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# Swiss national SARS-CoV-2 genomic and variants surveillance program: report of the month of Janurary

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## 1. Summary

In January, COVID-19 cases numbers continued to dramatically increase in Switzerland, largely driven by the B.1.1-529 (Omicron) BA.1 variant.

In the midst of this steep increase in case numbers, approximately 1.3% of the total number of cases identified in Switzerland in January were sequenced by the Surveillance program, yielding over 11,100 sequences.

Delta's prevalence continued to decline, although it continued to circulate. Unsurprisingly, B.1.1.529 (Omicron or its sub-lineages) was also the most frequent variant detected by sequencing and in wastewater during the month of January. Circulation of all variants other than Omicron and Delta was essentially nonexistent in January.

Omicron has already split into 3 sub-lineages: BA.1-3. BA.1 is currently the most common variant in Switzerland and worldwide, but BA.2 appears to be displacing BA.1 worldwide at varying rates. While it is still only rarely detected in CH, its frequency is increasing. All sub-lineages are still detected by RT-PCR tests, but S-gene target failure in some assays can be used as a proxy for BA.1 and BA.3, as previously seen with VOC Alpha, and is useful for tracking the rise of BA.2.

Notably, BA.1 and BA.2 are highly resistant to Casirivimab and Imdevimab. While Sotrovimab retains efficacy against BA.1, its efficacy against BA.2 is unclear and *in vitro* data suggests reduced efficacy – as a result there are no approved treatments in CH that are unambiguously effective against BA.2. No additional diagnostic or treatment issues were noted in January.

Omicron is apparently milder than Delta. It is unclear how much this is related to many of its infections being reinfections or vaccine breakthrough infection. Lines of evidence from *in vitro* and animal studies do support the idea that the virus is intrinsically milder. Concerningly, similar *in vitro* and animal studies suggest that BA.2 is more severe than BA.1 (but milder than Delta), but this has not been observed at the clinical level. Note that milder does not mean mild, and it is still capable of causing severe disease and death.

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

The overall goal of the program is to provide epidemiological trends and to highlight meaningful observations.

Because greater transmissibility and/or immune escape potential of the different VOCs and VOIs can result in new surges in COVID-19 numbers despite the vaccination campaign, this program aims to closely monitor each variant displaying mutations known to be linked with either increased transmissibility or immune escape potential.

Currently, 13 diagnostic laboratories are participating in the program, including university hospital centres in Switzerland (Geneva, Lausanne, Bern, Basel, Zurich, St-Gall, Ticino), in addition to 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), and 3 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).

Processed sequencing data are shared openly within 14 days from positive PCR result through the GISAID platform (https://www.gisaid.org) and eventually through the Swiss Pathogen Surveillance Platform (SPSP). 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 National COVID-19 Science Task Force and the Swiss Institute of Bioinformatics (SIB).

In order to complement the genomic surveillance based on patient samples, sequencing of SARS-CoV-2 in wastewater samples is also performed, initially funded for 6 months. Samples are collected daily in six wastewater treatment plants (WWTP), under the coordination of Eawag. Up to 50 samples per week over the first 26 weeks have been performed. The sequencing and analysis of these samples, including detection of variants, is done under the coordination of Prof Niko Beerenwinkel. It started in December 2020 for Lausanne and Zurich, and in February 2021 for all six WWTP (https://bsse.ethz.ch/cbg/research/computational-virology/sarscov2-variants-wastewater-surveillance.html). The analysis of wastewater samples is envisaged to run until the end of the surveillance program on 31.3.2022.

Immunological characterization of the variants within the surveillance program is coordinated by Professor Trono's team at EPFL.

This report has been produced by Erik Boehm, Pauline Vetter, Marc Friedli, Samuel Cordey, Richard Neher, Christian Althaus, Martina Reichmuth, Cornelius Römer, Niko Beerenwinkel, David Dreifuss, Chaoran Chen, Tanja Stadler, Louis Du Plessis, Priscilla Turelli, Didier Trono, Emma Hodcroft, Nadja Wipf, Damir Perisa, 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.

This report covers the period of January 3 to January 30, 2022 (weeks 1, 2, 3, 4). All data presented in this report are based on the sampling date.

## 3. Variants of concern (VOCs), variant of interest (VOI) and other surveilled variants: brief summary and special focus

Five variants and their sub-lineages are considered VOCs by the WHO, B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta), and B.1.1.529 (Omicron). While still a VOC for WHO, the European Centre for Disease Prevention and Control de-escalated Alpha as a VOC.

*Omicron*

A new B.1.1.529 VOC (Omicron), which spread worldwide, was first identified in southern Africa during November 2021. It carries an unprecedented number of mutations on the genome (>50), with most being on the gene coding for the Spike protein (>30) and in particular within the receptor binding domain (15). These mutations are associated with both immune escape and/or increased transmissibility, conferring this variant a growth advantage. It has already split into 3 sublineages: BA.1-3, with BA.1 being, by far, the most common variant, followed by BA.2. BA.1 has established itself in Switzerland, and became the dominant lineage in Switzerland by the end of December 2021. BA.2 has a unique set of N-terminal Spike mutations, which are less numerous than in BA.1; it retains the mutations within the RBD. BA.2 also has mutations that alter the glycosylation (affecting immunogenicity) as well as the furin cleavage site. BA.3 appears to be more closely related to BA.2 than BA.1. BA.2 and BA.3 are currently only rarely found in CH, but BA.2 is increasing in prevalence and there is a strong signal that BA.2 will outcompete BA.1, as it has in some locations (Denmark, India).

*Detection*

All sub-lineages are still detected by RT-PCR tests, but BA.1 and BA.3 (but not BA.2) exhibit S-gene target failure with some assays that can be used as a proxy prior to sequencing, as seen with VOC Alpha (and due to the same deletion as found in Alpha). Due to the dominance of BA.1 within Switzerland, S-gene target failure is currently a good proxy for Omicron infection, but this may change in time. All Omicron variants contain deletions in the N-gene that can result in N-gene dropout in certain PCR tests, but these tests are not used in Switzerland. Antigenic tests are still able to detect this variant.

*Immune escape*

Extensive data now demonstrates that BA.1 is able to evade neutralizing antibodies (nAbs) raised against previous variants or after 2 doses of vaccine. Early data indicates that BA.2 displays equal or greater evasion of nAbs raised against previous variants. Notably, all Omicron sublineages display complete escape from combination of casirivimab/imdevimab (REGN-CoV2), one of the monoclonal antibody treatments used in Switzerland. Sotrovimab is currently the only antibody available in Switzerland that retains substantial neutralizing activity against BA.1. According to *in vitro* data, BA.2 is more resistant than BA.1 and ancestral variants to Sotrovimab (4-6 fold and 16-27 fold reductions in neutralizing titers, respectively). Importantly, this resistance does not amount to essentially complete escape as in the case of casirivimab/imdevimab, and Sotrovimab can still neutralize BA.2 at higher concentrations. The clinical relevance is thus unclear at the moment. While Omicron largely escapes humoral immunity, cell mediated immunity remains mostly intact.

A 3$^{rd}$ vaccine dose or a combination of previous infection and 2 vaccine doses has been shown to retain moderate neutralization of Omicron. In the community setting, this moderately effective humoral response after a 3$^{rd}$ dose and the retained cellular response translates to moderate (>50%) vaccine effectiveness against symptomatic infection, high effectiveness against severe outcomes, and very high efficacy at preventing hospitalization and death.

*Severity*

Data on severity is mainly available for BA.1. This assessment is complicated by substantial population level immunity world-wide, having continually grown since the start of the pandemic through vaccination or exposure. Reinfections/vaccine breakthrough infections are over-represented in new Omicron cases. To date, no study assessing hospitalization and ICU admission rates has properly controlled for pre-existing immunity through serology studies. Despite this, studies using animal models and cell culture

support the idea that BA.1 causes intrinsically milder disease. Unfortunately, animal and in vitro studies also suggest that BA.2 is more severe than BA.1: infected hamsters lose significantly more weight, viral titers are higher, more syncytia are formed by infected cells, and more pneumocytes are recruited in lung tissue. In contrast, preliminary data from South Africa, using S gene dropout as a proxy, suggest no difference in clinical severity between the two sublineages. Similar data from Denmark also suggests no significant difference in severity between BA.1 and BA.2.

*The Delta VOC*

Delta was still circulating at significant levels in Switzerland and much of the world during early January. Its progressive replacement by Omicron continues, and it was only rarely detected at the end of January.

*Therapeutic intervention effectiveness*

Numerous mutations have been reported to substantially reduce the therapeutic effectiveness of mAbs currently used to treat COVID-19, as well as those under development (Table 1). Notably, the Delta variant retained susceptibility to all mAbs approved for use in Switzerland, while Omicron BA.1 escapes all except Sotrovimab. BA.2 is already known in vitro to substantially escape neutralization by Sotrovimab(16-27 fold reduction), and further mutations may the *in vitro* neutralizing effect of the Sotrovimab completely. Mutations known to do this will thus be closely followed (Table 1, and section 7).

| AA position | World | Europe | Switzerland | Mutations |
|---|---|---|---|---|
| 337 | 31 | 21 | 4 | R/L/H/T |
| 340 | 71 | 44 | 8 | K/A/G |
| 356 | 24 | 15 | 1 | T |

*Table 1: Positions where mutations are known to result in escape from sotrovimab, and their prevalence, and the specific amino acid mutations known to result in escape*

In addition to mAbs, there are a number of other antiviral treatments under development, such as 3CL like protease inhibitors like Paxlovid® (PF-07321332) or RNA nucleotide analogues (which interfere with replication of the viral genome such as Molnupiravir). No data is available regarding mutations enabling escape from these proteases. In contrast, serial passage of virus in the presence of Molnupiravir led to resistance to Molnupiravir at the cost of significantly reduced overall viral fitness. As such mutations are detrimental when Molnupiravir is not present, limited use is unlikely to lead to resistant strains. Preliminary data confirms that Molnupiravir, Paxlovid, and Remdesivir all retain full *in vitro* efficacy again Omicron.

The circulation of specific mutations leading to decreased effectiveness of known therapeutics available for clinical use in Switzerland will be surveilled (see Section 6 below).

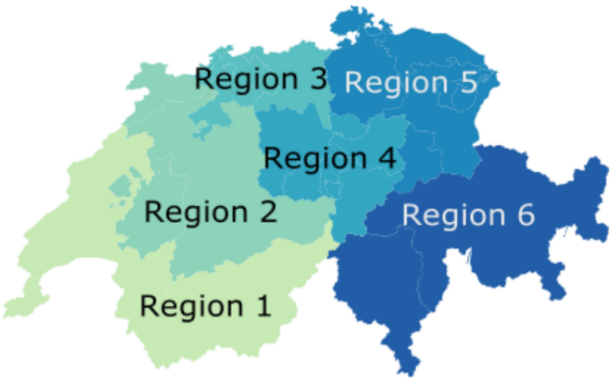
## 4. Epidemiology in Switzerland and number and origin of sequences produced through the program during the surveilled period

Data in this report comes 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).

General caveat: the numbers and denominators are fluid and variable over time; and are subject to change depending notably on the different databases used, and variable declaration delays. All data generated by this program is also submitted to SPSP.

The number and origin of sequences submitted to GISAID by each laboratory during January and February, 2021, prior to the start of the surveillance program can be found in the first report covering the months of March and April 2021.

Data will be presented here by regions, using the same region definitions that are used for the influenza sentinel surveillance system in Switzerland. Data 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

### Number of cases processed by the laboratories participating in the surveillance program

During January, the FOPH reported a total of 864,898 confirmed SARS-CoV-2 cases in Switzerland, representing a substantial increase from December. Supplementary Table 1 provides an overview of the number and incidence of confirmed cases, the effective reproduction number $R_e$, the number and incidence of tests, test positivity, the number and proportion of sequenced samples, and the number and proportion of VOCs by canton, region and for Switzerland overall.

As of the writing of this report, the laboratories participating in this program reported 323,017 positive tests during the surveilled program, which represents over 37% (as it did the previous months) of the total number of cases reported in Switzerland (including both PCR and antigen-based tests). Because of reporting delays, this number may be underestimated. Detailed data regarding the total number of tests performed each week by the laboratories participating in the surveillance program (including negative and positive tests numbers, and the number of the positive tests that have been sequenced) are available in appendix Table 3.

### Number of declared SARS-CoV-2 sequences produced through the surveillance program (presented by submission date, further declarations are still ongoing)

A total of over 11,100 SARS-CoV-2 sequences have been declared to have been submitted to GISAID during this period. There are 13,420 sequences are available for this period on GISAID as of 23 Feb 2022, and the difference may be explained by reporting delays.

This represents around 1.3% of all cases detected in Switzerland during the surveilled period (see Supplementary Table 2 and 3 in the Appendix for details). Of note, this number includes sequences from samples received from other laboratories at the request of the Cantonal physician teams.

Table 2 shows the number of sequences successfully submitted to GISAID through the surveillance program during the surveilled period by calendar week (data is incomplete).

| Week | Date | Number of sequences declared and successfully submitted to GISAID during the surveilled period, by all laboratories in the program |
|---|---|---|
| 1 | Jan 3 to Jan 9 | 2 916 |
| 2 | Jan 10 to Jan 16 | 3 009 |
| 3 | Jan 17 to Jan 23 | 2 467 |
| 4 | Jan 24 to Jan 30 | 2 714 |
| | **Total** | 11 106 |

*Table 2: number of sequences submitted to GISAID through the surveillance program. Note these data are not by sampling date but rather by submission to GISAID date. Data are incomplete due to late reporting by one laboratory*

The total number of SARS-CoV-2 sequences declared and submitted to GISAID by each laboratory during the month of November is available in Supplementary Table 3 in the appendix.

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

As shown in Figure 1, the total number of SARS-CoV-2 sequences submitted per week generally increased or remained stable through January (weeks 1-5), while the fraction sequenced continued to drop, reflecting the increase in cases within Switzerland in this period. Since the beginning of this program, almost all of the sequences available in GISAID (green curve) and those on which the surveillance is conducted, come from the national surveillance program.

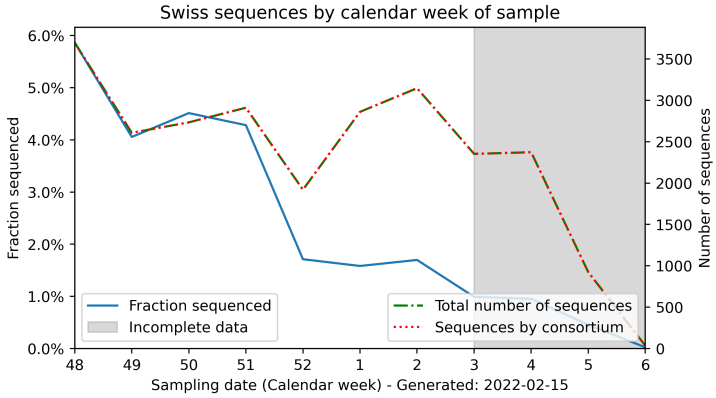



*Figure 1: Number of SARS-CoV-2 sequences available for Switzerland (total available Swiss sequences in GISAID in green, Swiss sequences submitted through the program in dotted orange) and fraction of the total number of positive cases declared to the FOPH that have been sequenced (blue curve).*

During the surveilled period, the total proportion of positive sequenced cases remained well below the 10% aim of the program due to high case numbers, despite relatively constant sequencing volume. The absolute number of sequences generated remains high, and includes sentinella sites with hospitalized patients; thus it should be adequate for surveillance.

Figure 2 displays the number and fraction of SARS-CoV-2 cases sequenced for each Swiss region. Regions 4 and 6 continued to have the lowest total number of sequences, while Region 4 continued to have the lowest fraction of cases sequenced. Notably, Region 6 actually increased its fraction sequenced during this period.

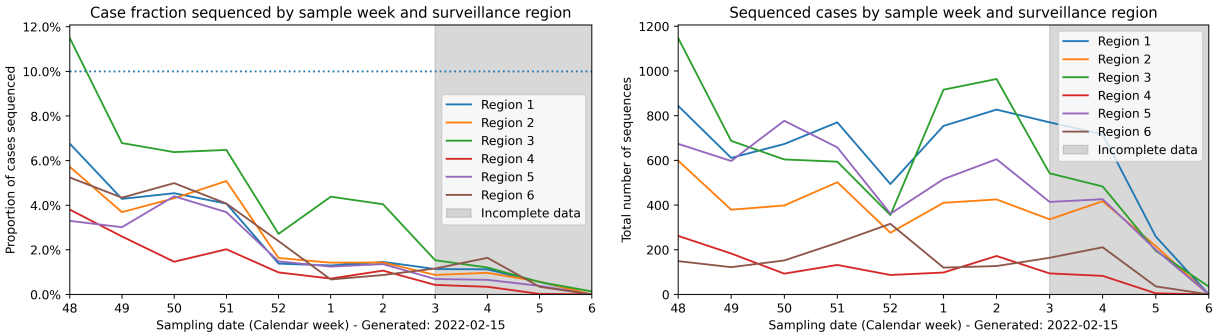



*Figure 2: Sequencing coverage among the different Swiss regions per week, presented by fraction of cases sequenced (left) and by number of sequences (right).*

## 5. Variants circulating in Switzerland since January 2021, with a focus on the surveilled period

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). Those results are based on the total number of sequences submitted to GISAID over the time period for Switzerland. Those data mainly, but not exclusively, come from the national genomic surveillance program since its beginning (see Figure 1).

Omicron sublineage BA.1 was the most commonly retrieved lineages early in January, followed by Delta and BA.2 (Figures 3-5, Table 3). Curiously, 1 Alpha sequence was identified, associated with a chronic infection dating back to early 2021.

| Region | Alpha | Delta | Omicron (BA.1) | Omicron (BA.2) | sequences | cases | % sequenced |
|---|---|---|---|---|---|---|---|
| All | 1 | 705 | 10360 | 199 | 11272 | 864898 | 1.3% |
| 1 | 1 | 178 | 3100 | 30 | 3310 | 249577 | 1.3% |
| 2 | 0 | 124 | 1483 | 46 | 1653 | 141786 | 1.2% |
| 3 | 0 | 198 | 2678 | 42 | 2922 | 121687 | 2.4% |
| 4 | 0 | 29 | 448 | 21 | 498 | 77373 | 0.6% |
| 5 | 0 | 129 | 1860 | 48 | 2038 | 213691 | 1.0% |
| 6 | 0 | 32 | 651 | 10 | 694 | 60784 | 1.1% |

*Table 3: number of sequences corresponding to selected variants in each region of Switzerland from 6 December 2021 to 2 January 2022, according to data received by January 21, 2022. Sequences with poor coverage where lineages could not be assigned are excluded.*

BA.2 overtook Delta by the end of January as the 2nd most common sequence in Switzerland, and appears likely to displace BA.1 (Figure 6).

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.

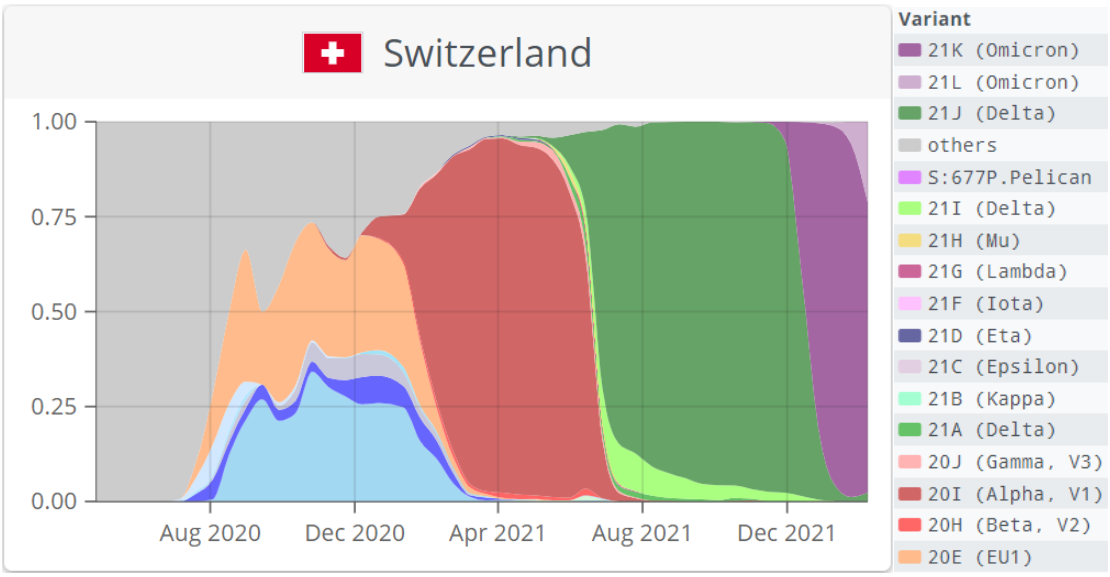



*Figure 4: proportion of the total number of sequences (not cases), over time, that fall into defined variant groups, for Switzerland. Screenshot from CoVariants website. Dynamic navigation is available at [https://covariants.org/per-country](https://covariants.org/per-country). Dark green indicates the currently dominant B.1.617.2 (Delta) lineage or its sub-lineages. Dark Red indicates B.1.1.7 (Alpha), the previously dominant lineage in Switzerland. Purple indicates.1.1.529 (Omicron), Light purple indicates Omicron sublineage BA.2, with 232 sequences detected in CH in in the last 2 weeks of January (24 Jan-6 February) 2022, amounting to 6% of all cases.*

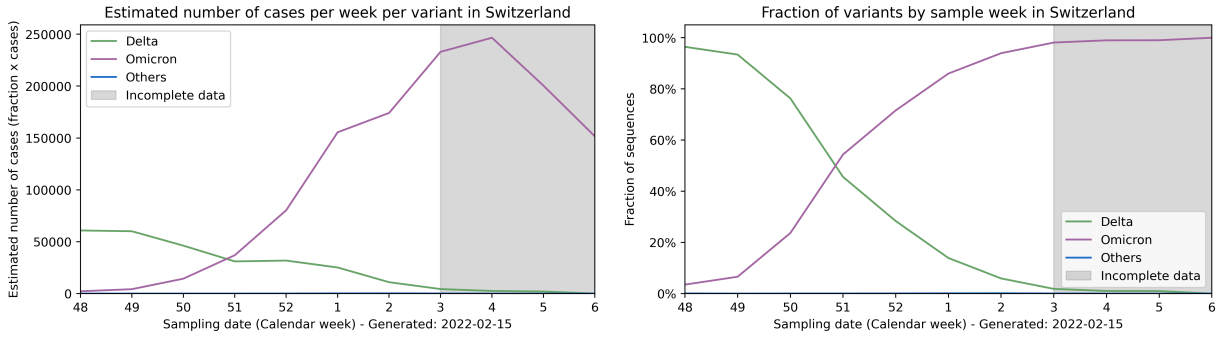



*Figure 5: (Left): Percentage of circulating VOCs and VOIs in Switzerland by week, up to the 6 first weeks of 2022 (total number of B.1.617.2 (Delta), and B.1.1529 (Omicron) sequences from Switzerland and successfully submitted to GISAID are shown here). Note the grey shaded area indicates a period of incomplete data.*
*(Right): Estimated number of sequences of Delta, Omicron, and others retrieved during the surveilled period.*

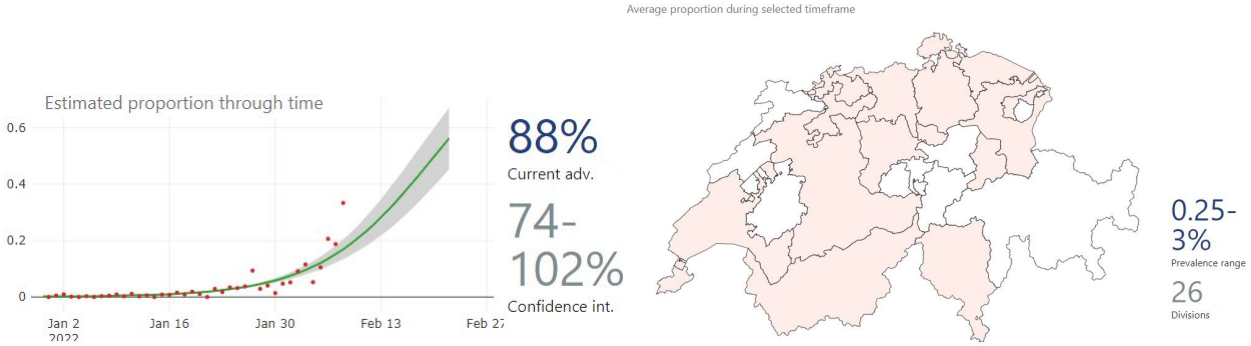



*Figure 6: B.1.1.529 (Omicron) estimated transmission advantage over time compared to co-circulating strains (left) and geographic distribution across Switzerland and average proportion during the surveilled period (right). Dynamic navigation available at [https://cov-spectrum.ethz.ch/explore/Switzerland.](https://cov-spectrum.ethz.ch/explore/Switzerland)*

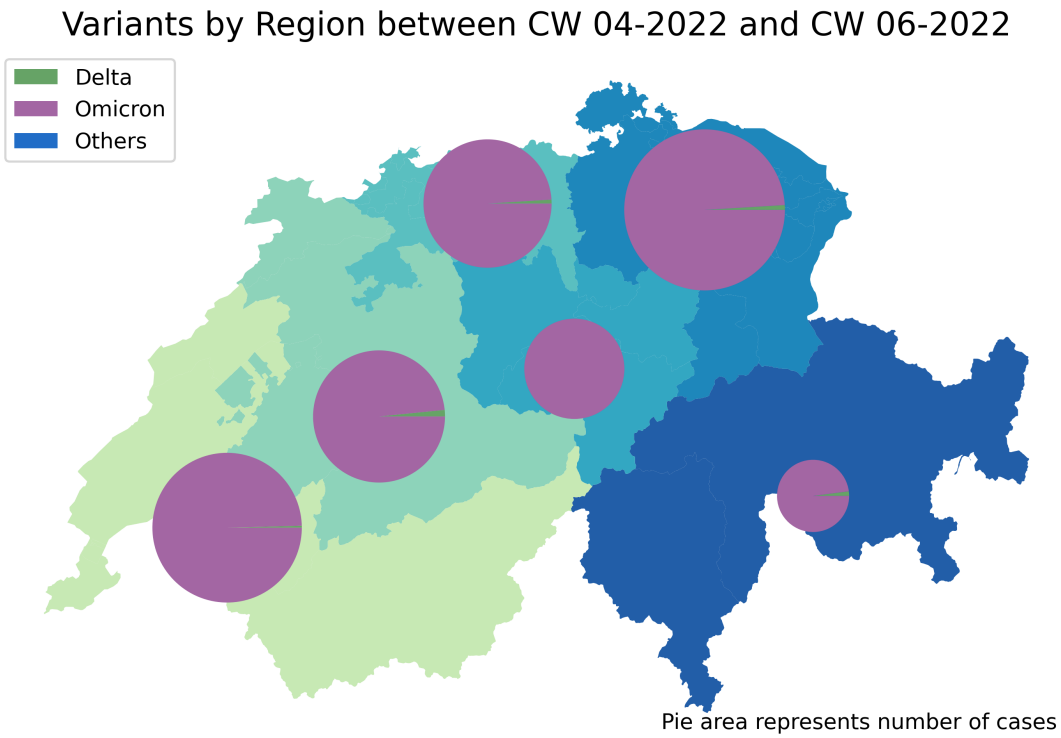



*Figure 6: Distribution of variants per region, for January 2022, shown on a map. The size of the pie chart corresponds to the total number of sequences. Note Omicron's extreme dominance in all regions as of the time of this report (bottom).*

## 6. Assessment of the competition between the different variants in Switzerland

The competition between different SARS-CoV-2 variants can be modelled using multinomial logistic regression. The analysis by Dr. Althaus' group is based on sequences retrieved from CovSPECTRUM. The results correctly predicted that Omicron would be the dominant SARS-CoV-2 variant in Switzerland. These predictive models suggest that the BA.1 sub-lineage will be replaced by the BA.2 sublineage. (figure 7)

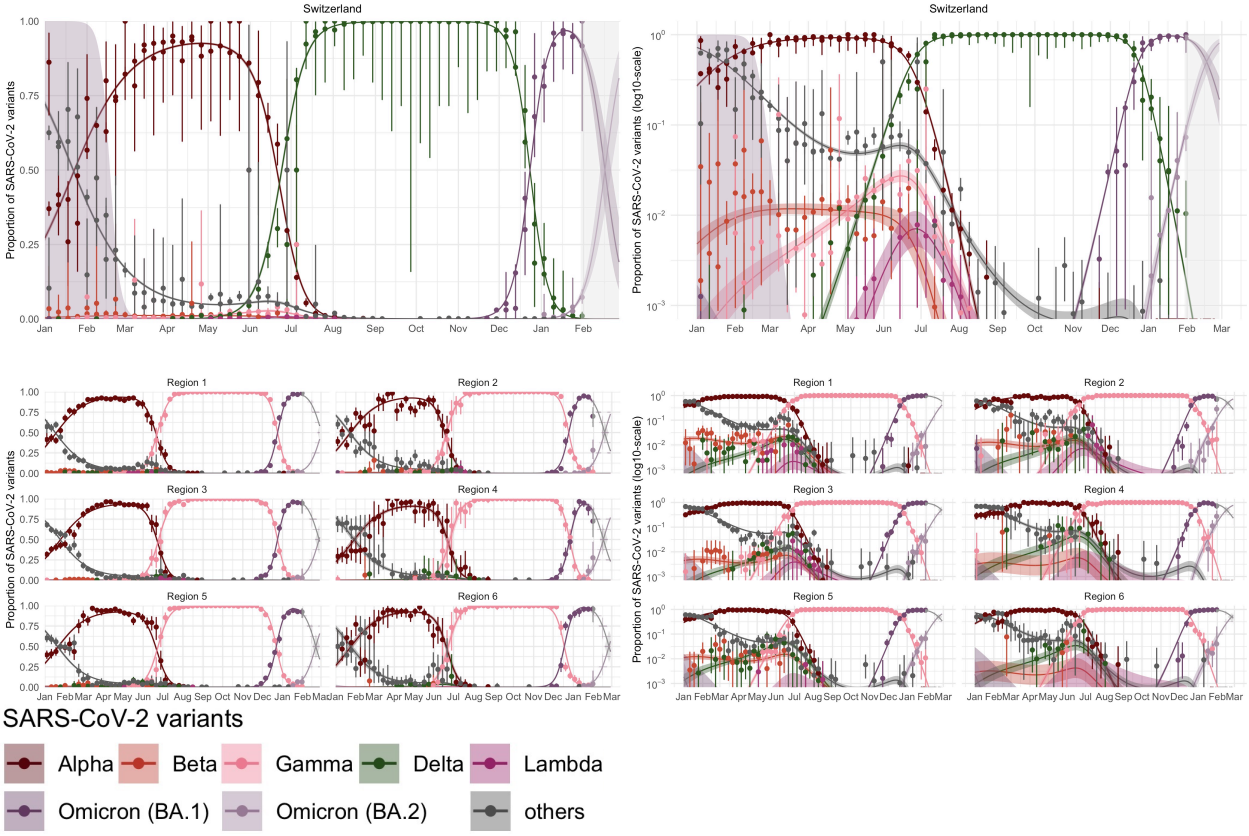



*Figure 7: Observed and modeled proportion of SARS-CoV-2 variants over time in Switzerland. In April and May 2021, Gamma and Delta started to replace Alpha, with Delta outcompeting all other variants. At the end of October, more than 99.9% of the retrieved sequences in Switzerland were due to Delta or one of its sub-lineages. In late November, Omicron arrived in Switzerland and began to rapidly displace Delta. Omicron BA.1 achieved dominance by the end of December, but is predicted to be replaced by Omicron BA.2. Model fits are based on a multinomial logistic regression with splines.*

## 7. Surveillance of mutations associated with reduced mAb treatment efficacy

A number of mutations have been reported to result in significantly reduced *in vitro* effectiveness of the Sotrovimab and Casirivimab/Imdevimab association monoclonal antibodies used to treat patients in Switzerland. Notably, Omicron is completely resistant to neutralization by Casirivimab/Imdevimab, and Sotrovimab remains the only mAb used in Switzerland that retains effectiveness against Omicron. Unfortunately, this effectiveness is expected to be significantly decreased for the BA.2 sublineage (that is expected to replace BA.1), on the basis of a 16-27 fold reduction of *in vitro* neutralizing titers. This escape is not complete, and Sotrovimab retains significant activity against BA.2 at higher titers – thus the frequencies of mutations reported to escape neutralization by Sotrovimab are still being followed.(Table 4).

| | 337H | | 337L | | 337R | | 337T | |
|---|---|---|---|---|---|---|---|---|
| Week | Global | Switzerland | Global | Switzerland | Global | Switzerland | Global | Switzerland |
| 03.01.2022 | 2 | 0 | 3 | **1** | 0 | 0 | 0 | 0 |
| 10.01.2022 | 2 | 0 | 2 | 0 | 3 | 0 | 1 | 0 |
| 17.01.2022 | 1 | 0 | 4 | 0 | 3 | **2** | 1 | 0 |
| 24.01.2022 | 2 | 0 | 2 | 0 | 2 | 1 | 3 | 0 |

| | 340A | | 340K | | 340G | | 356T | |
|---|---|---|---|---|---|---|---|---|
| Week | Global | Switzerland | Global | Switzerland | Global | Switzerland | Global | Switzerland |
| 03.01.2022 | 3 | 0 | 9 | 0 | 6 | 0 | 3 | 0 |
| 10.01.2022 | 2 | 0 | 17 | **3** | 0 | 0 | 6 | **1** |
| 17.01.2022 | 3 | 0 | 14 | 0 | 0 | 0 | 9 | 0 |
| 24.01.2022 | 4 | **1** | 13 | **4** | 0 | 0 | 6 | 0 |

*Table 4: Global and Swiss counts of sequences bearing escape mutations from therapeutic mAbs used in Switzerland*

Known mutations enabling escape from Sotrovimab have been detected in Switzerland, but remain rare.

## 8. Wastewater surveillance program

Sequences are obtained from six wastewater treatment plants (WWTPs) that are tested on a daily basis.

Signatures of the BA.1 (Omicron) variant were first detected at the earliest in sequenced sewage samples of the Basel-Stadt cantonal wastewater surveillance project, dating from November 21 onwards. Since then, Omicron has been detected in all other surveyed WWTPs, and quickly grew in relative prevalence during the month of December to become the major variant in wastewater samples. The logistic growth rate of the relative prevalence of Omicron can be estimated based on wastewater sequencing data, and the estimates range from 0.18 to 0.27 per day, depending on the location. During the month of January, the share of BA.2 fragments in wastewater has been steadily increasing.

Quantification of Omicron in sewage has exhibited some peculiar challenges (in Switzerland and in other countries): some data indicates that this variant is less shed in faeces compared to Delta. The differential shedding could lead to an underestimation of the prevalence of Omicron relative to Delta when using wastewater sequencing data. This should however not impact estimates of the logistic growth rate. This bias is not expected at the moment to impact quantification of BA.2 relative to BA.1.

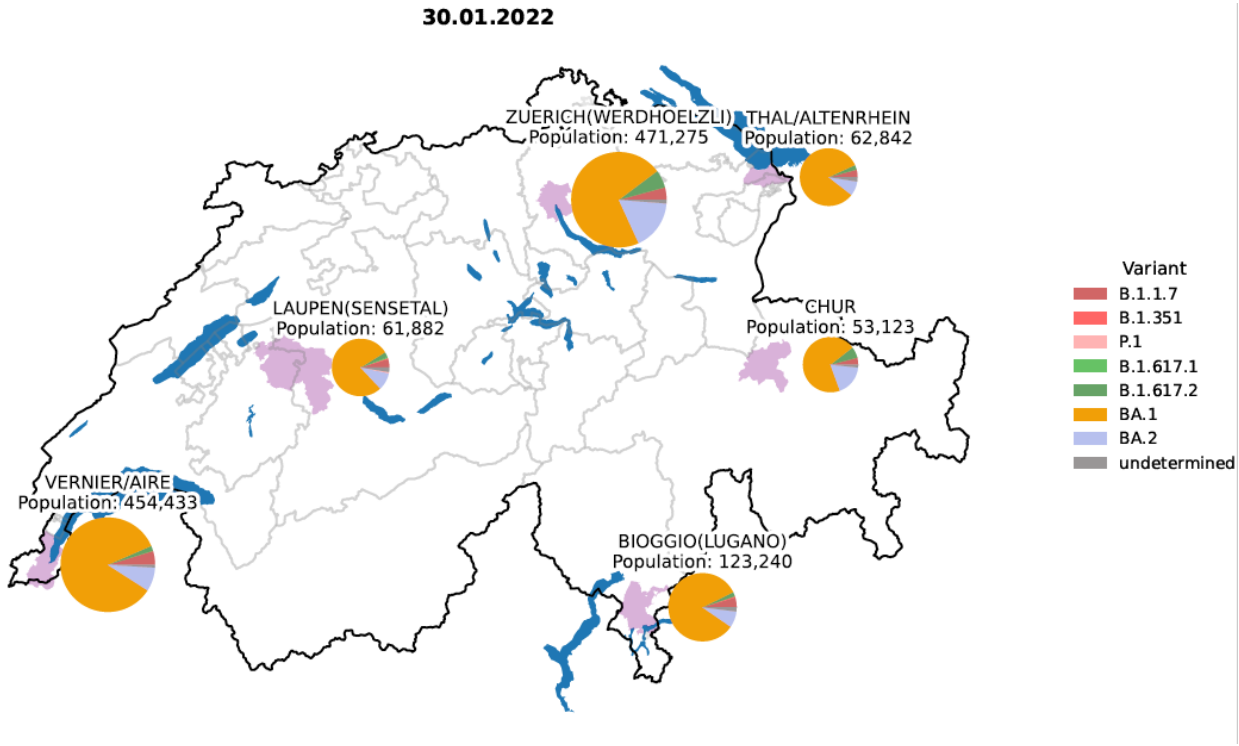



*Figure 8: Overview of the prevalence of variants of SARS-CoV-2 at the end of January 2022, estimated from wastewater samples collected daily during the month in WWTPs located in 6 different Swiss locations. Pie chart areas are proportional to population connected to the wastewater treatment plants. Pink shaded areas represent catchment areas (boundaries from 2017). Population connected to Vernier (GE) wastewater treatment plant also includes ~44,000 inhabitants from neighbouring French communities. B.1.617.2 (Delta) is represented in in dark green, B.1.617.1 in light green (Kappa), B.1.617.3 in purple, B.1.1.7 (Alpha) in dark red, B.1.351 (Beta) in light red, P.1 (Gamma) in pink, BA.1 (Omicron) in orange, and BA.2 (Omicron) in light blue.*

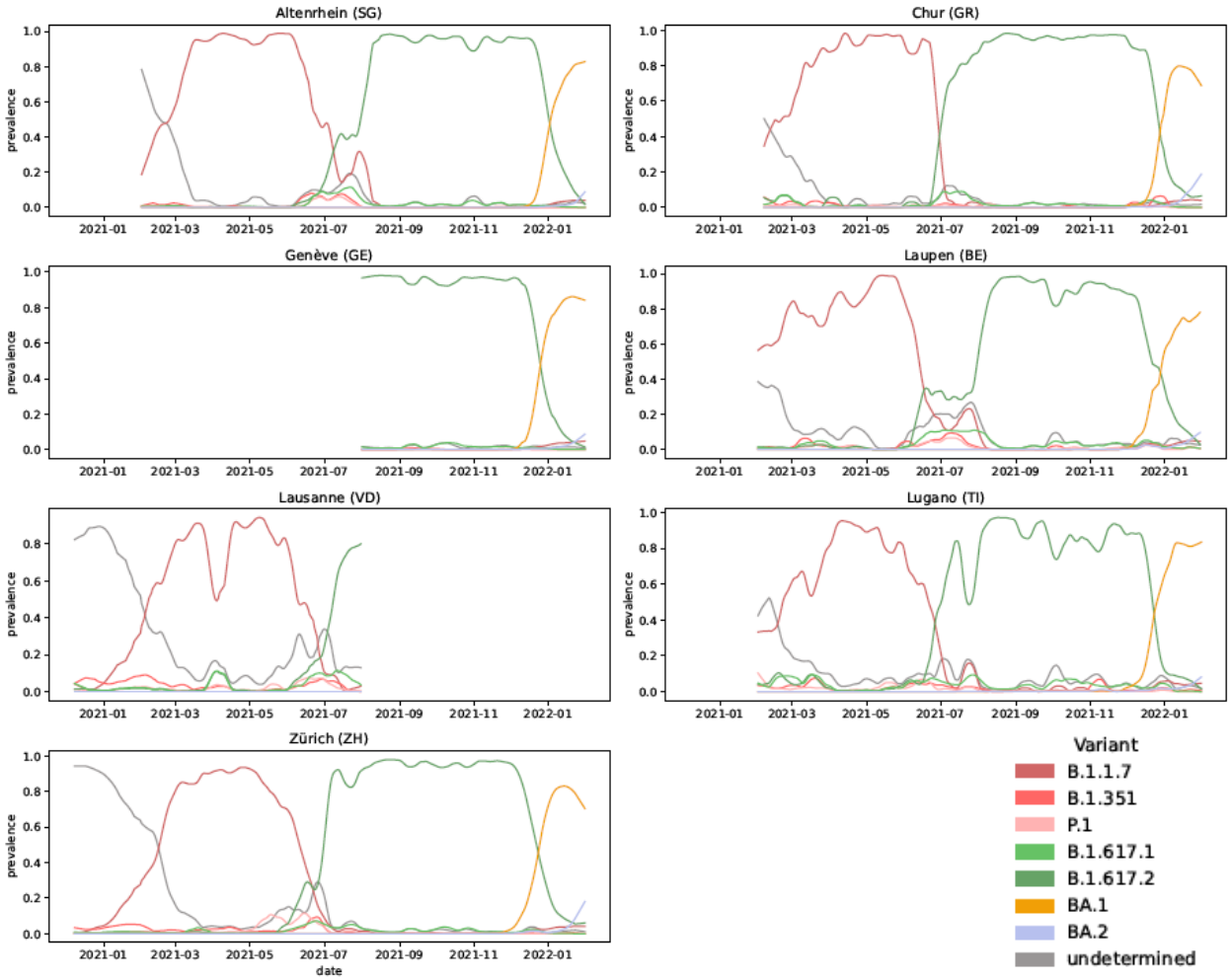



*Figure 9: Prevalence of variants of SARS- CoV-2 estimated from wastewater samples collected daily until December 31 (except Lausanne: July 31) in WWTPs located in 7 different Swiss cantons. B.1.617.2 (Delta) is represented in dark green, B.1.617.1 (Kappa), in light green, B.1.617.3 in purple, B.1.1.7 (Alpha) in dark red, B.1.351 (Beta) in light red, P.1 (Gamma) in pink, BA.1 (Omicron) in orange, and BA.2 (Omicron) in light blue. An online dynamic navigation is available at https://bsse.ethz.ch/cbg/research/computational-virology/sarscov2-variants-wastewater-surveillance.html .*

## 9. Immunological characterization of the variants

To assess neutralization by convalescent plasma, 104 blood specimens from convalescent individuals for were assessed their ability to neutralize seven authentic SARS-CoV-2 isolates (B.1, Alpha, Beta, Gamma, Delta, Zeta, Omicron) by plaque-reduction neutralization assay. These samples come after infection with early-pandemic SARS-CoV-2 (pre-VOC) or with Alpha, Beta, Gamma or Delta, infections, as well as post-vaccination (after 2 doses of mRNA-vaccines) infections due to Delta or Omicron.

The highest neutralization titers were found against the homologous variant: that is the same variant that caused the previous infection. Similarly, lower titers were found against heterlogous/different variants. In line with other studies, neutralization of Omicron was reduced to a varying degree depending on previously infecting variant, suggesting that infection-derived immunity varies, but infection by a non-Omicron variant is only poorly protective against Omicron (Figure 10).

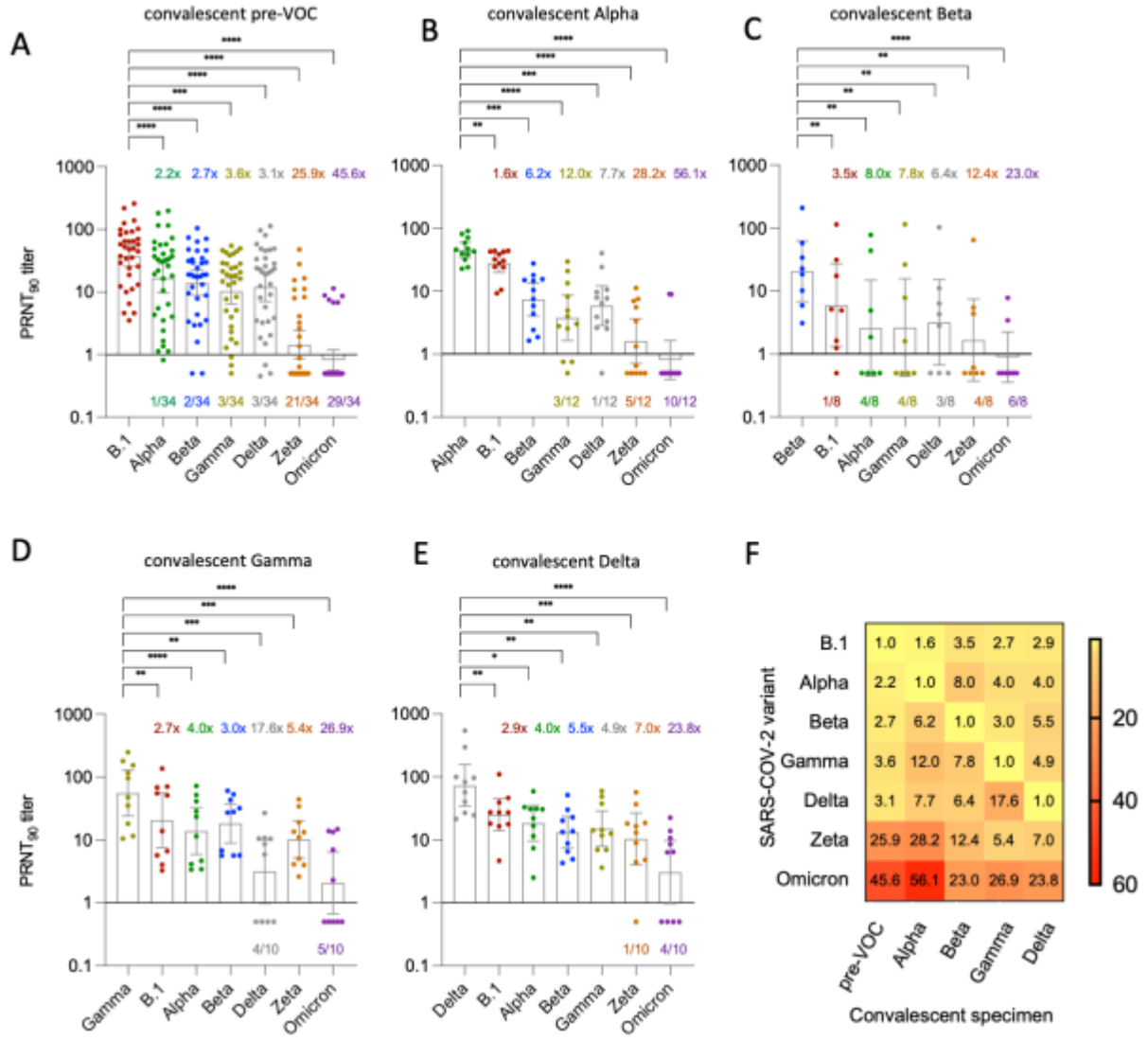



*Figure 10. Neutralization in infection-derived blood specimens against seven authentic isolates (B.1, Alpha, Beta Gamma, Delta, Zeta, Omicron). Bars represent geometric mean titers (GMT) of 90% reduction endpoint titers (PRNT90) with 95% confidence interval. Convalescent specimens are derived from individuals infected with (A) early-pandemic SARS-CoV-2 (pre-VOC), (B) Alpha (C) Beta (D) Gamma (E) Delta. Colored numbers above bars refer to fold change reduction of GMT versus the homologous (infecting) variant, shown as first bar of each figure. Colored numbers below each bar represents number of specimens with complete loss of neutralization (PRNT90 titer < 1).*

**p < 0.05, **p <0.003, ***p<0.0002 and ****p < 0.0001 (F) Heatmap of fold-reduction in neutralization based on PRNT90 data from A-E.*

Double dose vaccination showed robust neutralization for Alpha, Beta, Gamma, Delta and Zeta, while Omicron still showed a loss of neutralization of 85.7-fold compared to pre-VOC SARS-CoV-2. Combined immunity from infection followed by vaccination or vaccine breakthrough infection showed the highest titers and most robust neutralization for heterologous variants (Figure 11).

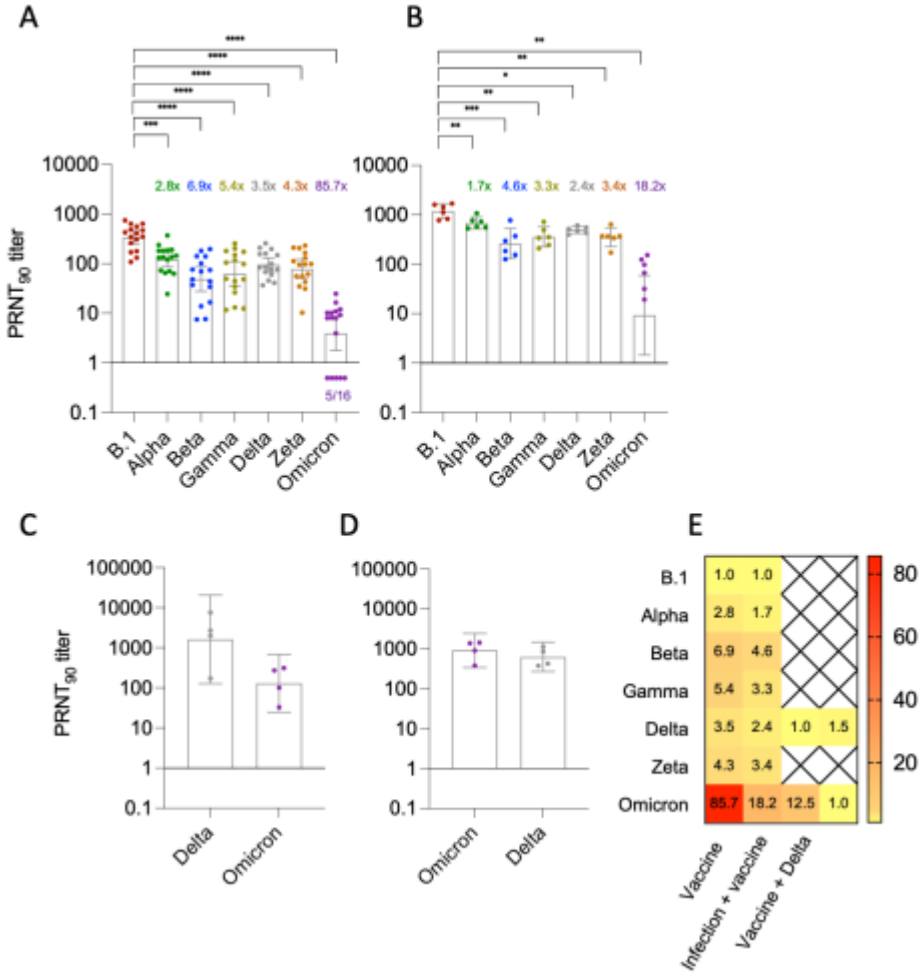



*Figure 2. Neutralization in vaccination + infection-derived blood specimens against seven authentic isolates (B.1, Alpha, Beta Gamma, Delta, Zeta, Omicron). Bars represent geometric mean titers (GMT) of 90% reduction endpoint titers (PRNT90) with 95% confidence interval. (A) double-dose mRNA vaccination, (B) prior SARS-CoV-2 infection followed by double-dose mRNA vaccination (C) Delta breakthrough infection of double-vaccinated individuals and (D) Omicron breakthrough infection following double (n=2) and single (n=2) mRNA vaccination. Colored numbers above bars refer to fold change reduction of GMT versus the homologous (infecting) variant, shown as first bar of each figure. Colored numbers below each bar represents number of specimenswith complete loss of neutralization (PRNT90 titer < 1). *p < 0.05, **p <0.003, ***p<0.0002 and ****p < 0.0001 (F) Heatmap of fold-reduction in neutralization based on PRNT90 data from A-D.*

Breakthrough infection with Delta showed only 12.5-fold reduced neutralization for Omicron, while breakthrough infection with Omicron showed only a 1.5-fold loss for Delta, suggesting that infection with antigenically different variants can boost immunity for antigens closer to the vaccine strain. Antigenic cartography showed also a tendency towards broader neutralizing capacity for heterologous variants. Combined infection/vaccination immunity could ultimately lead to broad 67 neutralizing capacity also against non-homologous variants.

## Conclusion

In January, over 11,100 sequences were obtained for Switzerland through this surveillance program, in the midst of high case numbers. Each week since this surveillance program started, it has contributed almost all of the Swiss SARS-CoV-2 sequences available on GISAID. Around 1.3% (below the goal of 10%) of the cases reported in Switzerland were sequenced, reflecting the high case numbers. With over 11 thousand sequences generated from all over Switzerland, coverage is still considered satisfactory. Region 4 and 5 remain the least represented geographical areas.

Notably, Omicron sublineage BA.1 has displaced Delta, but Omicron sublineage BA.2 appears poised to displace BA.1. All other variants were only rarely detected, both in clinical samples and in the wastewater surveillance part of the program.

BA.2 is not likely to be more severe than BA.1, but preliminary in viro data suggested that Sotrovimab, the currently used monoclonal antibody therapy, will be substantially less effective against it. BA.2 lack the S Dropout. No additional diagnostic or treatment issues were noted in January.

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

## Acknowledgements:

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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. Data presented here cover the period from 6 December 2021 to 2 January 2022.

sup_table_overview_Jan.xlsx

*Supplementary Table 1: Epidemiological data for Switzerland, its regions and cantons for January: population, number and incidence of confirmed cases, effective reproduction number $R_e$, number and incidence of tests, test positivity, number and proportion of sequenced samples, and number and proportion of VOCs. $R_e$ by region is represented as the median and range of the daily $R_e$ values for all cantons within a region.*

| week | date | Total PCR tests | Positive tests | Sequenced | % positives | % positives sequenced |
|---|---|---|---|---|---|---|
| 1 | Jan 3 to Jan 9 | 204 954 | 67 184 | 2 916 | 32.78% | 4.34% |
| 2 | Jan 10 to Jan 16 | 202 579 | 73 505 | 3 009 | 36.28% | 4.09% |
| 3 | Jan 17 to Jan 23 | 209 536 | 91 137 | 2 467 | 43.49% | 2.71% |
| 4 | Jan 24 to Jan 30 | 202 390 | 91 191 | 2 714 | 45.06% | 2.98% |
| | **Total** | 819 459 | 323 017 | 11 106 | 39.42% | 3.44% |

*Supplementary Table 2: Total number of tests performed by the laboratories participating in the surveillance program from 6 December 2021 to 2 January 2022.*

| Week | Date | Basic Surveillance | | | | | | Augmented Surveillance | | | | | | Sentinella Laboratories | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | EOC | St-Gallen | Labor Team W | Risch | SRO | Synlab | USB | IFIK | Diana labs | CHUV | UZH | ICH-VS* | HUG | ETH/ Viollier | All |
| 1 | Jan 3 to Jan 9 | 80 | 96 | 0 | 0 | 107 | 0 | 58 | 163 | 87 | 66 | 300 | 92 | 313 | 1554 | 2916 |
| 2 | Jan 10 to Jan 16 | 80 | 94 | 0 | 96 | 88 | 0 | 186 | 185 | 0 | 82 | 206 | 92 | 301 | 1599 | 3009 |
| 3 | Jan 17 to Jan 23 | 123 | 95 | 0 | 95 | 88 | 0 | 145 | 186 | 86 | 87 | 244 | 92 | 338 | 888 | 2467 |
| 4 | Jan 24 to Jan 30 | 117 | 94 | 0 | 202 | 81 | 0 | 151 | 180 | 83 | 88 | 180 | 93 | 323 | 1122 | 2714 |
| | **Total** | 400 | 379 | 0 | 393 | 364 | 0 | 540 | 714 | 256 | 323 | 930 | 369 | 1275 | 5163 | 11106 |

*Supplementary Table 3: number of sequences submitted to GISAID by each laboratory during the surveilled period (3 January 2022 to 30 January 2022). *including sequencing sent to high-throughput platforms. ND = No data*

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