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FACULTÉ DE MÉDECINE

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Swiss national SARS-CoV-2 genomic and variants surveillance program: 3-year report

1. Summary

Geneva Centre for Emerging Viral Diseases

Division of Infectious Diseases

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Laboratory of virology

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In March 2021, Switzerland instituted a national genomic surveillance program in response to the outbreak of SARS-CoV-2. The program's goals were to provide meaningful and actionable data to support public health efforts. Over the last 3 years, the genomic surveillance program has given us a picture of the epidemiology of circulating variants in Switzerland. The data produced and the work done for this program has made contributions to the pandemic response, not only at the local level, but also at the international level.

The program relies on a newly created network of Swiss laboratories connected with sequencing platforms, coordinated by the Geneva Center of Emerging Viral Diseases, under the umbrella of the Federal Office of Public Health.

Over the years, this program has been through three rounds of funding (phases), and testing and sequencing volumes have contracted with each new round. Initially, it included surveillance in clinical specimens and wastewater treatment plants, as well as immune characterization. In the third year, the wastewater sequencing was funded separately. In its first three years, centers participating in the program performed nearly 4 million PCR tests and produced over 75'000 genomic sequences to allow following SARS-CoV-2 genomics over time.

Initially, as the first "Variants of Concern" emerged and were designated by the WHO, there were considerable differences in the viruses circulating in Switzerland and Europe compared to other countries – while the Alpha variant dominated in Europe and North America, the Beta variant dominated in South Africa and Gamma dominated in South America. Then a succession of variants, starting with Delta in summer 2021 and followed by several Omicron sub-lineages, began achieving extreme but temporary dominance, leading to relatively homogenous worldwide circulation – during this time the variant circulation pattern in Switzerland closely matched that of other countries. Recently, since the emergence of XBB sublineages in spring 2023, the variant circulation pattern has become much more diverse and complex; various XBB sublineages are circulating at different frequencies in the different part of the world. Since October 2023, a new variant of interest, a distinct antigenic variant descending from BA.2.86 and called JN.1 is progressively taking off in Switzerland and in Europe, quickly replacing XBBs.

In terms of sequences per capita, the Swiss program compares favorably with most other countries. It is still above the sequencing rates of many countries (such as Germany, France, Italy, the USA, etc.), although it remains well below certain other countries, particularly Denmark and the UK.

In Switzerland, given the size of the country, this program allows for a dense, granular, and dynamic surveillance. By combining genomic surveillance data with existing Swiss surveillance systems such as Sentinella or CH-SUR databases, such a program grants access to critical information, providing the raw data for proper, useful, and actionable analysis.

Data from this program has informed decisions taken at the national and international levels on a variety of issues from testing and isolation strategy, to vaccination programs and updates, and patient treatment. Indeed, since the start of the program, several therapeutic antibodies and vaccines have been developed, and some began to show substantial and progressive loss in effectiveness after Omicron emerged and diversified. The surveillance program has monitored the emergence of these variants that display substantial immune escape and provided data relevance to patient treatment with monoclonal antibodies, and vaccine updates. Importantly, it has also helped discriminate between variants that were actually more competitive than others in Switzerland (such as BA.2.86), and those which ended up being of little concern (eg. BA.2.12.1).

The program also served as the core driver of many other national and international collaborations, which led to considerable public health related output, such as the validation of rapid diagnostic tests or the sharing of virus isolates, such as XBB.1.5, with the WHO biohub located in Spiez.

While the initial crisis may have passed, SARS-CoV-2 still causes significant mortality in the elderly and vulnerable. Maintaining such a strong laboratory network within Switzerland allows to continue to monitor respiratory pathogen circulation and to be prepared in case of a new outbreak.

This report has been produced by Erik Boehm, Pauline Vetter, Marc Friedli, Samuel Cordey, Richard Neher, Christian Althaus, Martina Reichmuth, Cornelius Römer, Priscilla Turelli, Didier Trono, David Dreifuss, and Laurent Kaiser. The list of the participants and collaborators of the program can be found at the end of this report in the appendix.

2. Introduction

SARS-CoV-2 emerged at the end of 2019, as a new virus which caused a pandemic in a population who had no pre-existing immunity to it. It already caused significant mortality, particularly in elderly and vulnerable populations, with more than 4.4 million cases and 14'000 deaths reported in Switzerland. In this context, the government of Switzerland implemented the national genomic surveillance program. This program aimed to improve our understanding of the virus, to provide data on epidemiological trends, and to highlight meaningful observations. The goal of this data was to allow informed decisions to be taken at all levels, from individual management of patients by doctors to population-wide measures.

3. Description of the Swiss national SARS-CoV-2 genomic and variants surveillance program.

In 2021 the Federal Office of Public Health (FOPH) launched a national SARS-CoV-2 genomic and variant surveillance program under the coordination of the Centre for Emerging Viral Diseases and the National Reference Laboratory for Emerging Viral Infections (CRIVE) at the University Hospitals of Geneva.

This national surveillance program has been funded in three phases so far:

The first phase started on March 1st 2021, and ran until March, 31st, 2022. The second phase ran from April 1st 2022 until December 31st 2022. The third and current phase ran from January 1st to December 31st, 2023.

The funding and operation of the program, the programs participants, and the epidemiological situation changed considerably over the course of the program. (Figure 1)

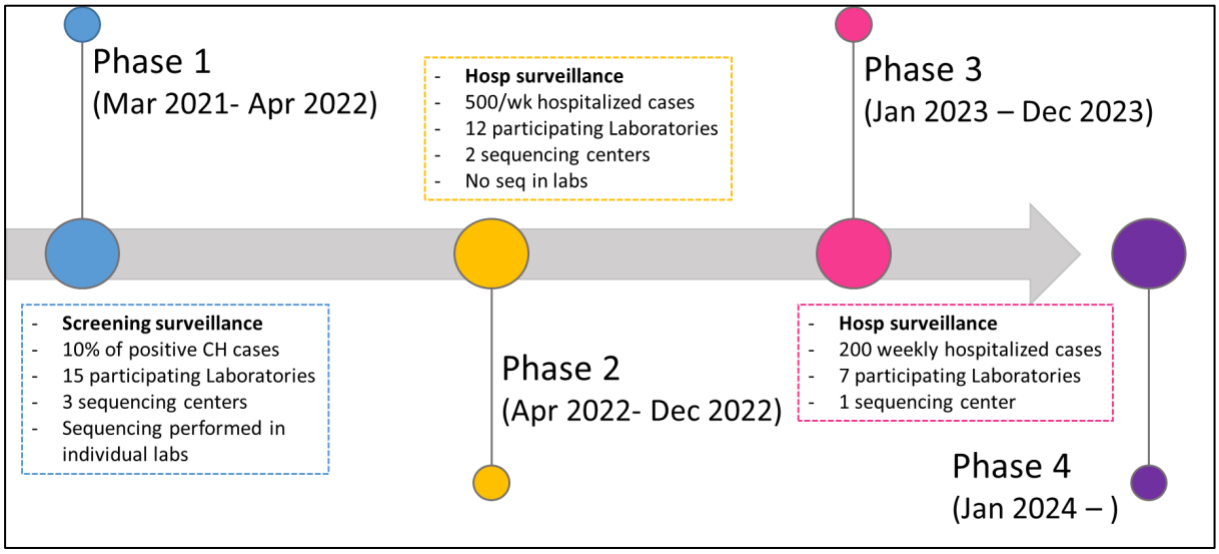


Figure 1: Schema of the different phases of the program over time

Phase 1 started with 8 diagnostic laboratories:

- University Hospital centres in: Geneva, Lausanne, Bern, Basel, Zurich, St-Gall, Ticino),
- Private laboratories (Viollier, Dianalabs Genève),
- A cantonal-based laboratory (Hôpitaux du Valais) and
- High-throughput sequencing platforms (Health 2030 Genome Centre in Geneva, Functional Genomics Centre in Zurich, D-BSSE ETH Genomics Facility in Basel).

By the end of phase one, it had expanded to 15 laboratories, including the private laboratories Polyanalytic, Dianalabs Valais, Proxilab and Bioanalytica; Labor Team W, Risch, and Synlab as well as the cantonal-based laboratory, Spital Region Oberaargau (Bern, Solothurn, Aargau, Luzern).

Phase 2 saw reduced participation, with 12 diagnostic laboratories are participating in the program:

- University hospital centres in Geneva, Lausanne, Bern, Basel, Zurich, Ticino;
- Private laboratories: Viollier; Medisupport including Dianalabs, Polyanalytic, Dianalabs Valais, Proxilab and Bioanalytica; Labor Team W, Risch
- Cantonal-based laboratories: (Hôpital du Valais – Institut Central), Spital Region Oberaargau (Bern, Solothurn, Aargau, Luzern),
- High-throughput sequencing platforms: Health 2030 Genome Centre in Geneva, Functional Genomics Centre Zurich run by ETH Zürich and University of Zürich, Genomics Facility Basel run by ETH Zürich and University of Basel).

Phase 3 saw the program focus on hospital surveillance and contract to 7 participating laboratories:

- University Hospital Centres in: Geneva, Lausanne, Bern, Basel, Zurich, and Ticino)
- the cantonal hospital in Valais (Hôpital du Valais – Institut Central), and
- the high-throughput sequencing platform (Health 2030 Genome Centre in Geneva).

The national program has included surveillance in clinical specimens and wastewater, as well as immune characterization. In phase 3, in 2023, the wastewater sequencing continued under a separate fund from the rest of the genomic surveillance program (still funded by the FOPH), and immune characterization was split from the program.

In addition, since the month of October 2022, surveillance and related work from Geneva has been partially funded by the EU grant for the COVICIS project (https://covicis.eu/).

In all phases processed sequencing data have been shared openly through the GISAID platform (https://www.gisaid.org) as well as through the Swiss Pathogen Surveillance Platform (SPSP) which also shares with the EU covid Portal. The centralized analysis of this National Surveillance will be performed by the groups of Pr. Neher, Pr. Stadler and Dr. Althaus, where variants of concern are counted, analyzed and all sequences scanned for new variants with potential changes in antibody-Spike interactions (https://nextstrain.org/groups/swiss, https://covariants.org/per-country, https://cov-spectrum.ethz.ch). This work is done in close collaboration with the Swiss Institute of Bioinformatics (SIB).

The number of sequences and other relevant information produced in each phase is included in table 1.

Phase	PCR tests	+ PCR tests	Sequences	Sequences/month	% sequenced
1	2’889’687	978’122	52’804	4’400	5.4%
2	790’219	270’845	19’526	2’170	7.2%
3	68’681	9’862	3’392	283	34.4%
All	3’748’587	1’258’829	75’722	2’443	6.0%

Table 1: Number of tests, positive tests, sequences, and sequences/month, as well as the percent sequenced in each phase of the project.

Immunological characterization of the variants within the surveillance program was included until the end of phase 2 (December 2022) and was coordinated by Professor Trono’s team at EPFL.

4. Comparison with other countries

The Swiss national SARS-CoV-2 genomic and surveillance program was among the 10 top countries in terms of metrics of SARS-CoV-2 sequences per capita. It surpassed the sequencing rates of the USA, Canada, Germany, France, Belgium, and Japan, to name a few. It has been significantly surpassed by Denmark, the UK, Austria, Sweden, and Slovenia. In February of 2022, the sequencing rate of this program was comparable to that of Sweden and Austria, but by December of 2023, it had fallen further behind (figure 2)

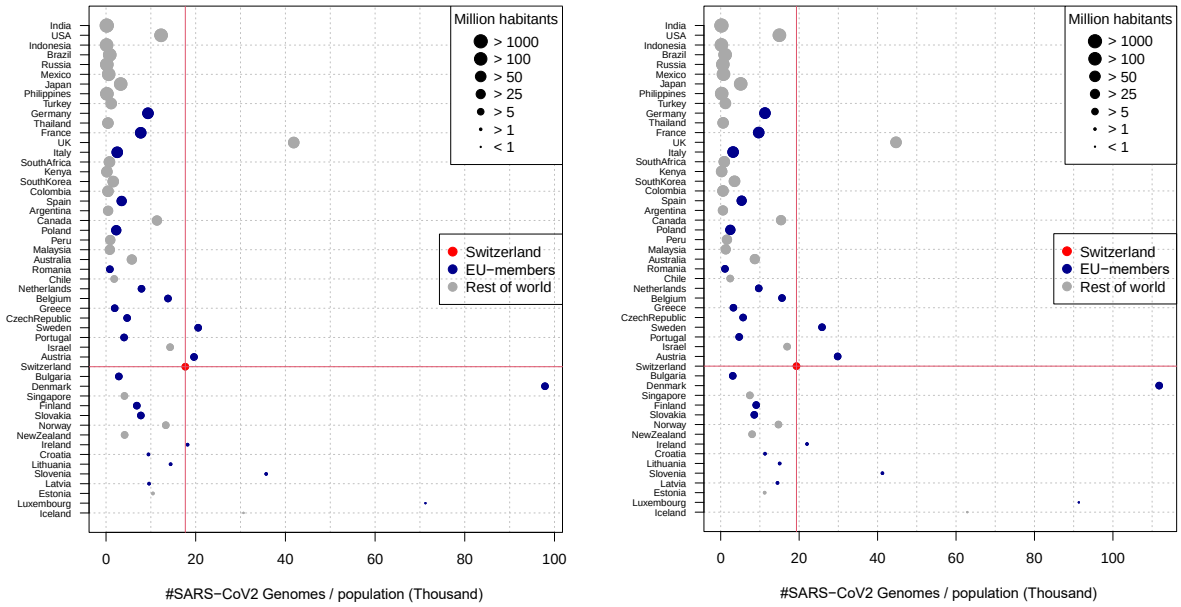
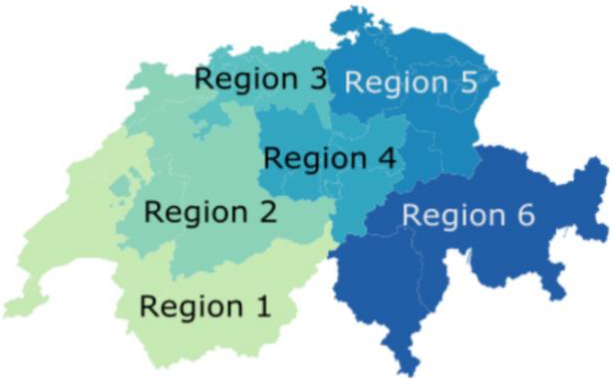


Figure 2: Per capita SARS-CoV-2 sequences generated by Switzerland and selected countries. Left: cumulative data as of February 2022. Right: Cumulative data as of December 2023. Note that Switzerland's position has slipped relative to countries such as Sweden, Austria, Ireland, etc. in between the two timepoints. Plots courtesy of Nexco Analytics.

5. Epidemiology in Switzerland and number and origin of sequences produced through the program during the surveilled period

Data used to produce the regular monthly report originate from 3 sources: 1) The publicly available data on COVID-19 as reported by the FOPH (https://www.covid19.admin.ch), including data that is declared to the FOPH by the different laboratories in Switzerland; 2) data originating from laboratories participating in the surveillance program; and 3) sequences submitted to GISAID, for which the corresponding infected person was in Switzerland (resident or recent travel history to Switzerland).

Data are presented by regions in monthly reports, using the same region definitions that are used for the influenza sentinel surveillance system in Switzerland and are presented according to residency post-code.



Region 1 includes the cantons of Geneva, Neuchatel, Vaud and Wallis

Region 2 includes the cantons of Bern, Fribourg and Jura

Region 3 includes the cantons of Aargau, Basel (Basel-Stadt and Basel-Land) and Solothurn

Region 4 includes the cantons of Luzern, Unterwalden (Obwalden and Niedwalden), Schwitz, Uri and Zug

Region 5 includes the cantons of Appenzell (Appenzell Ausserrhoden and Appenzell Innerrhoden), Glarus, Sankt Gallen, Schaffhausen, Thurgau and Zurich.

Region 6 includes the cantons of Graubünden and Ticino.

Divisions of the different regions, from https://covariants.org/per-country

All the monthly reports produced during the first 3 years of the program are publicly available at https://www.hug.ch/centre-maladies-virales-emergentes/programme-sequencage-national-du-sars-cov-2.

Cases detected in Switzerland

From 1 March 2021 to 30 September 2023, the FOPH reported 3’878’108 positive tests (including both RT-PCR and antigen-based tests). Positive tests from the labs participating in the national surveillance program from overlapping dates produced approximately a third of this number (1’258’829 positive tests – 32.5%). The highest incidence of positive tests was from December of 2021 to April of 2022, mainly at the end of phase I. The rate of testing decreased dramatically in phase 3, likely due to a change in testing policy (testing costs stopped being reimbursed by the government).

During phase 1, the highest positivity rates were among younger subjects, with the peak incidence rate peaking at 14’592 positive tests per 100’000 individuals aged 10-19 years. Phase one had the highest peak incidence of positive tests (Figure 3).

At the start of phase 2, the incidence across age groups was more balanced. As phase 2 progressed, overall incidence decreased, and trended towards higher incidences in older populations.

In phase 3, the positive test incidence dropped significantly, in parallel with overall test numbers. The 80+ age group has consistently had the highest positive test incidence during this phase, likely due to the focus on hospitalized patients.

In all phases, positive test incidence may not accurately reflect the actual incidences in the population. Due to testing requirements and social dynamics, younger age groups may have been over-represented during phases 1 and 2, although it is also possible that these age groups were more exposed to infection risk, and did actually have a higher incidence rate. During phase 3, the focus on testing in a hospital setting likely explains the highest incidences occurring in the 80+ year-old age group. The relative lack of cases in younger age groups strongly suggests that the current testing regime is biased and that a disproportionately large fraction of cases remain undetected in non-elderly populations.

Figure 3: Positive case incidence by age group for the three phases of the program. From : https://www.covid19.admin.ch/en/epidemiologic/test. For more information, please refer to the BAG dashboard (https://www.bag.admin.ch/bag/en/home/krankheiten/krankheiten-im-ueberblick/coronavirus/covid-19/monitoring.html).

Covering of sequencing in Switzerland and contribution of the national SARS-CoV-2 surveillance sequencing program

As shown in Figure 4, numbers of SARS-CoV-2 sequencing rates varied within phases (largely according to the circulation levels of the virus), but dropped sharply with each new phase. From the very start of the surveillance program, almost all of the sequences available, and all of those on which the surveillance is conducted, have come from the national surveillance program.

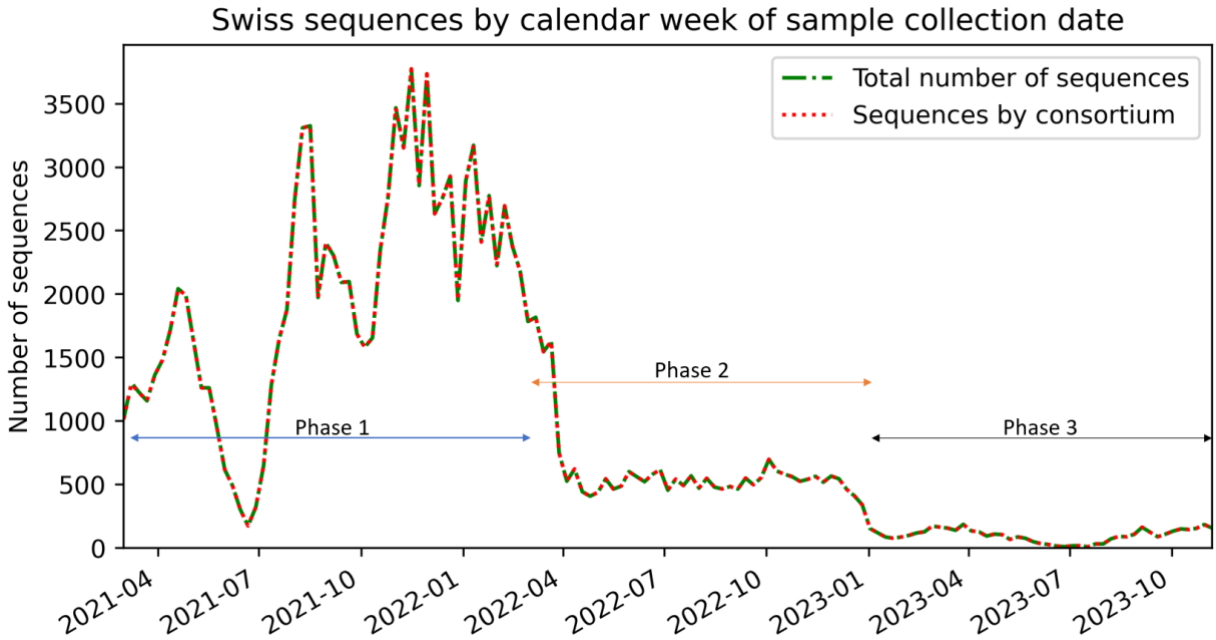


Figure 4: Number of SARS-CoV-2 sequences available for Switzerland (total available Swiss sequences in GISAID in green, Swiss sequences submitted through the program in dotted orange).

Figure 5 displays the number of SARS-CoV-2 cases sequenced for each Swiss region. During phase 1 and 2, all regions had good representation, although region 4 consistently had the lowest coverage. Regions 1 and 2 consistently produced the most sequences. In phase 3, region 4 (Luzern, Unterwalden, Uri, Zug and Schwyz) was no longer effectively represented due to the absence of a laboratory participating in the program in this region, after the switch to surveillance of hospitalized cases.

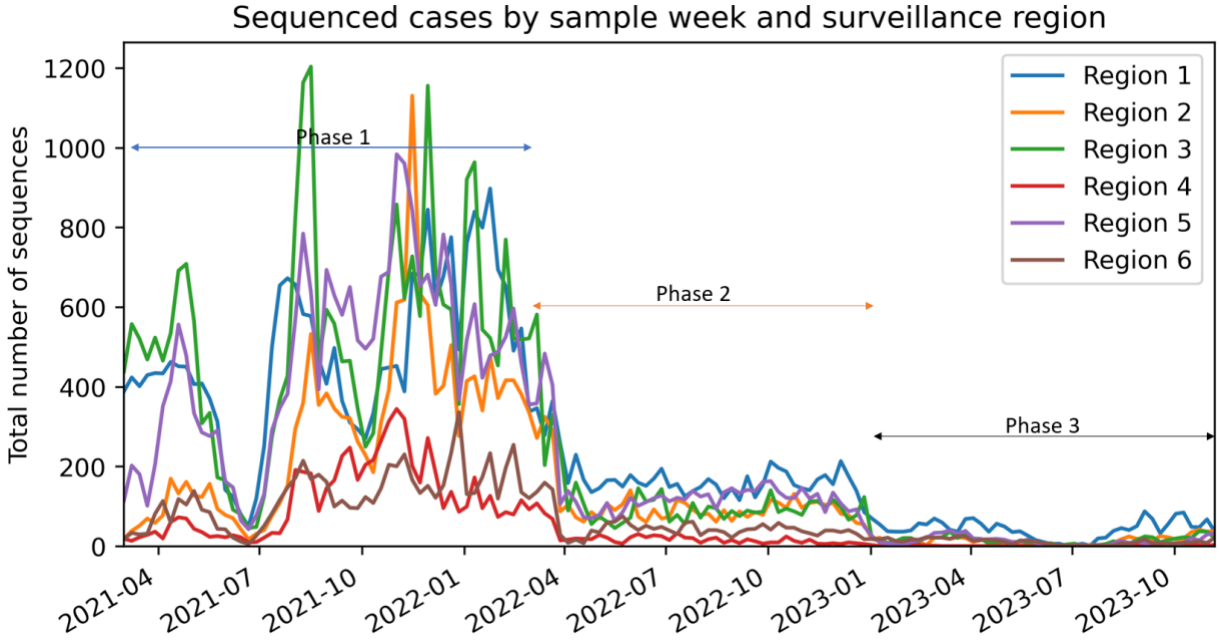


Figure 5: Sequencing coverage among the different Swiss regions per week, by number of sequences.

6. Dominant variants circulating in Switzerland

During the 3 years, there was massive variation over time of the circulating variants (Figures 6), but there was no significant regional difference noticed in the variants circulating within Switzerland (data not shown). Similarly, the circulation of variants within Switzerland has been largely consistent with observations worldwide, although there were key differences early in the pandemic, and more recently (Figure 7).

Indeed, note the variation by country early in the pandemic up to the first VOCs (Alpha, Beta, and Gamma), followed by a period of relative homogeneity from the Delta to Omicron BA.5 waves (with minor variations like BA.2.12.1 in North America). Since spring 2023, there is a recent trend towards a diverse group of co-circulating variants (rather than a single extremely dominant one) with more variation by country.

An estimate of the total number of VOCs circulating in Switzerland, corrected by taking in account the fraction of sequencing in Switzerland is available through the covSPECTRUM program, developed at ETHZ, at https://cov-spectrum.ethz.ch/explore/Switzerland.

Phase	Time period	Most common variant	Other notable variants
1	1.3.2021 - 27.6.2021	B.1.1.7 (Alpha)	B.1.617.2 (Delta), B.1.351 (Beta), P.1 (Gamma)
1	28.6.2021 -24.12.2021	B.1.617.2 (Delta)	BA.1
1	25.12.2021 – 28.2.2022	BA.1	B.617.2, BA.2
2	1.3.2022-2.6.2022	BA.2	BA.1, BA.5
2	3.6.2022 - 23.11.2022	BA.5	BQ.1, BA.2.75
2-3	24.11.2022 – 5.2.2023	BQ.1 (BA.5 sublineage)	BA.2.75, XBB
3	6.3.2023- Now	XBB	BA.2.86, BQ.1

Table 2: Dominant variants in Switzerland over time, as well as other variants that achieved substantial circulation in Switzerland or worldwide.

Replacement of a previously dominant variant by a new variant occurred in all phases, often associated with new waves, but the case numbers in each of these waves varied considerably. The time interval between replacement of one major variant by another appears to have been smallest in the latter half of phase 1 and the first half of phase 2. In phase 3, the variant situation has become much more complex and less characterized by largely homogenous circulation of a single dominating variant.

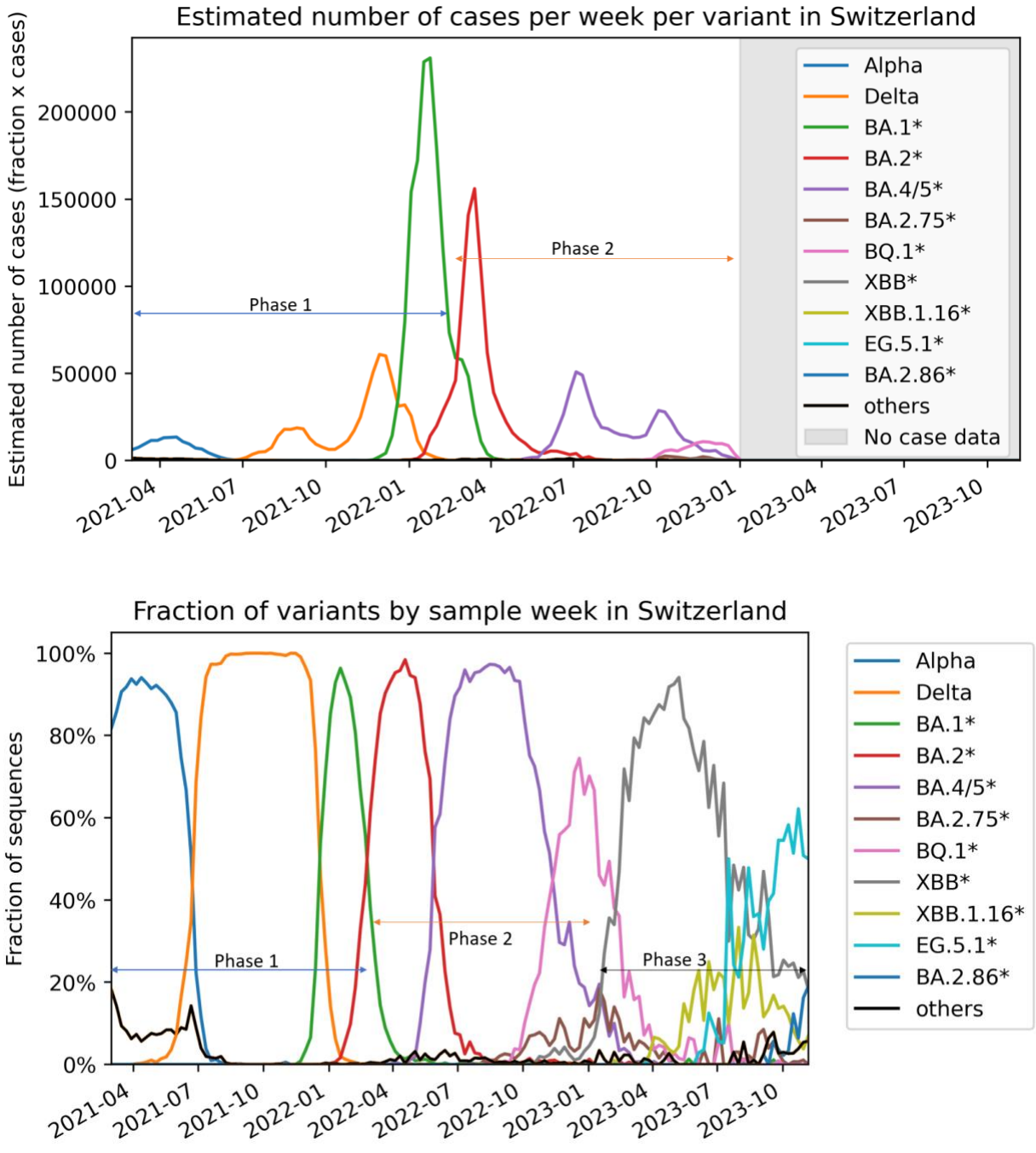


Figure 6: Major variant circulations in Switzerland over time. Top: estimated absolute circulation numbers (data missing for phase 3. Due to low testing rates in phase 3, with many infections going unreported, it is not possible to give estimates of the number of cases due to each variant. Bottom: Proportion of sequences over time belonging to each major variant in Switzerland.

Determination of the proportion of total number of sequences over time falling into defined variant groups is done by Emma Hodcroft's team and displayed on the CoVariant website (https://covariants.org/per-country), and are based on the total number of sequences submitted to GISAID over the time period for Switzerland. Those data mainly, but not exclusively, have come from the national genomic surveillance program since its beginning (see Figure 4). No Significant variation in variant circulation has been observed between regions.

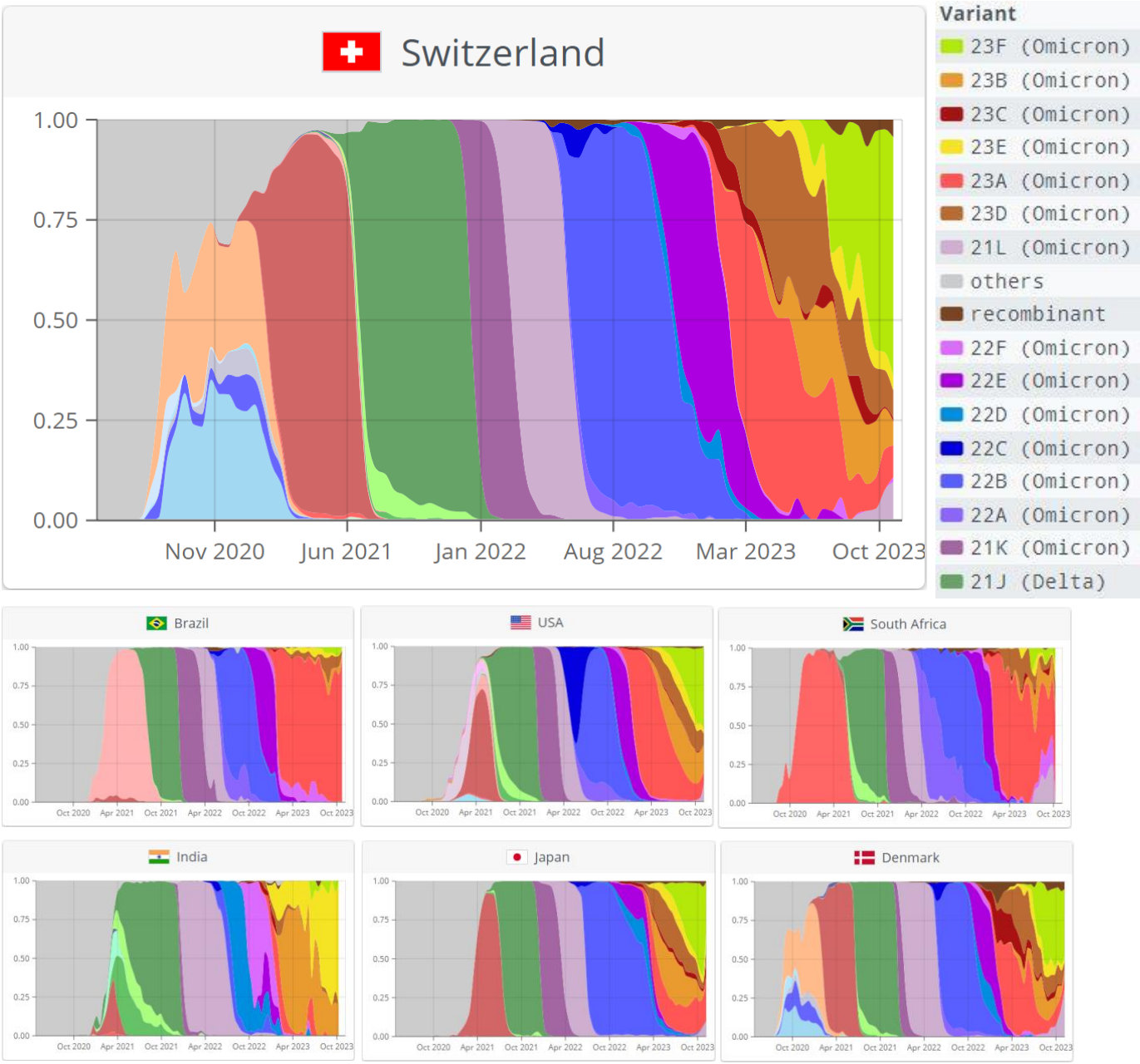


Figure 7: proportion of the total number of sequences (not cases), over time, that fall into defined variant groups, for Switzerland and other countries . Dynamic navigation is available at https://covariants.org/per-country. Nexstrain lineage correspondence with pango lineages are as follows: 21 J- B.1.617.2 (Delta); 21K- BA.1 (Omicron, as are all the following lineages); 21L- BA.2; 22C- BA.2.12.1; 22A- BA.4; 22B- BA.5; 22C- BA.2.12.2; 22D- BA.2.75; 22E- BQ.1 (a BA.5 sublineage); 22F- XBB (Omicron recombinant); 23A- XBB.1.5; 23B- XBB.1.16; 23C- CH.1.1 (a BA.2.75 sublineage); 23D- XBB.1.9; 22E- XBB.2.3; and 23F- EG.5.1 (an XBB sublineage). Note that the 21L variants progressively increased in proportion over the last month. BA.2.86 has not been given its own Nexstrain designation yet, and is still grouped with basal BA.2 in these graphs. Basal BA.2 is not resurging.

7. Surveillance of mutations associated with reduced available treatment efficacy

In late 2020, the first of many monoclonal antibody cocktails for treatment of Covid-19 became available. Since then, the virus has evolved rapidly, and one of the major effects of this has been an escape from neutralization by mAb cocktails (table 3).

mAb therapy	Alpha	Beta	Delta	BA.1	BA.2	BA.5	XBB.1
Bamlanivimab/etesevimab	1.3	990	1	980	744	588	>1,000
Casirivimab/imdevimab	0.9	1.6	1.3	>1'000	387	387	887
Sotrovimab	1.8	1	1.1	3.8	20	22	15
Tixagevimab/cilgavimab	0.8	1.7	1	63	8	25	>1'000

Table 3, fold change in nAb titers to mAb cocktails. Color coded by fold change of neutralizing antibody titer reduction: Green, <4; Yellow, < 16; Orange, <64; Red, ≥64. Values are those obtained from https://covdb.stanford.edu/susceptibility-data/table-mab-susc/, although results sometimes vary significantly from study to study.

As seen in table 3, to choose the best monoclonal antibody therapy, it is critical to know which variant is circulating in Switzerland. Early in the pandemic, when Beta achieved low level circulation outside of southern Africa, identifying the Beta lineage would indicate that administering bamlanivimab/ etesevimab would not neutralize the virus. As the pandemic progressed, more mAbs became available, although resistance was generally not a problem during the Delta wave. With the arrival of the Omicron waves (BA.1/2/5 and XBB.1*), it became important to know which variant was circulating to make the best choice between treatment with sotrovimab or tixagevimab/cilgavimab (Evusheld®). As more mAbs make it to the market, and as resistance develops in new variants, knowing which variants are circulating within Switzerland will continue to be important for patient care.

Resistance mutations to available monoclonal antibodies

AA position	World	Europe	Switzerland
Sotrovimab	(Spike mutations)		
337	0.02	0.01 (4)	0
340	0.04	0.06	0.21 (1)
356	1.21	1.66	2.48
371	92.98	93.1	100
377	0.01 (8)	0	0
449	0.01	0.01 (2)	0
476	0.04	0.02 (5)	0
494	1.54	2.11	2.69

Resistance also varies within a lineage, depending upon the presence of specific escape mutations. Often these mutations will convergently appear in multiple lineages. Therefore, monitoring for specific mutations, rather than more generally identifying which lineage a virus belongs to, is also important for managing this pandemic. Table 4 provides an example of such monitoring, displaying the prevalence of known escape mutations to sotrovimab in samples from September 2023.

Table 4: Frequency (%) of mutations at residues linked (by deep mutations scanning or other experimental results) to escape from sotrovimab, or Paxlovid® (5-fold cutoff), June 2023 (according to data as of 6 September, 2023). Numbers in parentheses denote the total number of sequences detected with a given mutation when it is <10. Note, both BA.5 and BA.2 (including recombinants such as XBB and XBB 1.5) contain the spike S371F mutation leading to partial sotrovimab resistance.*

Furthermore, such monitoring is essential for the detection of new lineages, which are believed to arise mainly from chronic infections in patients. Such chronic infections often appear in immunocompromised people, and thus in areas with either high rates of HIV infection (as is apparently the case for Omicron first identified in South Africa) or a large elderly population (as is apparently the case for Alpha, first spotted in the UK). Such chronic infections have also been found in Swiss patients. Indeed, this program identified a Swiss patient infected with a divergent Alpha sublineage in 2023, approximately 2 years after Alpha had stopped significant circulation in Switzerland. Such cases and precedent highlight the need to continue sequencing efforts in Switzerland.

8. Wastewater surveillance

The Swiss wastewater surveillance project, running since late 2020, is an extensive initiative encompassing numerous wastewater treatment plants (WWTPs) across Switzerland allowing for a comprehensive and geographically representative analysis of the introduction and spread of SARS-CoV-2 variants. Raw wastewater samples from WWTPs are collected multiple times per week under the coordination of Eawag. The sequencing and analysis of these samples, including detection and quantification of variants(https://cov-spectrum.org/stories/wastewater-in-switzerland), is done under the coordination of Prof Niko Beerenwinkel in collaboration with NEXUS Personalized Health Technologies, ETH Zurich. The program started in December 2020 for Lausanne and Zurich, and was extended in February 2021 to six WWTPs, and later further extended to 10 and 14 WWTPs. The treatment plants are chosen to include major cities, different linguistic groups and to cover a significant portion of the Swiss population (~25% of the Swiss population with the 14 WWTPs).

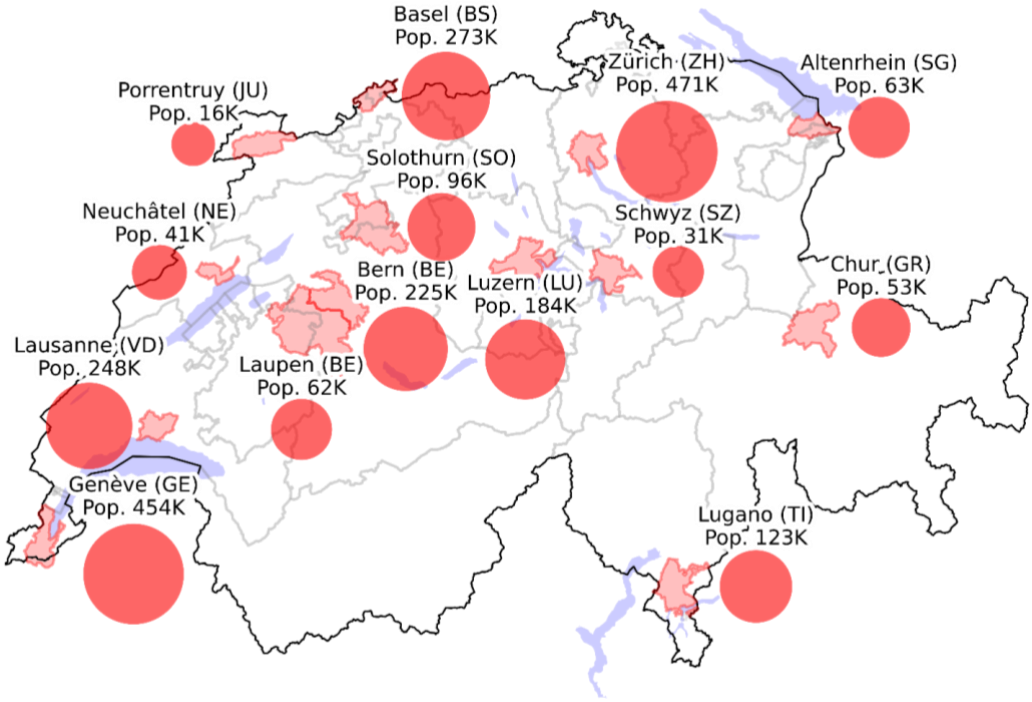


Figure 8: Map of the sampling scheme. The size of the discs are proportional to the population connected to the wastewater treatment plants. Pink shaded areas represent catchment areas (boundaries from 2017). A total of about 2.3 million people reside in catchment areas of the surveilled treatment plants. The population connected to the Vernier (GE) wastewater treatment plant also includes ~44,000 inhabitants from neighboring French communities.

The project has enabled early detection of the introduction of variants at pivotal moments in the pandemic, such as the replacement of Alpha by the Delta variant in 2021, the transition from Delta to Omicron towards the end of the same year, or more recently the introduction of the highly-mutated BA.2.86 which was detected in the wastewater one month before the first confirmed clinical case. The project generated quantitative assessments of the growth competition between variants, enabling the estimation of variant-specific fitness advantages informing on their epidemic potential. These modeling results have been used to provide short-term forecasts on the expected progression of the variant composition. Early estimation of the fitness advantage of variants has been crucial to inform about the possible threat on many occasions, notably in the time of the introduction of highly mutated variants such as BA.1, or more recently BA.2.86. Additionally, wastewater genomic surveillance is used to monitor for mutations linked to possible treatment escape from commonly prescribed drugs.

9. Immunological characterization

The goal in the Swiss national SARS-CoV-2 genomic and variants surveillance program was to do basic immunological characterization of emergent variants presenting significant sequence deviation in spike-coding region compared with previously prevalent strains and representing putative future variants of interest (VOI) or variants of concern (VOC).
It included monitoring of their sensitivity to neutralization by sera from previously infected or vaccinated individuals and by therapeutic / preventive monoclonal antibodies, some already FDA-approved and some in development. For this, their spike proteins (the main target of antibodies neutralization) were synthesized and analyzed through cell-based or cell-free assays. Of note, the cell-free surrogate neutralization assay also provides semi-quantitative information on the relative affinity of each spike variants for the ACE2 viral receptor, which likely plays an important role in viral infectivity and transmission. This analysis through a well-established and streamlined pipeline instantly provides essential information on the immunological characteristics of the variants circulating in Switzerland, allowing for immediate strategic adjustments.

Monitoring of the serological evolution of the swiss population

First analyses of sera from (re)infected cases: In a first round of tests in, samples were collected through a Geneva-based serological survey. Using sera from different recovered donors we could illustrate the heterogeneity in strength and breadth of the sera against various spike variants. Shortly following the documentation of re-infection cases worldwide, we could examine the serum of one such case collected in Geneva and show that neutralization activity can be relatively weak and narrow after a first COVID episode but it was immediately boosted in both strength and breadth by a second episode of infection (Figure 9).

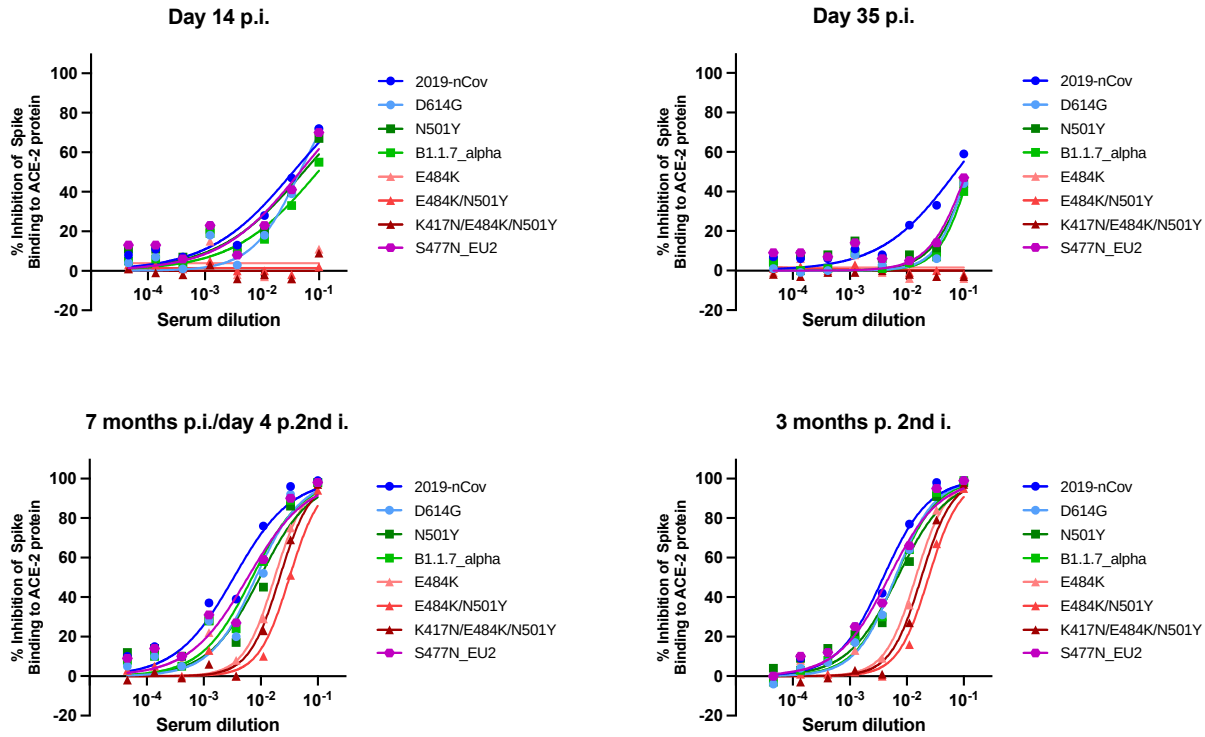


Figure 9. Neutralization activity against indicated SARS-CoV2 variants. Serum from a health care workers infected 7 months apart during the first and second Swiss waves was used. Samples correspond to 14 (top left) or 35 (top right) days after first infection and 4 days (bottom left) or 3 months (bottom right) after second infection.

Monitoring of the population immunity

Taking advantage of the ongoing serological monitoring of the population in the canton of Geneva, in November-December 2021 we expanded our analyses using sera from previously infected or vaccinated individuals. Neutralization titers of sera from vaccinated, convalescent, and convalescent & vaccinated were assessed against numerous Spike protein variants (Figure 10).
Our data revealed that the Beta and Delta strains were poorly neutralized after a single dose of vaccine. We also showed that the escape of the Delta variant could be attributed mainly to the L452R mutation. Furthermore, we showed neutralization titers were greatly improved by a second dose of vaccine for all tested Spikes variations (pre-Omicron).

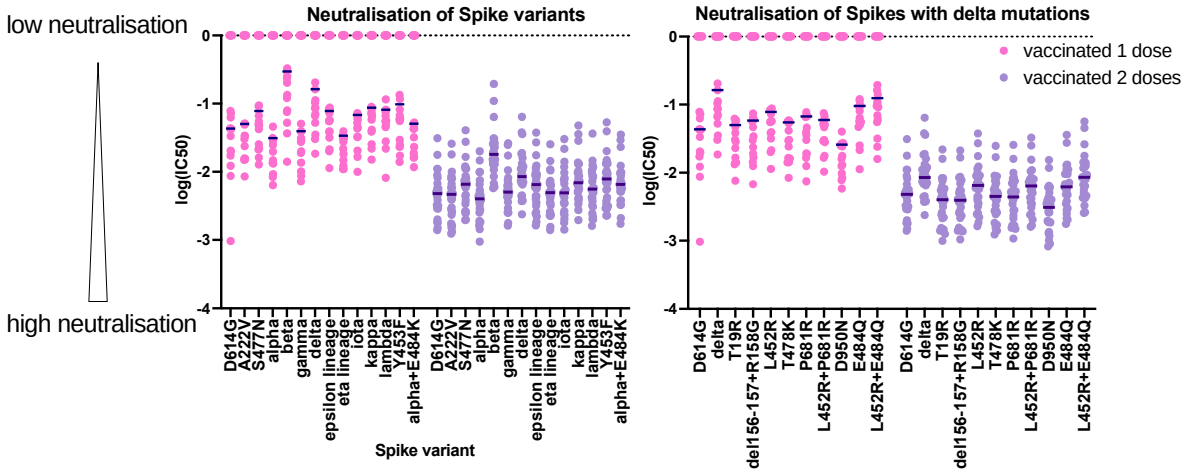


Figure 10: Comparison of nAbs titers for vaccinated versus infected people. The S[3]-ACE2 Luminex-based neutralization assay was used to determine the serum dilution giving 50% inhibition in neutralization (IC50). A higher IC50 dose corresponds to a lower serum dilution necessary to achieve the 50% inhibition of neutralization. Sera from people vaccinated either with only 1 dose (without previous known infection) or with 2 doses were compared. Spike variants from past or actual VOIs or VOCs or mutations found in B.1.617.2 were included in the assay. The Y453F was added as it was recurrently found in Mink-farm associated clusters.

Comparison of neutralizing antibody (nAbs) titers for vaccinated vs infected people

To provide useful information about the relative immune response following vaccination or infection (useful for informing decisions on Covid certificate policy, when relevant), we used a subset of sera collected within the same time frame after infection or vaccination. Before the emergence of Omicron, we found that vaccinated individuals had higher neutralization titers compared to infected individuals, especially against the Gamma and the Delta Spikes (Figure 11). A third group of people who were first infected and then received 1 dose of vaccine displayed on average higher titers of nAbs against all tested Spikes compared to “vaccinated only” people, indicating that “hybrid immunity” is likely the most protective of all. Notably, with most of the population having been infected at least once now, the majority of the Swiss population now has hybrid immunity.

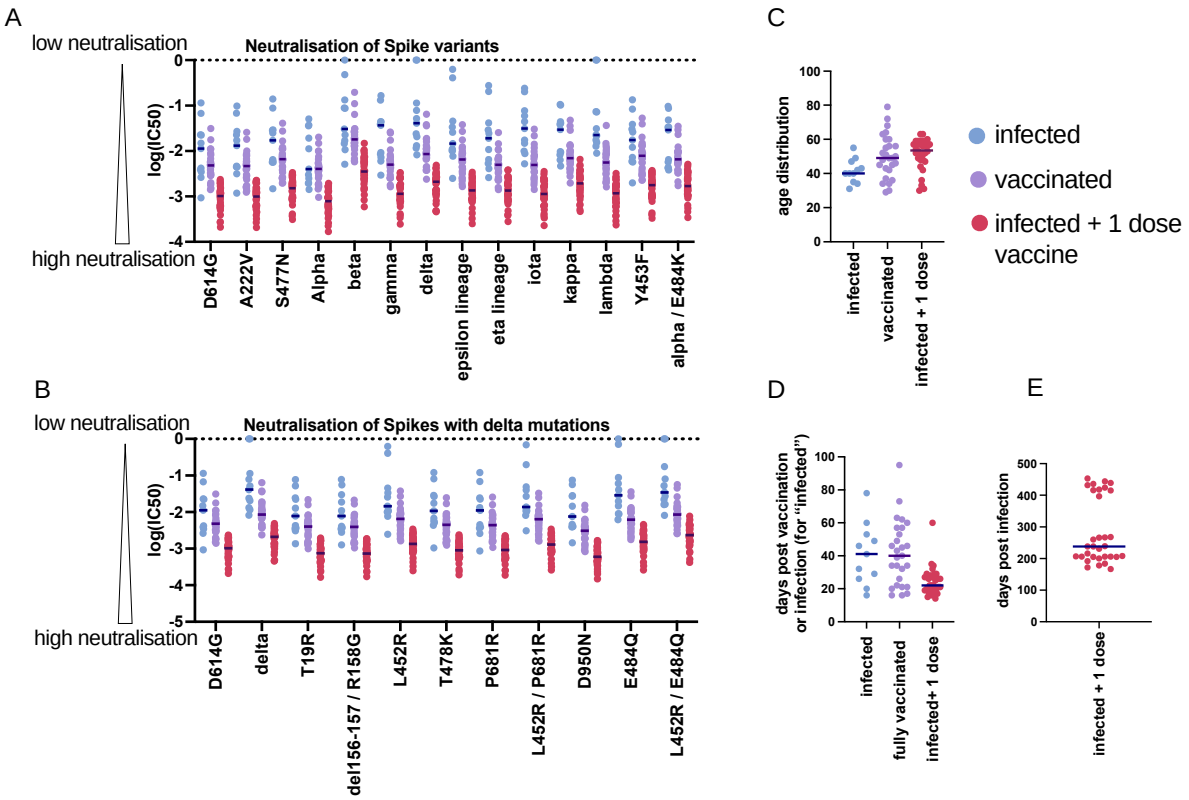


Figure 11: Comparison of nAbs titers for vaccinated versus infected people. (A-B): The S³-ACE2 Luminex-based neutralization assay was used to compare neutralization of the indicated Spike variants or mutations by sera from people either infected (n=11), fully vaccinated (n=27), or infected then vaccinated with a single dose of vaccine (n=32). Of note, infected individuals were all infected before March 2021, before the expansion of the Delta lineage. (C): Distribution by age of the different groups. (D): Time after infection, full vaccination or single vaccination for the different groups. (E): Time after infection for the group of people both infected and vaccinated with 1 dose of vaccine.

Comparison of nAbs titers after Moderna versus Pfizer-BioNTech vaccination

For public health purposes, it was important to determine if one vaccine gave superior results to another, and we had access to sera from individuals vaccinated with 2 doses of either with Moderna (n=8) or Pfizer-BioNTech (n=19) vaccines. Therefore, we ran our own analyses to compare them, and found (in line with reports from other countries) that nAbs titers against were similar in both cases (Figure 12).

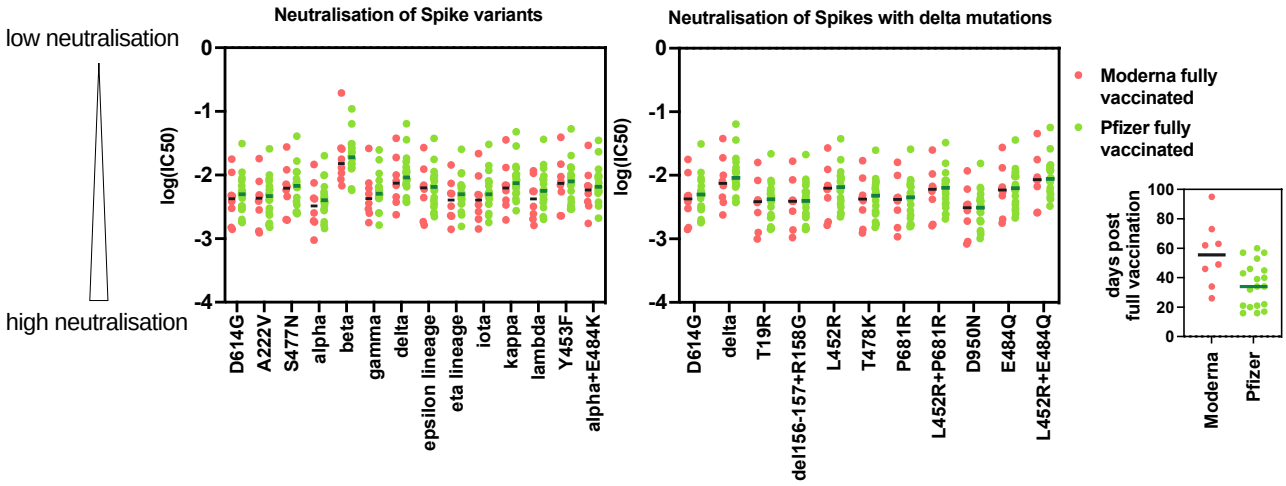


Figure 12: Neutralization titers obtained after Moderna versus Pfizer vaccinations. The S³-ACE2 Luminex-based neutralization assay was used to compare neutralization of the indicated Spike variants or mutations by sera from people vaccinated with 2 doses of either Moderna or Pfizer-BioNTech vaccines.

Heterogeneity in nAbs titers for Spike variants in the population

It was also important to determine how much protection varied within the population, to get a better idea of whether there would still be substantial vulnerable populations even after a successful vaccination campaign (or failing that, unchecked spread). We were able to group the sera from the population (n=151) in 3 classes depending on the anti-S serological titers determined by the standard procedure (Roche Elecsys anti-S): positive but low (anti-S titer<50 U/mL), medium (>50 U/mL, <2000 U/mL) and high (>2000 U/mL). In the pre-omicron era, neutralization of Spike variants with high anti-S titers sera was homogeneous in the tested population, with loss of efficiency only in the case of the Beta Spike (Figure 13). However, we noticed that results were markedly heterogeneous for sera with low or even medium anti-S titer, whether for neutralization of Beta, Eta, Lambda, Alpha+E484K or Delta Spike proteins. This trend likely continued with Omicron, and may explain the high rate of vaccine breakthrough infections.

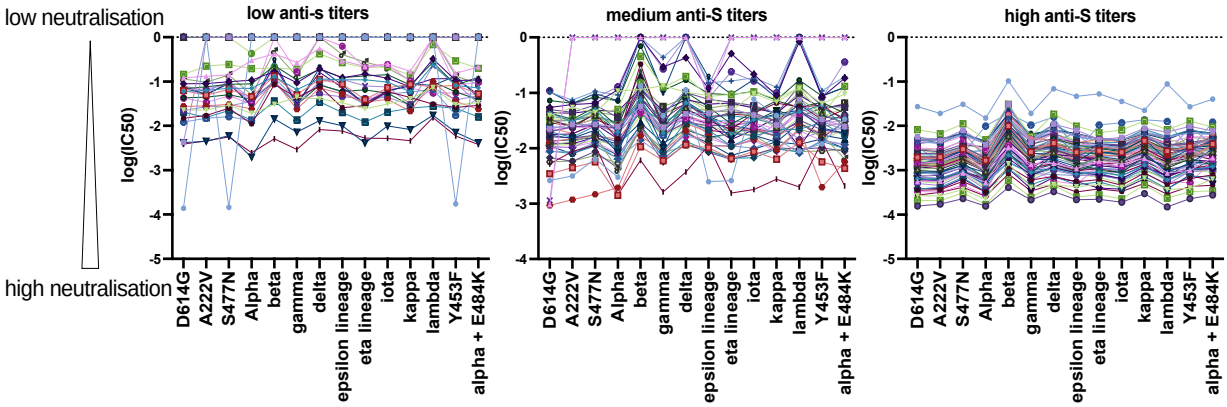
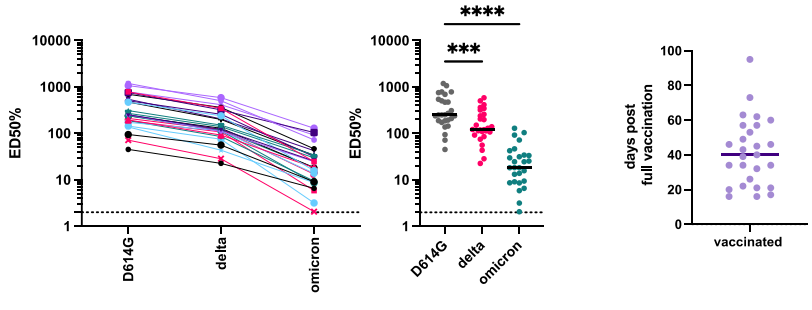


Figure 13: People with low anti-S response have heterogeneous nAbs titers. Sera from infected, vaccinated, infected then vaccinated people were classified in 3 groups depending on their anti-S serological status: low (n=30), medium (n=46) or high (n=75) anti-S. The log value of the serum dilution necessary to achieve 50% inhibition of neutralization for each individual and for each Spike variant is plotted.

Sensitivity of vaccinees to the omicron VOC

After Omicron emerged, we did our own analyses on its escape from nAbs. As published by few different groups at the same time, we could show that neutralizing activity of sera collected from Pfizer or Moderna vaccine recipients (sampled on average 41,5 days after the second dose administration) displayed a 10-fold reduced neutralizing activity against Omicron (Figure 14).



	D614G	delta	omicron
Mean	389.8	187.4	31.19

*Figure 14: Sensitivity to vaccinees sera is reduced for Omicron. Neutralizing activity of sera from 27 fully vaccinated people was assessed for D614G, Delta B.1.617.2 and Omicron Spike variants in the S3-ACE2 assay. The mean serum dilution needed to achieve 50% of neutralization (ED50%) is indicated in the table for each variant. **p< 0.01, ****p< 0.0001*

We also tested the effects of common single mutations, such as Omicron (B.1.529) with the R346K mutation and our results suggested that there should be no change in vaccines effectiveness against the B1.529 + R346K Omicron variants compared to the original Omicron strain (data not shown).
With the rapid growing number of re-infections worldwide, we decided to use both live replicating viruses and the S^3-ACE2 assay to assess the breath of protection of plasma from convalescent individuals infected with early-pandemic, Alpha, Beta, Gamma and Delta viruses or omicron viruses. We could show that the highest neutralization was obtained against homologous variants – with infection by a non-Omicron variant providing only low protection against Omicron (Figure 15). This data supports the idea that the best vaccine strategy matches the vaccine sequence to the currently circulating variants.

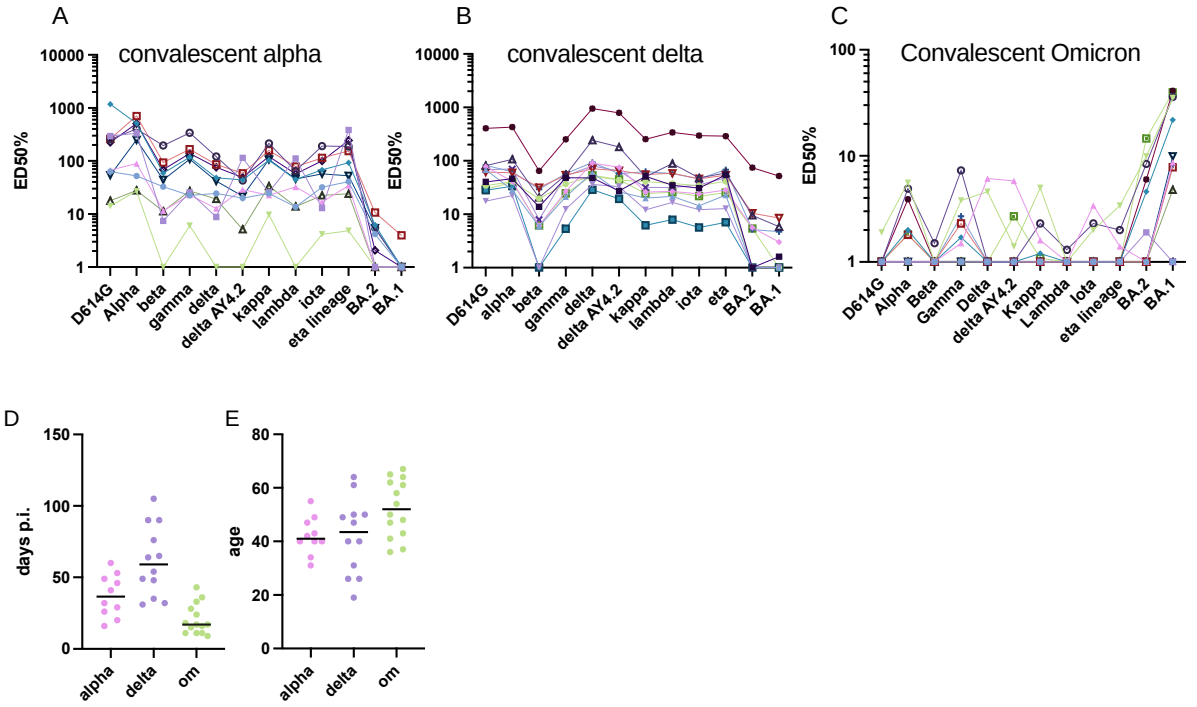


Figure 15: Sera from pre-omicron infections are poorly blocking omicron strain. Neutralizing activities of sera from convalescent people infected either with alpha (A), delta (B) or omicron(C) variants were assessed for their ability to neutralize D614G-ancestral or indicated Spike variants in the multiplex S^3-ACE2 assay. The mean serum dilution needed to achieve 50% neutralization inhibition (ED50%) is indicated for each variant. The time post infection (D) and age (E) distributions of the 3 different groups are indicated. Of note, individuals were all tested positive for total anti-RBD IgGs (Elecsys® Anti-SARS-CoV-2 S, Roche).

On a larger scale we could also contribute to the analysis of the immune landscape of the Geneva population by providing a snapshot of cross-variant neutralization capacity of the antibodies found in the population.

Assessment of the efficacy of monoclonal antibodies

With the successive emergence of VOCs with immune escape mutations, we probed the efficacy of monoclonal antibodies, as such results were directly applicable to patient treatment. We conducted tests on a variety of antibodies. Efficacy of these antibodies or cocktails of antibodies was tested on Spikes corresponding to the diverse variants emerging during the course of the pandemic.
The results showed that some of the VOCs and notably Omicron, have evolved to escape neutralization by therapeutic monoclonal antibodies clinically approved for prophylaxis or treatment, with the recently emerged XBB lineage being completely resistant to these antibodies (Figure 16). In accordance with results published by different groups, these results show the urgent need to develop broader spectrum antibodies to treat vulnerable patients.

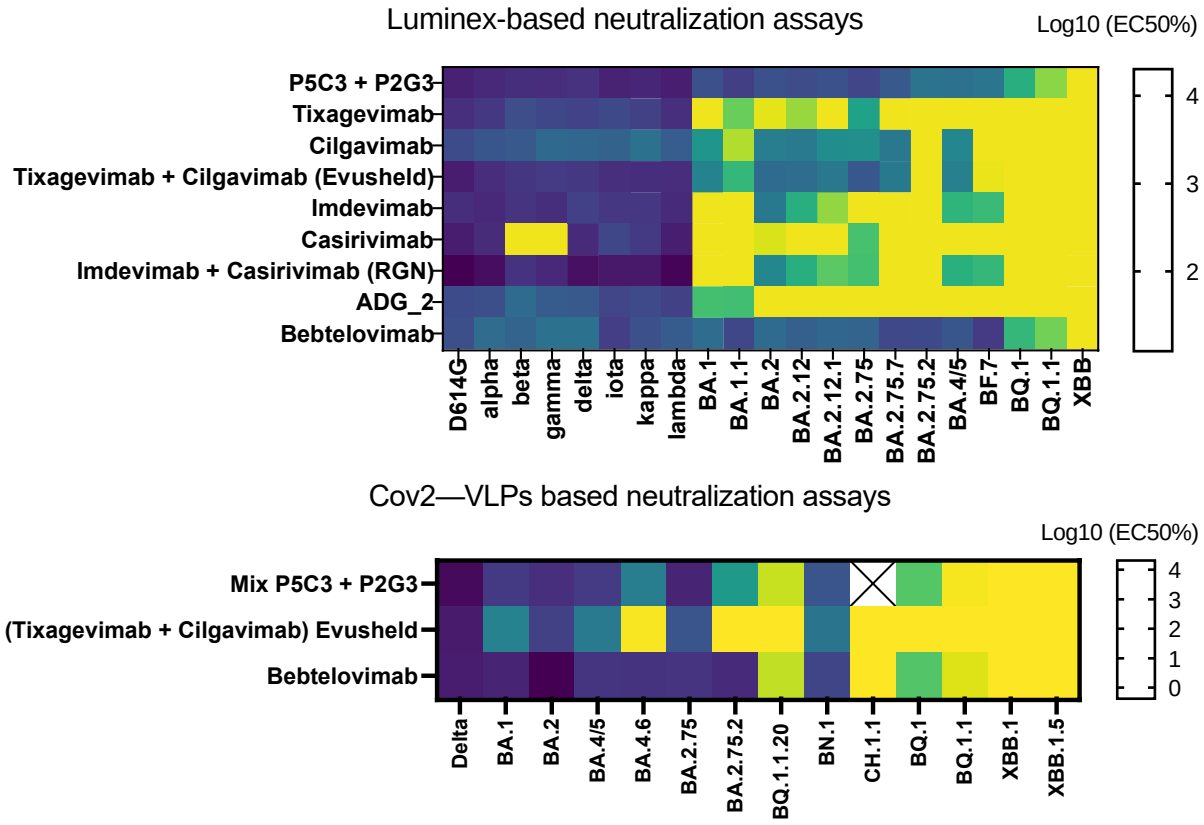


Figure 16: Clinically-approved monoclonal antibodies lost their efficacies to control recent Omicron sublineages. Indicated Spikes were used to test the neutralization potential of indicated monoclonal antibodies with the S[3]-ACE2 (A) or the SARS-Cov2-VLPs-based (B) neutralization assays.

10. Public health impact of the program

The goal of this program was to provide meaningful and actionable data, so that appropriate informed decisions could be taken. Over the last 3 years, the genomic surveillance program has given us a picture of the epidemiology of circulating variants in Switzerland. The data produced and the work done for this program has made contributions to the pandemic response, not only at the local level, but also at the international level.

The international pandemic response requires coordination of centers in many countries. Identification of a rapidly growing variant in only one region is not very informative to the international community. Indeed, multiple times we saw local variants that appeared concerning, but failed to be competitive outside of their local situation (such as the Beta and Gamma variants). Rapid and independent confirmation of a variant's spread in other countries is required for identifying new variants of global concern. In this regard, the Swiss surveillance program has made important contributions to the world's understanding of the variant dynamics. In particular, Switzerland was among the first to confirm detection and spread of the BA.2.86 variant (after its initial identification in Israel), through wastewater sequencing. This rapid sharing of data allowed the international community to quickly recognize the potential of the BA.2.86 lineage, which is now dominant in many regions across the world, and begin prioritizing the study of it.

While wastewater sequencing was crucial in the early detecting of BA.2.86, clinical sampling allows for full length sequences, greatly aiding the surveillance and identification of new variants and new mutations leading to increased fitness or immune escape. Indeed, BA.2.86 and the currently dominant JN.1 (BA.2.86 sublineage) were first identified in clinical samples, and this identification was then used to guide the wastewater search.

This program has served as the nucleus for many productive national and international collaborations. In particular, it played a key role in obtaining clinical samples that were used in collaborations with FIND to evaluate various rapid diagnostic tests. Results were quickly shared with Swiss authorities, the WHO, and then published in internationally read journals, thus helping shape testing policies at both the national and international levels. Regular *in vitro* evaluations of the performance of rapid tests continue to be performed by the Geneva Center for Emerging Viral Disease, to ensure the sensitivity of the tests remains appropriate despite the accumulating mutations.

Another such benefit has been the growth of the network sharing viruses for the WHO biohub located in Spiez, which will benefit research into infectious diseases and contribute more broadly (beyond just Covid-19) to public health in the future. By quickly identifying specific variants from clinical samples through this program, viral isolates have been growth by the Geneva Center for Emerging Viral Diseases and shared with the biohub, to serve the international effort to characterize SARS-CoV-2 variants.

At the local level, Switzerland's unique situation, allows us to have a dense, granular, and dynamic surveillance. By combining genomic surveillance data in an existing database such as our sentinella or CH-SUR databases, we have had access to critical information, providing the raw data for proper, useful, and actionable analysis. This data helped to highlight changes in transmission, as well as treatment and vaccine escape. In particular, it allowed us to highlight differences with other countries (such as the limited spread of basal BA.2.75, or BA.2.12.1 – in contrast to the situation in the USA) and have an overview tailored to the Swiss situation.

These differences highlight the value of having our own surveillance program rather than relying on the surveillance programs of other countries : i) these countries data does not always reflect the situation in Switzerland, ii) such data is more delayed than data produced locally within Switzerland, iii) such programs may end according to the self-interests of other countries, which may be significantly different from Swiss interests .

At the national level, the genomic surveillance program allowed (and still do) for the determination of the best available treatment options for infected patients – particularly with respect to monoclonal antibodies

administered to seronegative patients hospitalized with severe disease, and to outpatients to limit the progression to severe disease. While this research was also valuable at the international level, and international research was of value to use in Switzerland, we note that the mAbs approved and available differ from country to county, and this program provided results tailored for Switzerland.

More generally, this program had brought together partners all across Switzerland, and created a network of laboratories and sequencing platforms connected together, thus creating a strong network. Such connections between university hospital laboratories and the private sector is unprecedented, and have been proven to be fruitful during the pandemic.

11. Perspectives

In line with the WHO and ECDC recommendations, surveillance will continue in 2024, both in wastewater and in clinical samples. The virus continues to evolve and evade immune responses, which may impact therapeutics used to treat vulnerable patients as well as vaccines used to protect larger portions of the population that are at risk. Therefore, surveillance should be able to detect and respond as the virus changes.

The newly built network of laboratories created for this program, which varied in size during the different phases of the surveillance, may be (re)enlarged and activated in case of a new epidemic/pandemic. Then, much of infrastructure in place can be used for surveillance of other pathogens, and/or be used to enlarge the current existing surveillance on respiratory pathogens.

Acknowledgements:

https://bsse.ethz.ch/cevo/research/sars-cov-2/swiss-sars-cov-2-sequencing-consortium.html

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Appendix:

SARS-CoV-2 epidemiology in Switzerland:
We used publicly available data on COVID-19 as reported by FOPH (https://www.covid19.admin.ch) and sequence data submitted to GISAID to provide a summary of the SARS-CoV-2 epidemiology in Switzerland.

Phase	HUG	CHUV	ICH-VS	IFIK	UZH IMV	USB	EOC	Diana-labs	ETH / Viollier	Labor-team W	Risch	St-Gallen	Synlab	SRO	Biolytix	All
1	11695	3631	3065	5191	8719	6034	3587	3283	9802	4549	2685	2875	366	1922	67	67471
2	2566	1291	733	1208	2548	1368	743	729	2924	716	1849	-	-	359	-	17034
3	812	777	387	402	547	608	451	-	-	-	-	-	-	-	-	3984
Total	15073	5699	4185	6801	11814	8010	4781	4012	12726	5265	4534	2875	366	2281	67	88489

Supplementary Table 1: number of sequences submitted to GISAID by each laboratory during each of the phases, as of October 31st 2023.

MUTATIONS
D614G + L5F
D614G + L18F
D614G + del69-70
D614G + D80Y
D614G + W152R
D614G + M153T
D614G + M153I
A222V-EU1
D614G + K417N
D614G + D80A / K417N
D614G + N439K
D614G + del69-70 / N439K
D614G + Y453F
D614G + del69-70 / Y453F
D614G + S459Y
S477N_EU2
D614G + S477R
D614G + E484K
D614G + E484K/ N501Y
D614G + K417N / E484K / N501Y
D614G + E484Q
D614G + L452R /E484Q
D614G + F486L
D614G + N501T
D614G + N501Y
D614G + del69-70 / N501Y / P681H
D614G + del69-70 / del144 / N501Y / A570D / P681H
D614G
D614G + P681H
D614G + P681R
D614G + A701V
del69-70 / del144/ E484K/ N501Y / A570D / D614G / P681H / T716I / S982A / D1118H
D80A / D215G / del242-244 / R246I / K417N / E484K / N501Y / D614G / A701V
T20N / P26S / D138Y / R190S / K417T / E484K / N501Y / D614G / H655Y / T1027I / V1176F
L18F / T20N / P26S /D138Y / R190S / K417T / E484K / N501Y / D614G
H66D / G142V / del144 / D614G / G669S / N1187D
H66D / G142V / del144 / D215G / V483A / D614G / H655Y / G669S / Q949R / N1187D
T95I / D253G / D614G / A701V
D614G + E154K
D614G + Q1071H
D614G + T19R
D614G + del156-157 / R158G
D614G + L452R / P681R
D614G + T478K
D614G + D950N

Supplementary Table 2: Spike protein mutants synthesized for pseudotyped lentivector-based (LV) or cell-free-based (Protein) neutralization assays. Mutations are depicted using single letter amino acid code.

LINEAGES		LINEAGES
D614G B.1		Omicron CH.1.1
Alpha B.1.1.7		Omicron BA.4 and BA.5
Beta B.1.351		Omicron BF.7
Gamma P.1		Omicron BQ.1
delta B.1.617.2		Omicron BQ.1.1
delta AY.4.2		Omicron XBB.1/XBB.1.9
Kappa B.1.617.1		Omicron XBB.1.5/XBB.1.9.1
Lambda C.37		Omicron XBB.1.16
Iota B.1.526		Omicron XBB.1.16.1
Eta B.1.525		Omicron XBB.2.3
Epsilon B.1.427		Omicron EG.1
Omicron BA.1		Omicron EG.5
Omicron BA.1.1		Omicron EG.5.1
Omicron BA.2		Omicron GK.1
Omicron BA.2.12		Omicron GK.2
Omicron BA.2.12.1		Omicron BA.2.86
Omicron BA.2.75		Omicron FL1.5.1
Omicron BA.2.75.7		Omicron JN.1
Omicron BA.2.75.2		Omicron DV.7

Supplementary Table 3: Spike protein VOCs or VOIs synthesized for pseudotyped lentivector-based (LV) or cell-free-based (Protein) neutralization assays. Variant lineages are depicted using Pango lineage nomenclature.

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Complete network of participating laboratories over the course of the program (2021-present)

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- IFIK UNIBE
- UZH
- EOC Bellinzona
- Hopitaux du Valais – Institut Central
- Viollier laboratories
- Laboratory Risch
- Zlsmg St-Gallen
- Dianalabs (Genesupport)
- Laboratoire Bioanalytica
- Labor Team W AG
- Synlab CH-I
- Spital Region Oberaargau