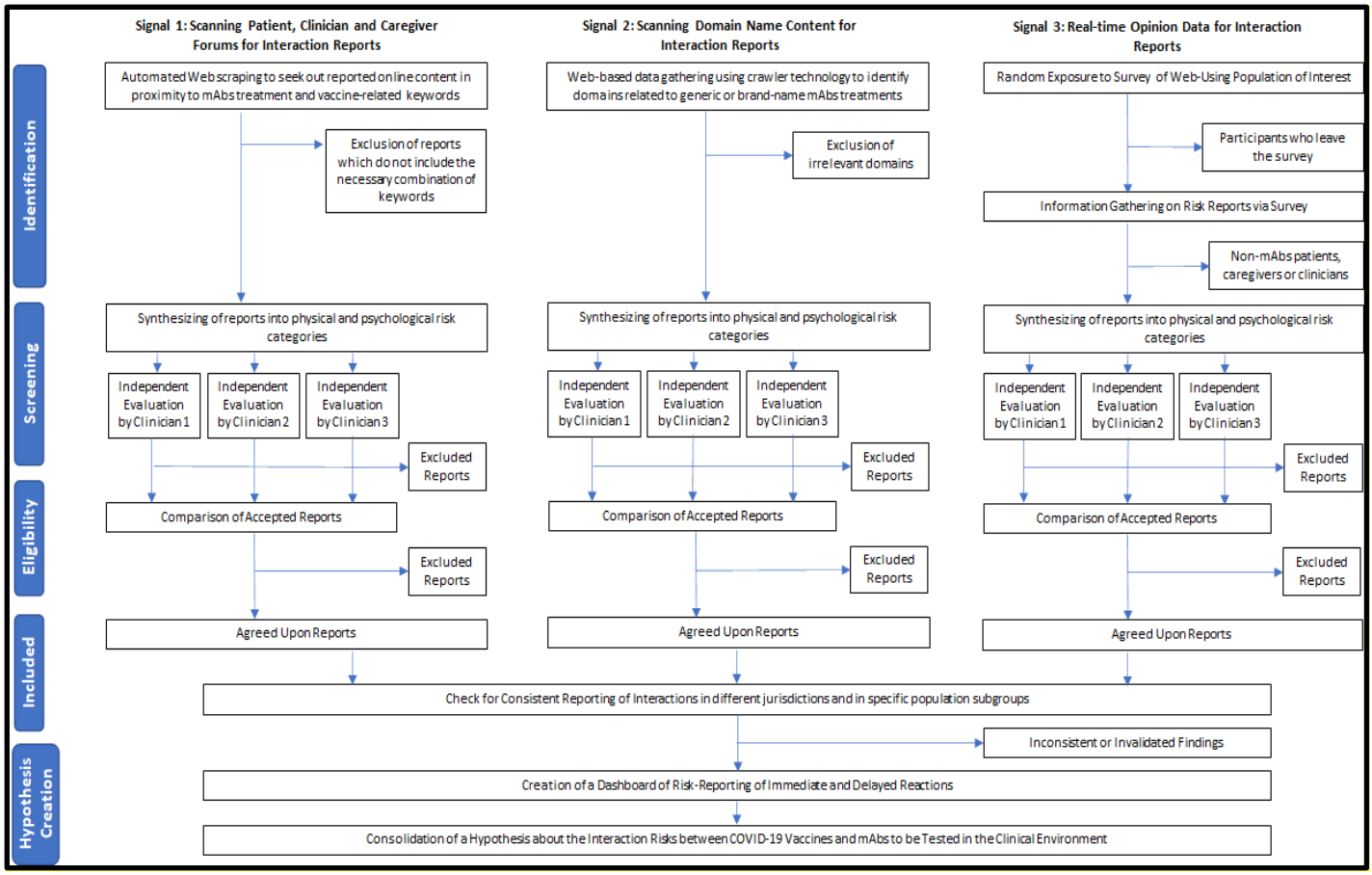
A third signal solicits diverse online opinion. Leveraging Random Domain Intercept Technology (RDIT), it can draw responses randomly from the entire Web-using population on a continuous, 24/7 basis [13]. Unlike traditional or online survey approaches, the technology's algorithms ensure that anyone on the Web in the region(s) of interest has an equal chance of being randomly exposed to questions each day. Unlike mail, panel or telephone surveys, all voluntary response data are gathered anonymously, reducing social desirability bias and eliminating a potential barrier to participation [14]. Respondents are not incentivized to participate in any way. The RDIT survey can ask online respondents across the world (different respondents daily), whether they have a condition for which they are being treated with mAbs, whether they have been given a vaccine for SARS-CoV-2, the timing of this vaccination, and their response (if any). The RDIT survey data is then segmented by sex, age, reproductive status and region. Caregivers and clinicians are posed similarly worded questions about people under their care. In order to obtain actual risk reports of observed or experienced drug/vaccine interaction, the synthesis approach described above is used, with three clinicians evaluating the survey data.

Conclusion: Synthesis of findings to reduce the frequency of adverse events

The continuous and growing accumulation of these data will create a novel dashboard of risk reporting. Timelines associated with adverse events are easily extracted from the three signals. While there is no specific hypothesis about geographic region, vaccination guidelines in different parts of the world may yield different interactive results. Reports of interaction that emerge consistently across all three online signals – whether by sex, age or reproductive status – can be fed into a dashboard. Clinicians and public health officials can then determine how best to reduce the frequency of reported adverse events, and, further, how to increase tolerance to the vaccine in affected groups. It is hoped that understanding the risks of adverse interactions will, ultimately, increase worldwide acceptance of Covid-19 vaccines.

Appendix 1

Figure: Using Real-Time Data Capture Systems to Identify Unwanted Risks between mAbs and COVID-19 vaccinations and reduce interaction risks for affected populations



Appendix 2: Citations

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