Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Federal Office of Public Health FOPH
Public Health Directorate Communicable Diseases Division

Schwarzenburgstrasse 157
3003 Bern
Switzerland

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# Swiss national SARS-CoV-2 genomic and variants surveillance program: report of the month of June 2023

Geneva Centre for Emerging Viral Diseases

Division of Infectious Diseases

Department of Medicine

Laboratory of virology

Division of Laboratory Medicine

Diagnostic Department

## 1. Summary

During the month of June, the number of positive SARS-CoV-2 tests decreased in Switzerland, and the test positivity rate within the program dropped to 11.5% from May's 17.2%. Notably, testing rates are at an all-time low. The number of hospitalizations due to COVID-19 continues to be low.

The 694 positive tests processed by laboratories participating to the program constituted around 1/3$^{rd}$ of the reported positive tests in Switzerland.

A total of 239 new sequences were submitted to GISAID during the reporting period, covering the month of June (May 22 to July 2), which represents around 35% of the program's positive tests. Note that since the beginning of 2023, the program has been adapted to focus on samples originating from hospitalized patients.

The majority of the sequences in Switzerland belong to the XBB.1.5, 1.9, or 1.16, with none of these sublineages exceeding 50%. XBB.1.16 appears to be slowly increasing in proportion, while XBB.1.9's proportion is holding steady and XBB.1.5's proportion is declining. Another subvariant, XBB.2.3 appears to be slowly increasing in proportion as well. Circulation of the EG.5 subvariant (designated as a VUM by the WHO) appears to have begun in Switzerland, with 5 sequences detected in this reporting period. Data suggests this variant will outcompete XBB.1.5/1.9/1.16, although the reason for this is unclear at the moment. These variants are all sublineages of XBB (a recombination between two BA.2 sublineages) with additional accumulated mutations. XBB* variants have dominated in Switzerland since the month of February. Current data does not suggest that any of these subvariants are more severe.

## 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. It began in March 2021 and is currently funded through 2023.

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.

As of the beginning of January 2023, the program was adapted and restricted to 7 participating laboratories, comprising the University Hospital Centres in Geneva, Lausanne, Bern, Basel, Zurich, and Ticino), in addition to the cantonal hospital in Valais (Hôpital du Valais – Institut Central), and 1 high-throughput sequencing platform (Health 2030 Genome Centre in Geneva). In addition, since the month of October 2022, sequencing in Geneva has been partially funded by the EU grant for the COVICIS project (https://covicis.eu/). Due to reduced numbers of samples available for sequencing, and it being more economical to sequence samples in large batches, the frequency of sequencing has decreased: batches are now sequenced every two weeks, and this has had to be further decreased to once every 4 weeks for July and August 2023.

Processed sequencing data are shared openly 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 Institute of Bioinformatics (SIB).

In order to complement the genomic surveillance based on patient samples, the program includes sequencing of SARS-CoV-2 in wastewater samples. Samples are collected daily in 10 wastewater treatment plants (WWTP), under the coordination of Eawag. 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 six WWTP (https://bsse.ethz.ch/cbg/research/computational-virology/sarscov2-variants-wastewater-surveillance.html). Since the beginning of January 2023, the surveillance in wastewater expanded to 10 facilities and is no longer included in the national surveillance program but benefits from another source of funding.

Immunological characterization of the variants within the surveillance program was included until December 2022 with an update in the present report and was 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, David Dreifuss, Chaoran Chen, Tanja Stadler, Emma Hodcroft, Erik Studer, Priscilla Turelli, Didier Trono, 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 May 22 to July 2, 2023 (weeks 21-26). 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 VOCs have been designated 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). Worldwide, all VOCs except Omicron have essentially disappeared from samples collected since the beginning of 2022 (https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---24-august-2022).

On March 15, 2023, WHO updated its definitions for VOCs and VOIs, mainly consisting in making the VOC definition more specific. Greek letters will thus only be assigned to VOCs. Currently, the WHO will only consider a variant as a variant of concern if it "meets at least one of the following criteria when compared with other variants:

- Detrimental change in clinical disease severity; OR
- Change in COVID-19 epidemiology causing substantial impact on the ability of health systems to provide care to patients with COVID-19 or other illnesses and therefore requiring major public health interventions; OR
- Significant decrease in the effectiveness of available vaccines in protecting against severe disease."

Variants under monitoring (VUM) are suspected to have altered characteristics (transmissibility, virulence, antibody evasion, susceptibility to therapeutics or detectability), and signals of a growth advantage, but with a low level of evidential support. Meanwhile, a Variant of Interest is predicted or known to have altered characteristics, and an identified growth advantage in more than one region.

The WHO currently assesses that the currently circulating VOIs are XBB.1.5 and XBB.1.16. Currently circulating VUMs consist of BA.2.75, CH.1.1, XBB*, XBB.1.9.1, XBB.1.9.2, EG.5, and XBB.2.3.

*Omicron*

The Omicron VOC (B.1.1.529) is characterized by a high divergence in the spike protein, which has allowed it to substantially escape immunity conferred by vaccination (using the original Wu-1 sequence) and prior infection with pre-Omicron variants. This VOC currently has multiple sublineages. Despite all being considered "Omicron", these sublineages may differ from each other (in terms of mutation counts) more than the earlier VOCs differed from the original Wu-1 strain.

Notably, this is the first VOC to have subvariants causing multiple successive waves. These sublineages have successively replaced each other, with the BA.5 sublineage BQ.1 being dominant in most of January, and then being quickly replaced by the XBB.1.5 variant since mid-February 2023 (see below).

XBB* is a highly derived BA.2 sublineage which derives from a recombination event between two sublineages (BJ.1 and BM.1.1.1). Most circulating Omicron subvariants now contain mutations that enable complete escape from monoclonal antibodies available on the market.

In March, 2023, XBB.1.5 was classified as a VOI by WHO. Notably, the XBB.1.5 sublineage seems to have similar immune escape properties to BQ.1.1, but has a higher ACE2 affinity, presumably enhancing its inherent transmissibility. The three most prominent XBB sublineages are currently XBB.1.5/9/16. The XBB.1.9 sublineage has the same spike protein as XBB.1.5 (and is distinguished from XBB.1.5 by non-spike mutations) while the XBB.1.16 spike protein differs from by only a few mutations.

In July 2023, a sublineage of XBB.1.9.2 with and additional Spike mutation (F456L) called EG.5 was classified as a VUM. Data using the EG.5.1 spike in pseudoviruses does not indicate any significant additional immune escape or infectivity, so the reasons for EG.5's spread are unclear. All major XBB sublineages (XBB.1.5/1.9/1.16) show and relatively poor neutralization titers following an XBB breakthrough infection, possibly due to previous immune imprinting, indicating that it may be able to cause more frequent cause reinfections.

Notably XBB.1.9 and XBB.1.16 have overtaken XBB.1.5 in some parts of the world. In Switzerland, XBB.1.5 had been seeing competition from XBB.1.9 and XBB.1.16 from April to May, and was definitively overtaken by XBB.1.9 as of week 21.

*Detection*

All sub-lineages are still detected by RT-PCR tests There is no evidence that the new subvariants pose any particular detection challenges to these tests. As XBB lineages are currently dominant, S-gene target failure with the Roche PCR assays regularly used in Switzerland is not very informative, and mostly indicates residual BA.5/BQ.1 circulation. Further discrimination between subvariants is not feasible at this time by any method other than genomic sequencing, although variant specific PCRs could be developed.

*Immune escape*

Extensive data demonstrates that Omicron variants are substantially able to evade neutralizing antibodies (nAbs) from non-Omicron infections and after 2-3 doses of vaccine. Current evidence suggests that vaccines updated against BA.4/5 have substantially reduced neutralization of the currently circulating XBB.1.5 and XBB.1.16 lineages. XBB.1.5 and XBB.1.16 only differ antigenically by a few residues, but differ substantially from the BA.5 sublineages that were recently replaced. The latest data suggests that both and vaccines updated against either XBB.1.5 or XBB.1.16 perform similarly against both variants. Therefore, a vaccine update against either sequence would be similarly beneficial.

Escape from monoclonal antibodies is extensive and is covered by the “Therapeutic intervention effectiveness” section.

*Severity*

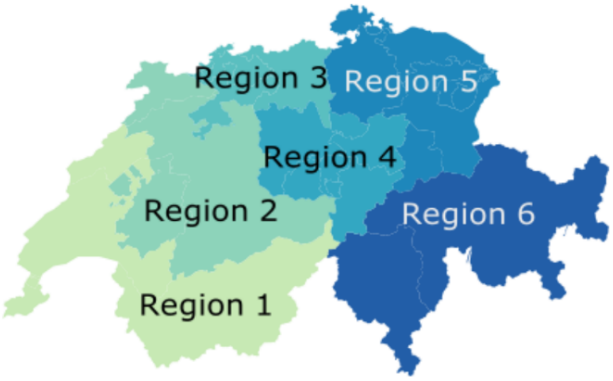
There is currently no evidence that the severity of the new subvariants has significantly changed. Indeed, some studies provide evidence that XBB sublineages are not more severe. There is currently weak evidence that XBB.1.16 may have an increased incidence of non-severe conjunctivitis.

## 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.

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

From 4 June to 26 June, the FOPH reported about 900 positive tests (including both RT-PCR and antigen-based tests). Positive tests from the labs participating in the national surveillance program from overlapping dates constitutes produced approximately 1/3 of this number. From 22 May to 2 July, the labs participating in the national surveillance program produced 694 positive tests. Along with the number of tests performed in the country, the number of positive tests continued to decrease in Switzerland during the month of June relative to May, and since the beginning of the year. Notably, the percent of positive sequenced within the program was 34.4%, which is similar to that of May (35.4%). The test positivity rate within the program was for 22 May to 2 July was 11.5%, while the overall rate (including tests performed by centers that do not participate in the surveillance program) was 7.81% (for 4 June to 26 June). The higher rate within the program may reflect the focus on testing hospitalized patients.

Although case ascertainment rates may be too low to identify meaningful trends, there has not been any sign that the currently low hospitalization rates (≤5 per week over the last month at the HUG, mostly patients with pauci-symptomatic or mild disease) are rising.

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. 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 supplementary Table 2.

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

A total of 239 SARS-CoV-2 sequences have been declared to have been processed during this period. There are 472 sequences available that were submitted during this period on GISAID (and 217 collected during this period) as of 7 August 2023. This contrast between the numbers of submitted and collected sequences is likely due to reporting delays, which were low during the month of June.

Table 1 shows the number of sequences successfully submitted to GISAID through the surveillance program during the surveilled period by calendar week.

| Week | Date | Number of sequences declared and successfully submitted to GISAID during the surveilled period, by all laboratories in the program |
|---|---|---|
| 21 | May 22-May 28 | 133 |
| 22 | May 29-June 4 | |
| 23 | June 5- June 11 | 84 |
| 24 | June 12-June 18 | |
| 25 | June 19- June 25 | 22 |
| 26 | June 26- 2 July | |
| | **Total** | 239 |

*Table 1: 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.*

The total number of SARS-CoV-2 sequences declared and submitted to GISAID by each laboratory during this period 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 again declined during the month of June 2023 (Calendar weeks 21 - 26). Since the beginning of this program, almost all of the sequences available, and all of those on which the surveillance is conducted, come from the national surveillance program.

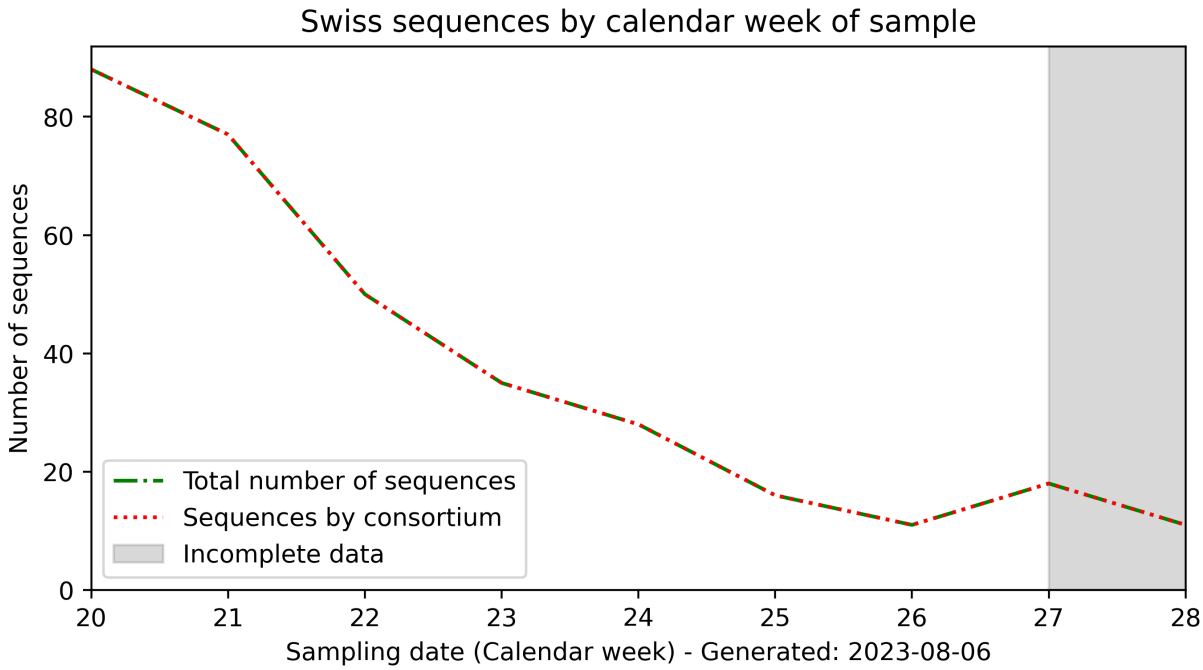



*Figure 1: Number of SARS-CoV-2 sequences available for Switzerland (total available Swiss sequences in GISAID in green, Swiss sequences submitted through the program in dotted orange).*

Figure 2 displays the number of SARS-CoV-2 cases sequenced for each Swiss region. Sequences declined in all regions. Notably, region 4 (Luzern, Unterwalden, Uri, Zug and Schwyz) is 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.

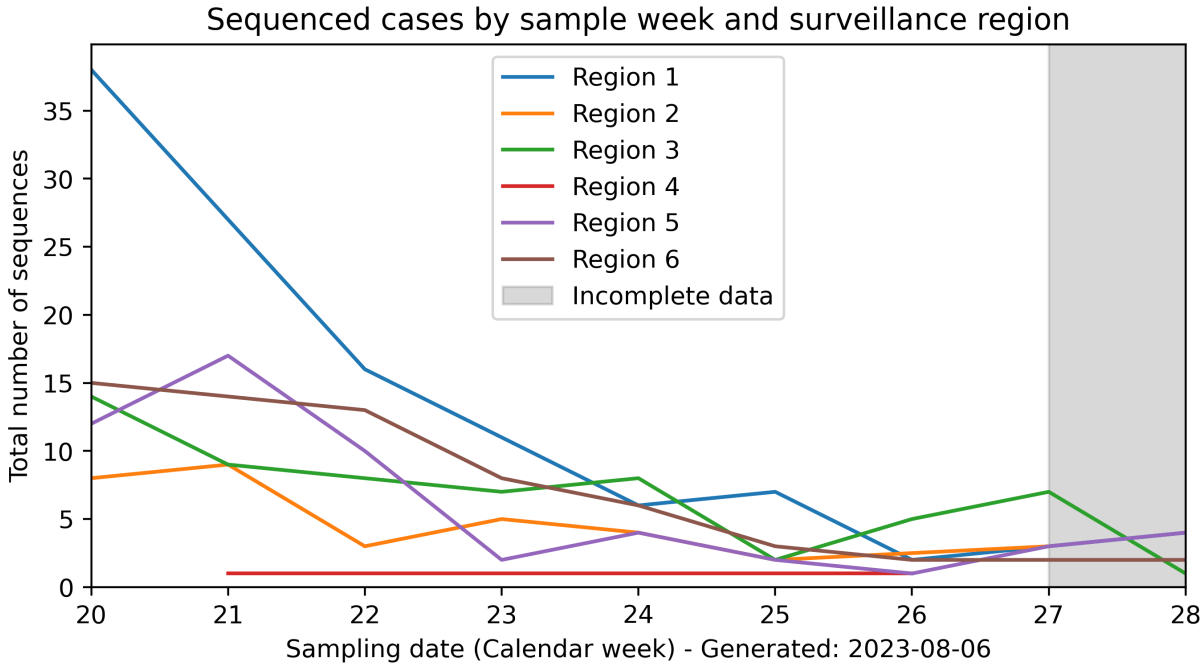



*Figure 2: Sequencing coverage among the different Swiss regions per week, by number of sequences.*

## 4. Recently circulating variants 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). 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).

BA.2.75 was not detected in Switzerland during June. BA.5 continues to circulate at low levels. Most circulating viruses are XBB sublineages now. XBB.1.9 has established dominance over XBB.1.5, not by increasing in proportion, but due to XBB.1.5 declining. XBB.1.9 still does not make up the majority of the sequences in Switzerland due to significant circulation of XBB.1.16 and XBB.2.3, as well as still substantial circulation of XBB.1.5 (Tables 2 and figures 2 and 3). Notably, XBB.1.16 and XBB.2.3 seem to be slowly but progressively increasing in proportion, although their absolute proportions are still low. Notably, five EG.5 sequences were detected during this period (only one had been found previously), indicating the start of EG.5 circulation in June.

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.

| Region | BA.2.75* | BA.5* | XBB* | XBB.1.16* | XBB.1.5* | XBB.1.9* | XBB.2.3* | Others | Recombinant | Sequences |
|---|---|---|---|---|---|---|---|---|---|---|
| All | 0 | 9 | 18 | 33 | 51 | 78 | 17 | 2 | 0 | 208 |
| 1 | 0 | 6 | 6 | 8 | 16 | 27 | 2 | 1 | 0 | 66 |
| 2 | 0 | 0 | 0 | 3 | 10 | 5 | 1 | 1 | 0 | 20 |
| 3 | 0 | 0 | 3 | 6 | 9 | 12 | 8 | 0 | 0 | 38 |
| 4 | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 3 |
| 5 | 0 | 3 | 0 | 6 | 5 | 18 | 3 | 0 | 0 | 35 |
| 6 | 0 | 0 | 9 | 8 | 11 | 14 | 3 | 0 | 0 | 45 |

*Table 2: number of sequences corresponding to selected variants in each region of Switzerland from May 22 to July 2, according to data received by 7 August, 2023.*

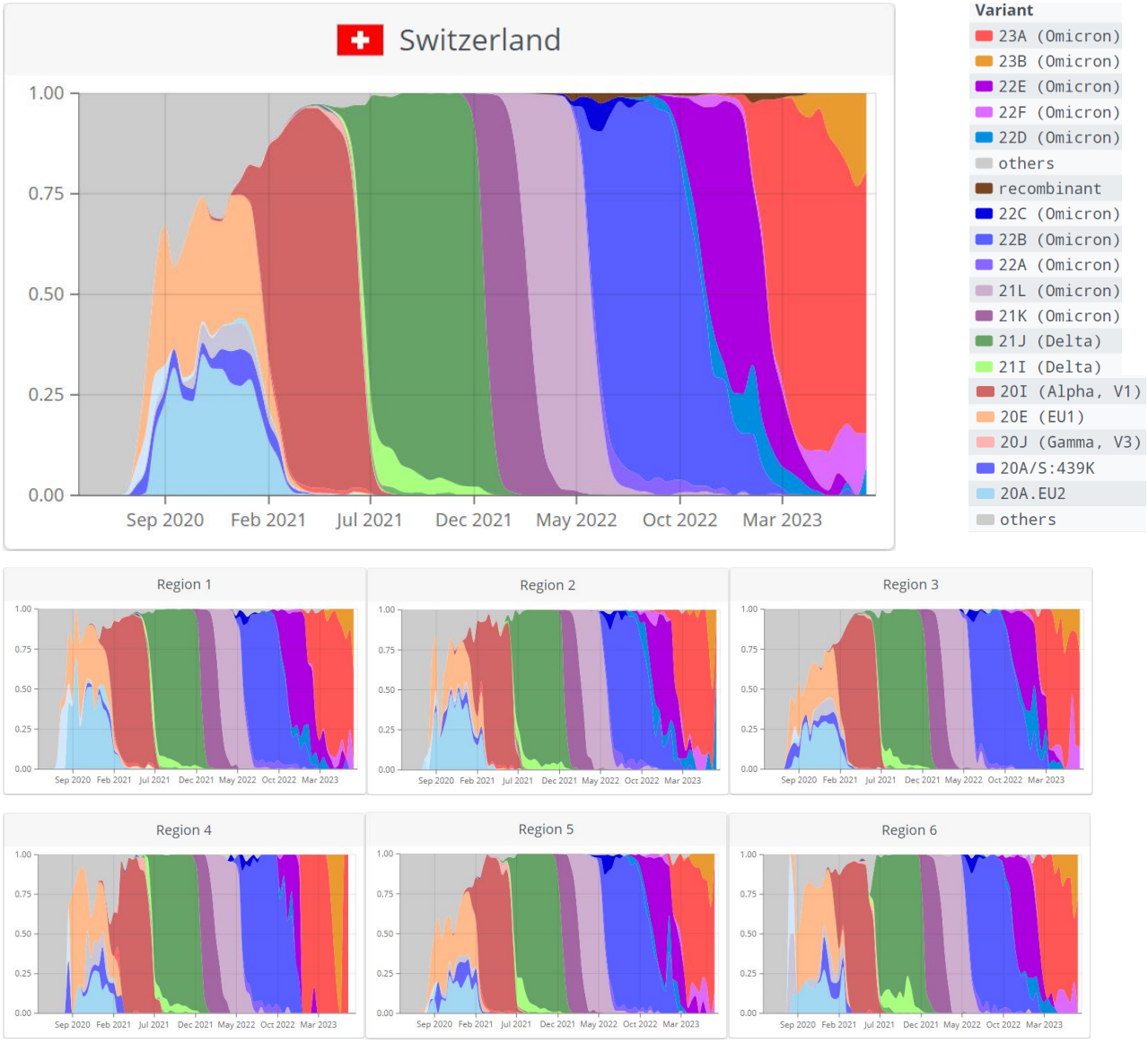



*Figure 3: proportion of the total number of sequences (not cases), over time, that fall into defined variant groups, for Switzerland. Screenshot from CoVariants website. Dynamic navigation is available at [https://covariants.org/per-country](https://covariants.org/per-country). 21 A/I/J indicates B.1.617.2 (Delta) sub-lineages. 20I indicates B.1.1.7 (Alpha). 21K indicates Omicron BA.1, 21L indicates Omicron BA.2. 22C indicates Omicron BA.2.12.1, while 22B indicates Omicron BA.5 and 22A indicates Omicron BA.4. 22D indicates BA.2.75. 22E indicates BQ.1, 22F indicates the recombinant XBB lineage, and 23A indicates XBB.1.5/XBB.1.9. 23B indicates XBB.1.16. Note: No separate Nextstrain clade has been designated for XBB.1.9*

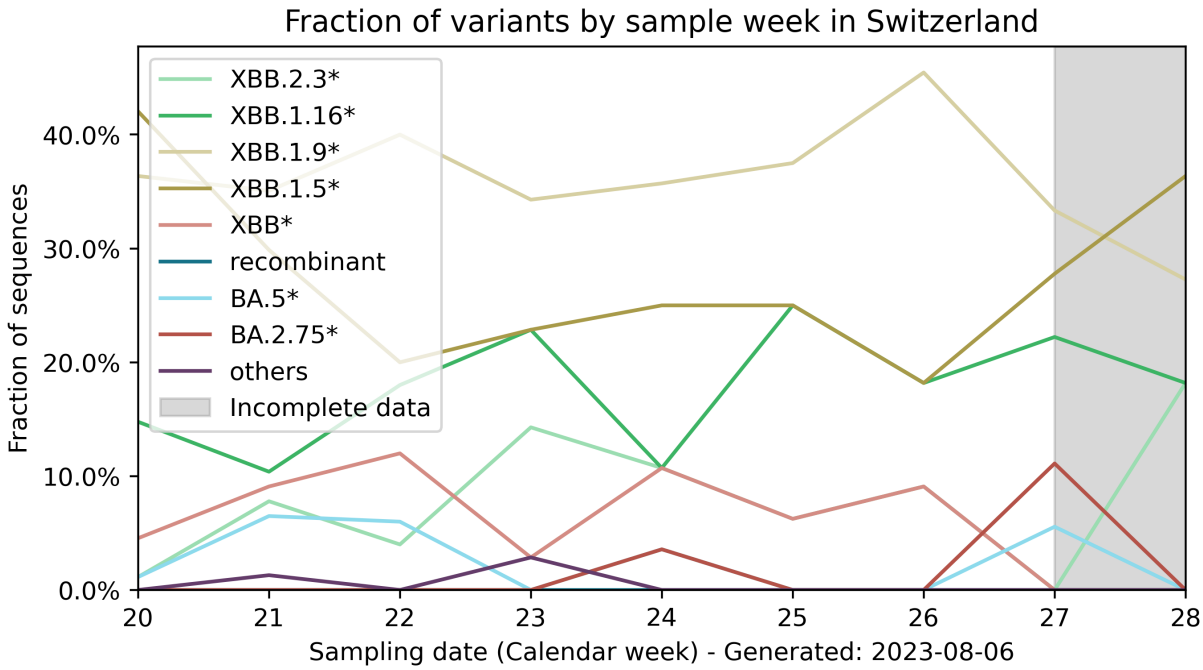



*Figure 4: Percentage of circulating VOCs and VOIs in Switzerland by week, up to week 24 of 2023, according to the sequences from Switzerland that were successfully submitted. Note that as of week 21, XBB.1.9 was the most common variant, as XBB.1.5 declined. Additionally, XBB.2.3 and XBB.1.16 have been slowly but progressively increasing in proportion.*

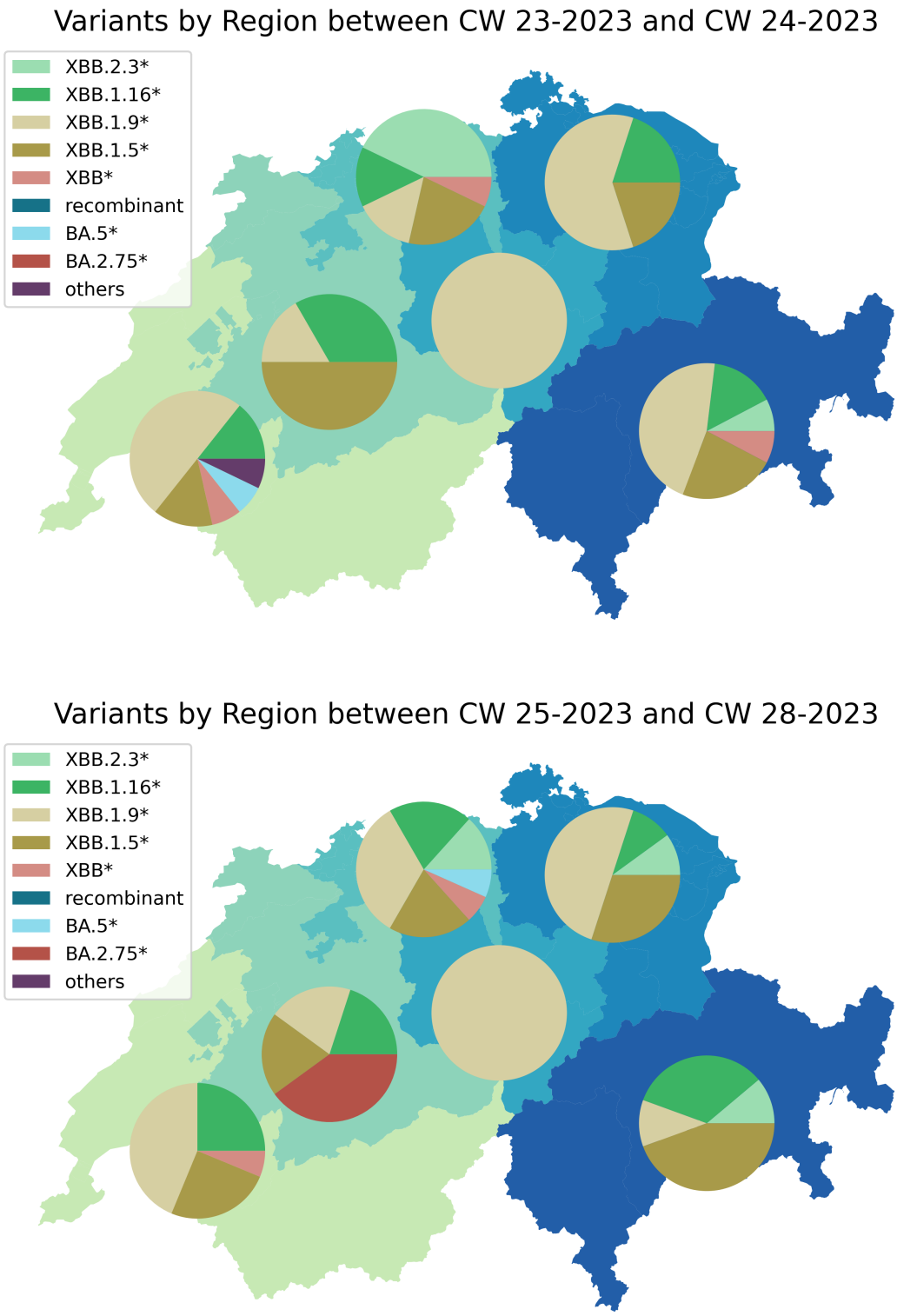



*Figure 5: Distribution of variants per region, by Calendar Week (CW), for the end of June 2023. Note the co-dominance of the XBB.1.5, XBB.1.9, and XBB.1.16 lineages. Region 4 was underrepresented and had just 2 samples of XBB.1.9. Also note, 1 sample of XBB.1.16 was detected in region 4 in calendar week 21.*

## 5. 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 current estimate suggests that while the XBB.1.5 lineage will not stay dominant, instead multiple XBB* sublineages will compete with each other with none able to achieve dominance. At a larger scale, XBB* (including all of its sublineages) will still be dominant.

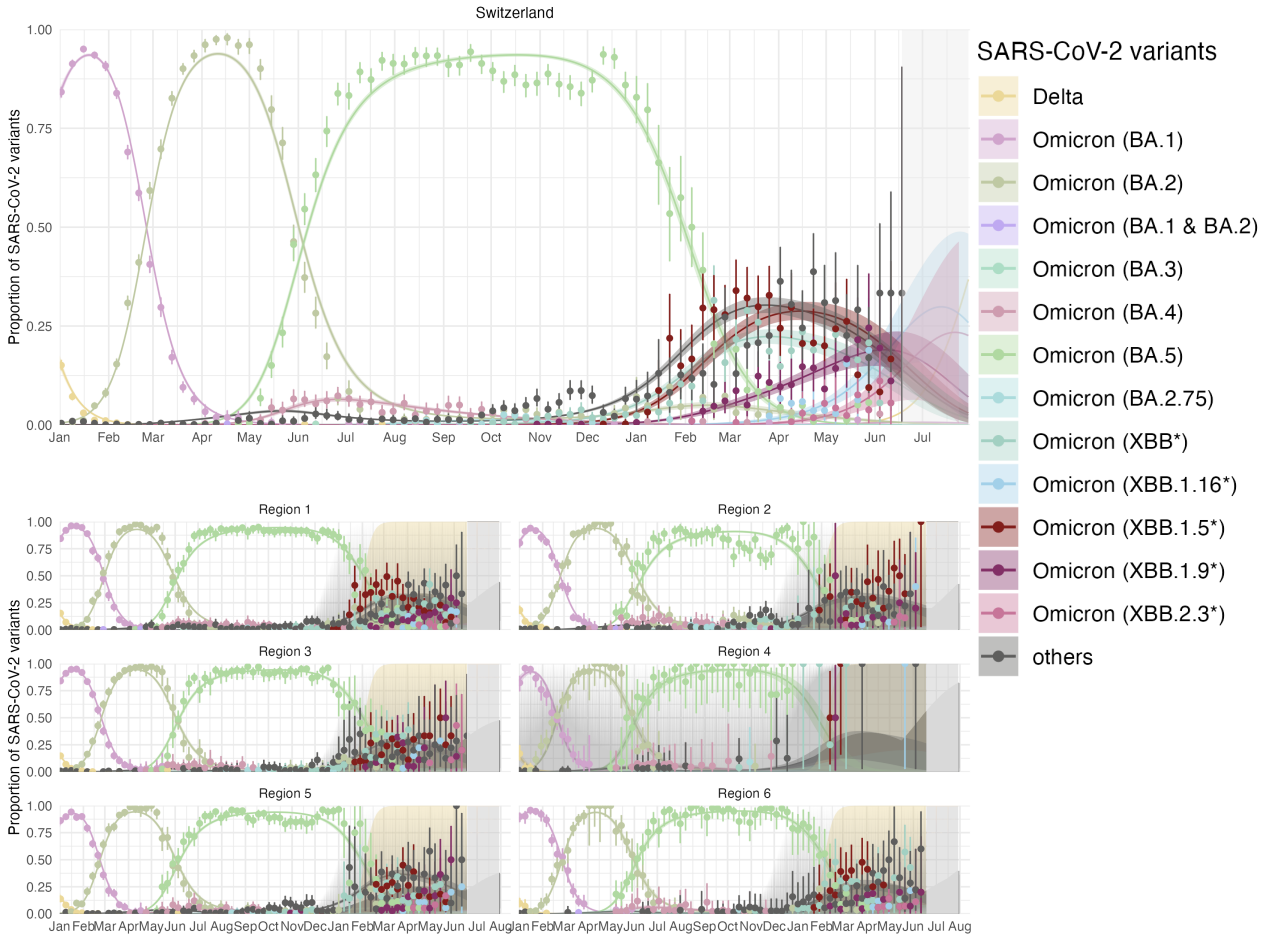



*Figure 6: Observed and modeled proportion of SARS-CoV-2 variants over time in Switzerland. Since early 2021, multiple successive variants have been observed to displace all previous variants (often achieving a dominance of >99.9% of the circulation). Alpha was replaced by Delta, followed by Omicron BA.1, then Omicron BA.2, Omicron BA.5, Omicron BQ.1, and now Omicron XBB.1.5. Model fits are based on a multinomial logistic regression with splines.*

## 6. Surveillance of mutations associated with reduced available treatment efficacy

*Resistance mutations to available monoclonal antibodies*

All sublineages display complete escape from combination of casirivimab/imdevimab.

| AA position | World | Europe | Switzerland |
|---|---|---|---|
| Sotrovimab (Spike mutations) | | | |
| 337 | 0.13 | 0.04 (6) | 0 |
| 340 | 0.16 | 0.18 | 0.92 (2) |
| 356 | 1.38 | 0.58 | 0 |
| 371 | 92.14 | 90.74 | 99.54 |
| 377 | 0.10 | 0 | 0 |
| 449 | 0.00 (2) | 0.01 (1) | 0 |
| 476 | 0.04 | 0.03 (4) | 0 |
| 494 | 0.64 | 0.69 | 0.46 (1) |
| Paxlovid® (Nsp5 mutations) | | | |
| 48 | 0.02 | 0 | 0 |
| 49 | 0.01 (7) | 0.01 (2) | 0 |
| 140 | 0 | 0 | 0 |
| 143 | 0 | 0 | 0 |
| 144 | 0 | 0 | 0 |
| 165 | 0.00 (1) | 0 | 0 |
| 166 | 0.00 (2) | 0.01 (1) | 0 |
| 167 | 0 | 0 | 0 |
| 168 | 0 | 0 | 0 |
| 172 | 0 | 0 | 0 |
| 173 | 0.00 (2) | 0.01 (2) | 0 |
| 186 | 0.01 (8) | 0.01 (2) | 0 |
| 188 | 0.01 (6) | 0 | 0 |
| 189 | 0.01 (5) | 0.01 (1) | 0 |
| 192 | 0.01 (7) | 0.01 (1) | 0 |
| 252 | 0.01 (3) | 0.01 (1) | 0 |

Current data suggests that *in vitro* neutralization of the currently circulating variants by Sotrovimab is dramatically reduced. Despite this, it may retain some clinical efficacy due to its ability to act as an effector even when it binds to the viral particles without neutralizing them, although this is unclear.

Since January 2023, variants with resistance mutations expected to lead to complete escape from both cilgavimab and tixagevimab (the components of Evusheld) represented over 95% of the sequences identified in Switzerland.

Additional (beyond those found in BA.2 and BA.5) Sotrovimab escape mutations remained rare in Switzerland and worldwide during June 2023 (Table 3).

*Table 3: 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 8 Augusty, 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 Sotrovimab resistance.*

*Resistance mutations associated with resistance to other available antivirals*

Other antivirals are available in Switzerland: the 3CL-like protease inhibitor Paxlovid® (PF-07321332, nirmatrelvir/ritonavir) or RNA nucleotide analogues (such as remdesivir). Preliminary data confirms that Paxlovid® and remdesivir all retain full *in vitro* efficacy against Omicron sub-lineages. Notably all known escape mutations come at a fitness cost (although some are rather small); thus in the absence of any treatment with Paxlovid®, escape mutations are expected to be detrimental and not selected for. These mutations are not linked to general antigenic shift like the escape mutations to the therapeutic mAbs.

Mutations known to result in significant escape against Paxlovid remained extremely rare in June, both in Switzerland and worldwide (table 3).

## 7. Wastewater surveillance program

As of 2023, the wastewater surveillance program is no longer funded by the national surveillance program, but it continues using an alternate funding source. Data is presented here to be informative, and not to imply that this program is currently part of the national surveillance program.

In order to complement the genomic surveillance based on patient samples, the program includes sequencing of SARS-CoV-2 in wastewater samples. Notably, wastewater sequencing only recovers fragments of genomes and cannot produce full genome sequences to identify the emergence of a new variant unless that variant is highly divergent. Once a new variant emerges and is identified, wastewater sequencing can be useful to track its spread.

Samples are collected multiple times per week from in total ten wastewater treatment plants (WWTPs), coordinated by Eawag, Microsynth AG, and the canton Basel. The sequencing and analysis of these samples, including detection and quantification of variants, is done under the coordination of Prof. Niko Beerenwinkel, in collaboration with NEXUS Personalized Health Technologies, ETH Zurich. The wastewater sequencing program started in December 2020 for Lausanne and Zurich, and since then has been gradually extended (https://cov-spectrum.org/stories/wastewater-in-switzerland). In February, the wastewater program expanded from 6 sampling centers to 9, in March it increased to 10.

During the Month of June, the quasi-totality of the sequenced SARS-CoV-2 genetic material was estimated to originate from XBB* and its subvariants (Figure 7). The viral loads of SARS-CoV-2 in surveyed treatment plants were particularly low during that month, leading to an increase in the noise in the sequencing data, but it was still possible to identify XBB subvariants. The relative abundances of subvariants XBB.1.5 and XBB.1.9 tended to shrink in most localities, while the XBB.1.16 and XBB.2.3 variants were growing in relative abundance in most treatment plants.

Modelling of the competition between XBB subvariants (Figure 8), shows XBB.1.16 and XBB.2.3 having a growth advantage over XBB.1.5 and XBB.1.9, but does not show a significant growth advantage of XBB.2.3 over XBB.1.16.

During the month of June, different mutations linked to Paxlovid® resistance were detected in 4 samples of 4 treatment plants (Table 4). These sporadic detections at a low level could be attributed to protocol artefacts.

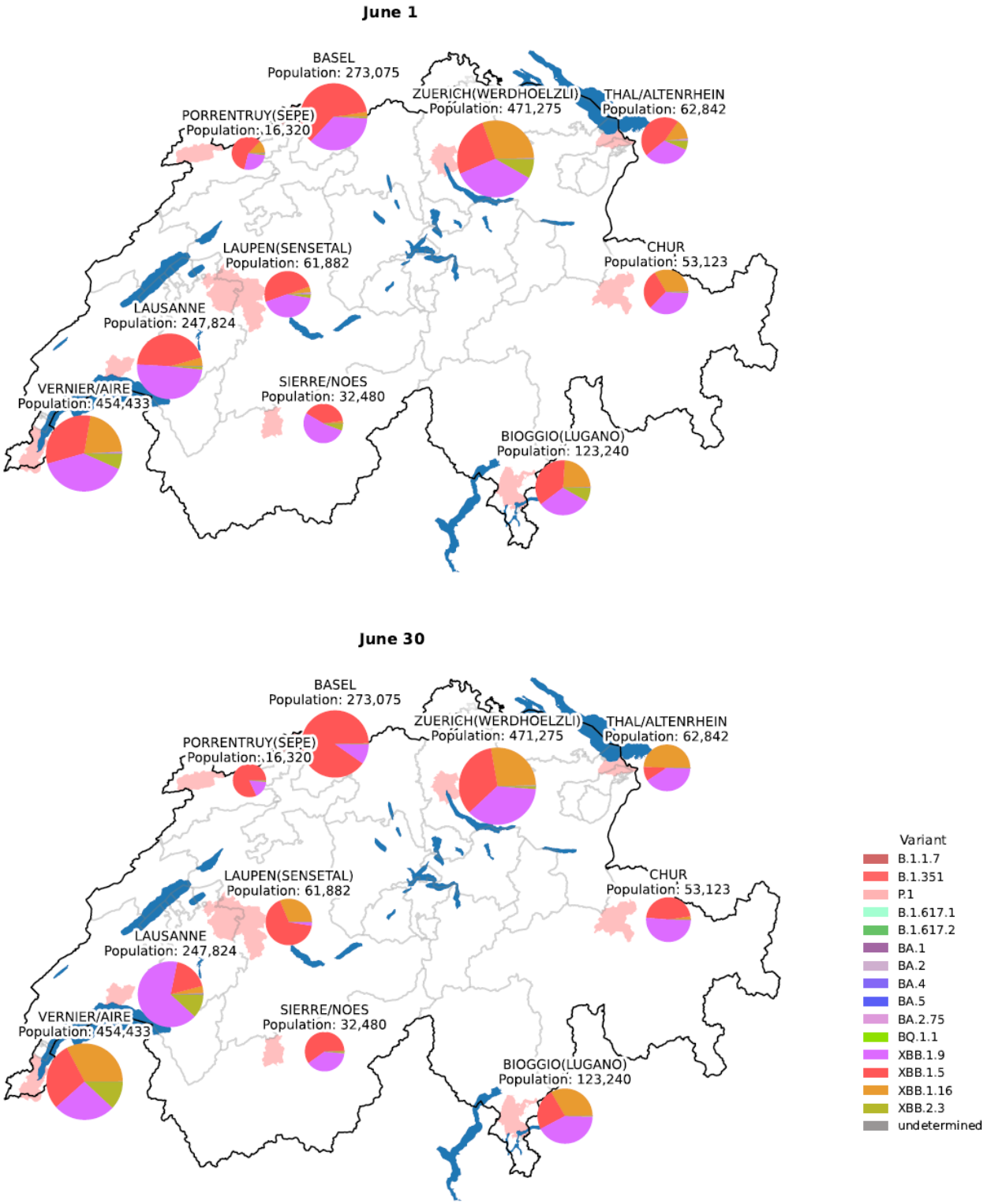
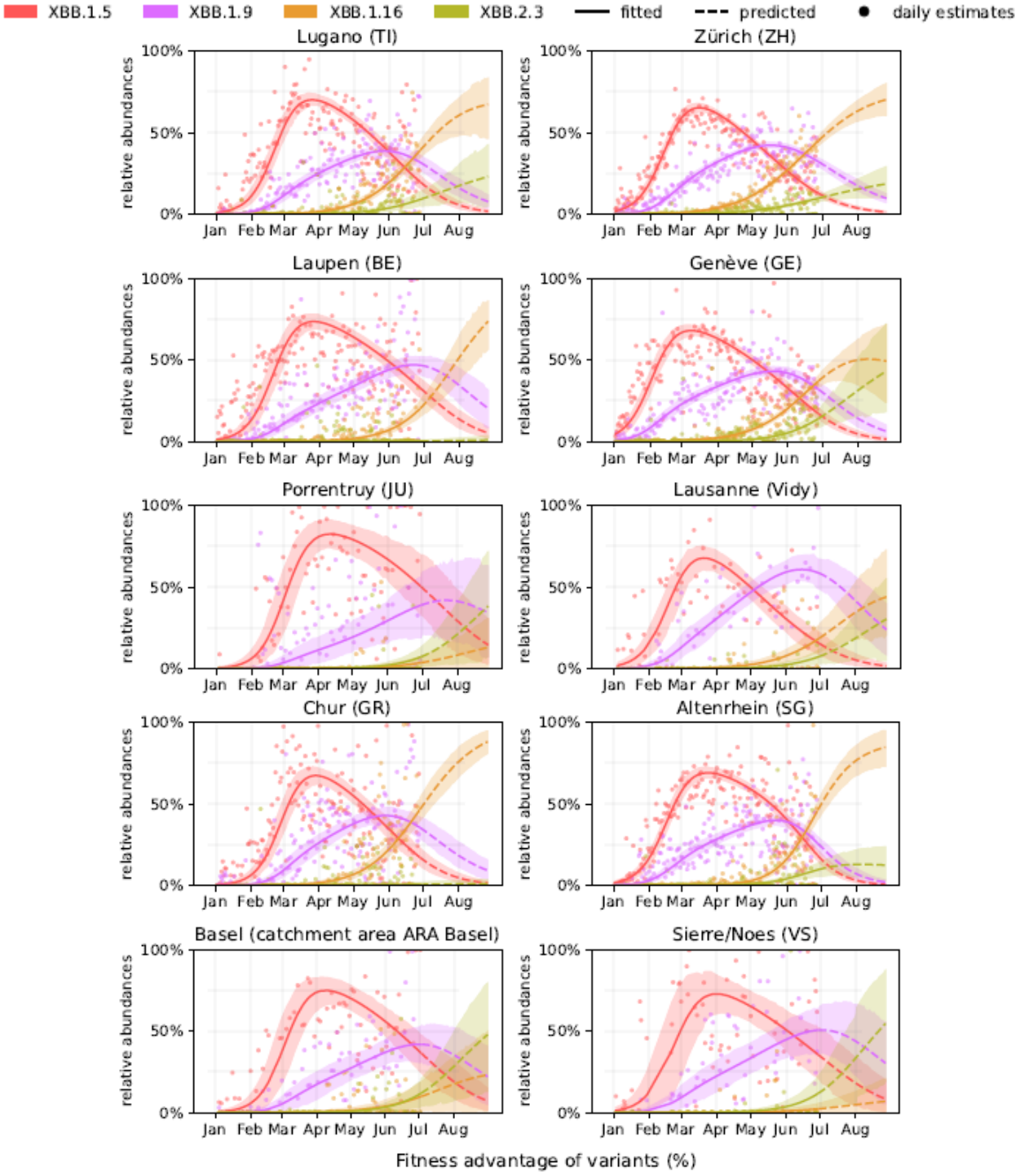



*Figure 7: Overview of the relative abundances of variants of SARS-CoV-2 at the beginning and end of May 2023, estimated from wastewater samples collected daily in WWTPs located at 10 different Swiss locations. The size of the pie charts are proportional to the population connected to the wastewater treatment plants. Pink shaded areas represent catchment areas (boundaries from 2017). The population connected to the Vernier (GE) wastewater treatment plant also includes ~44,000 inhabitants from neighbouring French communities*




Fitness advantage of variants (%)

| | XBB.1.5 | XBB.1.9 | XBB.1.16 |
|---|---|---|---|
| XBB.1.9 | 8.8 (4.6 – 12.7) | | |
| XBB.1.16 | 26.9 (21.6 – 31.7) | 16.6 (11.8 – 21.5) | |
| XBB.2.3 | 29.6 (23.2 – 36.2) | 19.1 (12.9 – 25.2) | 2.2 (-3.4 – 7.4) |

*Figure 8: Modelling of the competition XBB subvariants using a hierarchical logistic growth model fitted on the estimated relative abundances of variants. Relative abundances were estimated from wastewater samples collected from January 2023 until the end of May 2023 in WWTPs from 10 different Swiss locations. Plots show fitted models (solid lines) to the daily estimates of variant relative abundances (points), predictions from the models (dashed lines) and 95%HDI for the model fits and predictions (shaded bands). An online dynamic navigation of daily prevalence is available at [https://cov-spectrum.org/stories/wastewater-in-switzerland](https://cov-spectrum.org/stories/wastewater-in-switzerland)*

| AA position | Lugano (TI) | Laupen (BE) | Altenrhein (SG) | Chur (GR) | Genève (GE) | Zürich (ZH) | Lausanne (Vidy) | Sierre/Noes (VS) | Porrentruy (JU) | Basel (catchment area ARA |
|---|---|---|---|---|---|---|---|---|---|---|
| 140 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 143 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 144 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 165 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 166 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 167 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 168 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 172 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| 173 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 186 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 188 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 189 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 192 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 252 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

*Table 4: Overview of the surveillance of potential treatment escape mutations. Entries show for each location the number of samples during the month of June that had a positive detection of mutations leading to amino acid changes linked to resistance to Paxlovid®. Mutations to be monitored were selected from https://covdb.stanford.edu/drms/3clpro.*

## 8. Immunological characterization of the variants

Neutralization of SARS-CoV-2 VOC and multiple Omicron subvariants variants by currently used monoclonal antibodies was assessed at EPFL. The results show 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 9). Therefore development of pan-SARS-Cov2 monoclonal antibodies or combination thereof is still an urgent need to treat vulnerable patients.

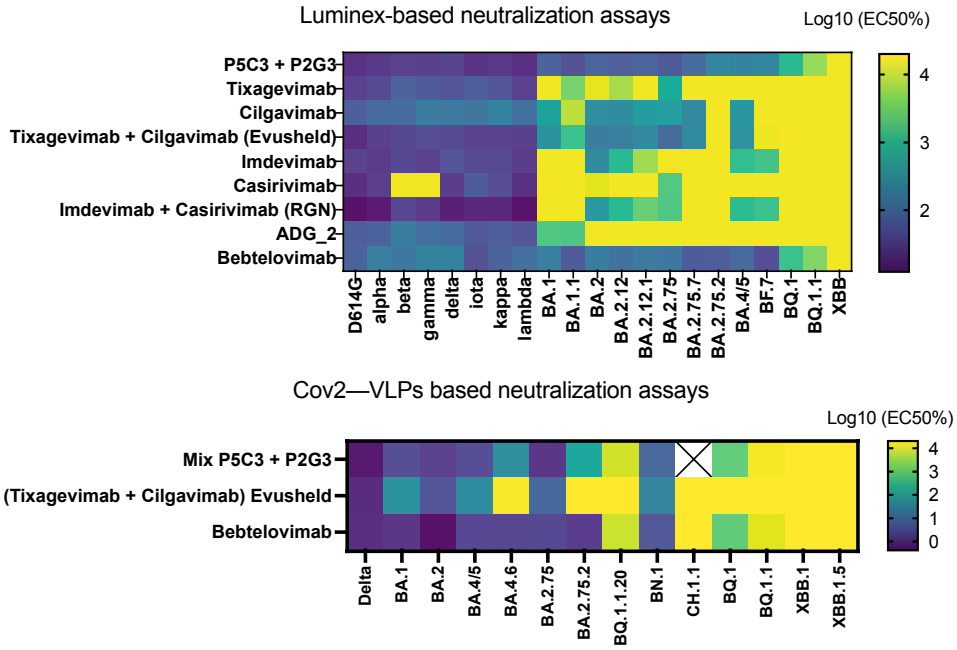



*Figure 9 : The neutralization potential of monoclonal antibodies was evaluated using either trimeric Spikes in a in-house developed cell-free Luminex-based assay (top panel) or SARS-Cov2 viral like particles in a conventional cell-based assay (bottom panel). In-house developed P5C3 and P2G3 antibodies, AstraZeneca Evusheld (Tixagevimab AZD8895 + Cilgavimab AZD1061) or Regeneron (Imdevimab RGN10987 + Casirivimab RGN10933) mixes of antibodies, Adagio (ADG-2) and Eli Lilly bebetelovimab (LyCov-1404) antibodies efficacy was tested on Spikes corresponding to the diverse variants energing during the course of the pandemic.*

**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.

sup_table_overview_Jun.xlsx

*Supplementary Table 1: Epidemiological data for Switzerland, its regions and cantons for June 2023: 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 sequenced |
|---|---|---|---|---|---|
| 21 | May 22-May 28 | 1 306 | 205 | 133 | 37.4% |
| 22 | May 29-June 4 | 1 110 | 151 | | |
| 23 | June 5- June 11 | 1 076 | 115 | 84 | 42.0% |
| 24 | June 12-June 18 | 940 | 85 | | |
| 25 | June 19- June 25 | 826 | 83 | 22 | 15.9% |
| 26 | June 26- 2 July | 766 | 55 | | |
| | Total | 6 024 | 694 | 239 | 34.44% |

*Supplementary Table 2: Total number of tests performed by the laboratories participating in the surveillance program from 22 May to 2 July 2023.*

| week | date | HUG | CHUV | ICH-VS | IFIK | UZH IMV | USB | EOC | All |
|---|---|---|---|---|---|---|---|---|---|
| 21 | May 22-May 28 | 28 | 30 | 0 | 14 | 23 | 16 | 22 | 133 |
| 22 | May 29-June 4 | | | | | | | | |
| 23 | June 5- June 11 | 19 | 7 | 0 | 8 | 23 | 16 | 11 | 84 |
| 24 | June 12-June 18 | | | | | | | | |
| 25 | June 19- June 25 | 8 | 6 | 0 | 0 | 8 | 0 | 0 | 22 |
| 26 | June 26- 2 July | | | | | | | | |
| | **Total** | 55 | 43 | 0 | 22 | 54 | 32 | 33 | 239 |

*Supplementary Table 3: number of sequences submitted to GISAID by each laboratory during the surveilled period (22 May to 2 July 2023).*

Contact list as of 24.05.23:

| Coordination committee mailing list | |
|---|---|
| Name | e-mail address |
| Laurent Kaiser | Laurent.Kaiser@hcuge.ch |
| Samuel Cordey | Samuel.Cordey@hcuge.ch |
| Marc Friedli | marc.friedli@epfl.ch |
| Richard Neher | richard.neher@unibas.ch |
| Tanja Stadler | tanja.stadler@bsse.ethz.ch |
| Louis Du Plessis | louis.duplessis@bsse.ethz.ch |
| Emma Hodcroft | emma.hodcroft@ispm.unibe.ch |
| Christian Althaus | christian.althaus@ispm.unibe.ch |
| Ioannis Xenarios | ioannis.xenarios@unil.ch |
| Philippe Le Mercier | Philippe.Lemercier@sib.swiss |
| Pauline Vetter | Pauline.Vetter@hcuge.ch |
| Erik Boehm | Erik.Boehm@hcuge.ch |
| Lorenzo Cerutti | lorenzo.cerutti@health2030.ch |
| Erik Studer | Erik.Studer@bag.admin.ch |

| Laboratories mailing list | | |
|---|---|---|
| Laboratory | Name | e-mail address |
| HUG | Laurent Kaiser | Laurent.Kaiser@hcuge.ch |
| HUG | Samuel Cordey | Samuel.Cordey@hcuge.ch |
| HUG | Pauline Vetter | Pauline.Vetter@hcuge.ch |
| HUG | Erik Boehm | Erik.Boehm@hcuge.ch |
| CHUV | Gilbert Greub | Gilbert.Greub@chuv.ch |
| CHUV | Claire Bertelli | Claire.Bertelli@chuv.ch |
| Universtätsspital Basel | Pascal Schlaepfer | Pascal.Schlaepfer@usb.ch |
| Universtätsspital Basel | Karoline Leuzinger | Karoline.Leuzinger@usb.ch |
| Universtätsspital Basel | Hans Hirsch | Hans.Hirsch@usb.ch |
| IFIK UNIBE | Alban Ramette | alban.ramette@ifik.unibe.ch |
| UZH | Alexandra Trkola | trkola.alexandra@virology.uzh.ch |
| UZH | Michael Huber | huber.michael@virology.uzh.ch |
| EOC Bellinzona | Gladys Martinetti Luchini | Gladys.MartinettiLucchini@eoc.ch |
| Hopitaux du Valais – Institut Central | Alexis Dumoulin | Alexis.Dumoulin@hopitalvs.ch |

| BAG mailing list: | |
|---|---|
| Name | e-mail address |
| Erik Studer | Erik.Studer@bag.admin.ch |
| Katrin Schneider | katrin.schneider@bag.admin.ch |
| Anna Fesser | Anna.Fesser@bag.admin.ch |
| Ursina Roder | ursina.roder@bag.admin.ch |
| Lionel Rohner | lionel.rohner@bag.admin.ch |
| Michael Bel | Michael.Bel@bag.admin.ch |
| Urs Mayr | urs.mayr@bag.admin.ch |
| Damir Perisa | Damir.Perisa@bag.admin.ch |
| Martine Bourqui | Martine.Bourqui@bag.admin.ch |
| Mirjam Mäusezahl | Mirjam.Mäusezahl@bag.admin.ch |
| Tobias Schuster | tobias.schuster@bag.admin.ch |

| Sequencing centers: | | |
|---|---|---|
| Center | Name | e-mail address |
| Health 2030 Genome Center | Keith Harshman | keith.harshman@health2030.ch |
| Health 2030 Genome Center | Ioannis Xenarios | ioannis.xenarios@health2030.ch |
| Genomics Facility Basel-ETH Zurich | Christian Beisel | christian.beisel@bsse.ethz.ch |
| The Functional Genomics Center Zurich (FGCZ)- ETHZ and UZH | Ralph Schlapbach | ralph.schlapbach@fgcz.ethz.ch |

| Wastewater surveillance program mailing list: | |
|---|---|
| Name | e-mail address |
| Niko Beerenwinkel | niko.beerenwinkel@bsse.ethz.ch |
| David Dreifuss | david.dreifuss@bsse.ethz.ch |

| Immunological characterization program of the variant mailing list: | |
|---|---|
| Name | e-mail address |
| Priscilla Turelli | priscilla.turelli@epfl.ch |
| Didier Trono | didier.trono@epfl.ch |