After having explored and analyzed Figure 2 alongside epidemiologists, we noticed that the reconstructed phylomemy clearly retrieves five major COVID-19 vaccine platforms in the form of complete branches. These platforms include the classical vaccine platforms i.e., ‘*non-replicating viral vector’*, ‘*inactivated virus’* and ‘*protein subunit’* as well as the next-generation vaccine platform i.e., ‘*DNA based vaccines’* and ‘*RNA based vaccines’*. The visualization (see Figure 2.a) shows the continuous development of each branch and the way that some interacted and eventually blended while others stopped. Interestingly, trials of ‘*RNA based vaccines*’ were registered very early in the course of the pandemic (February 2020) with trials evaluating the vaccine developed by *Moderna TX* (mRNA-1273) followed by the vaccine developed by *Pfizer/BioNTech* (BNT162b2). The number of these trials increased rapidly and interactions with other widely explored techniques were observed, notably with the ‘*non-replicating viral vector*’ family (ChAdOx1- Astra Zeneca). The latest interaction involved the ‘Protein subunit’ branch in July 2021. In contrast, ‘*DNA based vaccines*’, with a first trial registered in April 2020, had a very limited number of trials planned and its branch stopped rapidly in 2020. Similarly, other platforms of ‘*replicating viral vector vaccine*,’ ‘*virus-like particle vaccine’* and ‘*live attenuated virus vaccine’* showed a very limited development.

As the development and approval of COVID-19 vaccines was expected to take time, researchers also explored repurposing non-COVID vaccines. Considering the lower severity of the disease in children and young adults, some researchers hypothesized the possible heterologous protective effect of these vaccines. Some evidence shows that live-attenuated vaccines such as Bacille Calmette–Guerin (BCG), Measles, Mumps, Rubella (MMR) can induce protective innate immunity, which could be central in controlling SARS-CoV-2 (ref PNAS). While this hypothesis was appealing, it did not seem to expand into a wider research domain. The branch of ‘*non-COVID vaccines*’ appears and expands at the beginning of the pandemic but progressively decreases towards the end of 2020 as other more promising vaccines arose. Nevertheless, some researchers highlighted the need to adequately assess the use of non-COVID live-attenuated vaccines as they could potentially boost response in high-risk populations, be used in addition to COVID-vaccines to increase effectiveness and durability of their effect, or be used to protect people exposed to COVID-19 patients (ref PNAS).

The interaction and merging of the branches reflect the exploration of a new approach to vaccine implementation moving from homologous prime vaccination (i.e., injections of two doses of the same vaccine) to heterologous prime vaccination (i.e., injection of the first dose of a given vaccine and the second dose of another vaccine). This is clearly shown in figure 3 with the assessment of the heterologous prime vaccination of ‘*RNA based vaccines’* (BNT162b2-*Pfizer/BioNTech*) and ‘*non-replicating viral vector’* (ChAdOx1-*AstraZeneka)* in early 2021. This new approach was motivated by concerns about waning vaccine immunity, but also by practical considerations. Following concerns about the safety of the AstraZeneca ChAdOx1 vaccine, the EMA recommended giving a second dose Pfizer BNT162b2 vaccine to patients under the age of 55 years who received one dose of ChAdOx1-S-nCoV-19. Furthermore, decision makers needed flexibility to overcome the issue of vaccine availabilities during the vaccine rollout. This new approach proved to be relevant and other associations were evaluated: ‘*non replicating viral vector’* and ‘*inactivated virus’* in June 2021 and later ‘*RNA based vaccine’* and ‘*inactivated virus’* in September 2021.

Phylomemies are essential in identifying shifts in research questions. While evidence of the beneficial effect of vaccines is mounting, research questions are moving toward exploring the effect of booster to overcome the waning of vaccine efficacy over time. Early 2021, new trials assessing the impact of administrating a third dose (see Figure 2, red outline) have been registered particularly for ‘*RNA based vaccines*’ and ‘*Non-replicating viral vector*’ (7). An important part of the research on the effect of a boosters is considering heterologous boosters.

Phylomemy also provides important information on research planning and reporting. As shown in Figure X, most trials registered are randomized controlled trials. Early in the pandemic, non-randomized trials were primarily early phase trials while those registered in 2021 include both early phase trials exploring new vaccines and phase 4 trials assessing vaccines safety. We can also explore the data to better understand how different countries participated in the overall research effort over time. For example, when filtering on the country (see maps.gargantext.org ), we see that trials conducted in the USA explored all vaccine platforms and that the first trials registered frequently involved a center in the USA, confirming their leading role in clinical research (e.g., ‘*DNA based vaccine’*, ‘*RNA based vaccine’*, ‘*protein subunit’)*. Other important trials characteristics (e.g., funding source) can also be explored.

Finally, we explored publication of trial results (i.e., preprint or peer-reviewed articles). As shown in Figure X, we currently have access to the results of a very limited number of planned trials. While most of the COVID vaccine trials registered in early 2020 are published, most of the non-COVID vaccine trials are still unpublished. Understanding whether these trials were actually conducted with unpublished results or whether these trials were unable to recruit is important.

**Overall**

The COVID-19 pandemic highlighted the lack of coordination in clinical research and resulted in an important waste in research. To avoid this waste and improve research value, we need to provide tools such as phylomemy reconstruction which could be essential to guide trialists, funders and decisionmakers. It would enable them to follow emerging research questions and identify less promising domains. It could also facilitate identification of research gaps, research questions that may have been abandoned prematurely and redundancy in research. Such approach could be implemented for any disease or research field. It could also be enriched with other data (e.g., outcomes, number of patients actually included treatment effect estimates etc). Nevertheless, it would imply having access to high quality data on research planning and conduct. Such dynamic visualizations may thus become reflective tools to foster the collective coordination between researchers.

Ref

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Legends à rajouter aux figures

Related to boosting issue -> evaluating of a booster dose

Trials with publication -> Trials with publication (i.e., preprint or peer-reviewed publication)

Hétérologous

In red are highlighted all the trials evaluating heterologous primary vaccination and heterologous booster (to check). We highlighted only the heterologous vaccination involving different platforms.