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

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1. Summary

During the month of August, the number of positive SARS-CoV-2 tests increased in Switzerland, and the test positivity rate within the program increased to 13.9% from July's 7.8%. Notably, testing rates are near an all-time low (3'789 test for August vs the lowest value of 3'252 from July 2023). The number of hospitalizations due to COVID-19 continues to be low, but have peaked modestly at the beginning of September.

The 526 positive tests processed by laboratories participating to the program constituted around 27% of the reported positive tests in Switzerland and was over double July's number.

A total of 206 new sequences were submitted to GISAID during the reporting period, covering the month of August (July 31 to August 27), which represents around 39% 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 1.9 (particularly EG.5), or 1.16, with none of these sublineages exceeding 50%. The progressive increase in the percentage of the EG.5 subvariant (now designated as a VOI by the WHO) appears to have peaked in Switzerland during this reporting period, as other competitors have emerged. It accounts for 36% of the sequences detected in this reporting period. Numerous sublineages have picked up a pair of mutations, dubbed the "FLip" mutations, that are apparently beneficial and lead to increased immune escape. These mutations comprised <10% of sequences, and the limited data did not show strong signs of growth within Switzerland during August, however data for the entire European region clearly indicates growth.

The new highly divergent BA.2.86 variant was first detected in Switzerland in patient samples after this reporting period, during the week of 4-9-2023, but wastewater data suggests it was already present in multiple regions of Switzerland in August. 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 the end of 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 varied between once every 2 or 4 weeks in August and September, depending on the number of cases, the arrival of BA.2.86 and the "Flip" mutations.

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 has included sequencing of SARS-CoV-2 in wastewater samples. In 2023, the wastewater sequencing continued to be funded by the FOPH, but under a separate fund from the rest of the genomic surveillance program and is reported separately. Data is available at: https://cov-spectrum.org/stories/wastewater-in-switzerland.

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 July 31 to August 27, 2023 (weeks 31-34). All data presented in this report are based on the sampling date.

3. Variants of Concern (VOCs), Variants of Interest (VOI), Variants Under Monitoring (VUM) and other surveilled variants: brief summary and special focus

For an overview of the variant categories (VOC, VOI, and VUM) and their criteria, please refer to previous reports.

The WHO currently assesses that the currently circulating VOIs are XBB.1.5, XBB.1.16, and EG.5. Currently circulating VUMs consist of BA.2.75, CH.1.1, XBB*, XBB.1.9.1, XBB.1.9.2, XBB.2.3, and BA.2.86.

Omicron

For a general overview of the emergence of Omicron and the XBB lineage that resulted from recombination within Omicron, please refer to previous reports.

In August 2023, a sublineage of XBB.1.9.2 with and additional Spike mutation (F456L) called EG.5 was upgraded from a VOM to a VOI. All major XBB sublineages (XBB.1.5/1.9/1.16) show 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.

While BA.2.75 has never achieved widespread circulation in Switzerland, it is worth noting that one of its sublineages (DV.7.1) is still circulating in Switzerland, apparently able to compete with XBB sublineages.

In August, a new sublineage, BA.2.86, was identified and assigned VUM status due to the large number of mutations, with approximately 30 more mutations in the spike protein than the circulating XBB lineages.

In Switzerland, XBB.1.5 was definitively overtaken by XBB.1.9 in week 21, and EG.5 started overtaking basal XBB.1.9, but peaked at 44% of sequences.

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.

The S-gene target failure (SGTF) exhibited with the Taqpath PCR assays may be useful for detecting probable BA.2.86 cases, as currently dominant XBB lineages do not display it, whereas BA.2.86 does. BA.2.86 specific PCRs are being validated to confirm detection of probable BA.2.86 samples identified by SGTF assay. Discrimination between XBB subvariants is by now only feasible by genomic sequencing.

Immune escape

Please refer to previous reports for a summary of neutralization by vaccine sera against the XBB.1.5, 1.9, and 1.16 lineages.

EG.5, BA.2.86, in addition to other emerging XBB* sublineages all show further escape from the already low neutralization. One particular combination of mutations, dubbed “FLip” (Spike positions 455 and 456 *flip* from LF to FL), has been observed to arise in multiple lineages, and has been shown to lead to increased immune escape (especially when both are present together).

Despite the large number of additional spike mutations, BA.2.86’s escape from neutralization appears to be similar to the escape of multiple XBB* sublineages according to multiple preprints using pseudoviruses. This may be due to “immune imprinting”, as even updated boosters perform much worse in human test subjects (who are no longer immunologically naïve) against the targeted strain than the original virus. In contrast, this disparity is not seen in the data from naïve primate studies.

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, including animal studies provide evidence that XBB sublineages including EG.5 are not more severe.

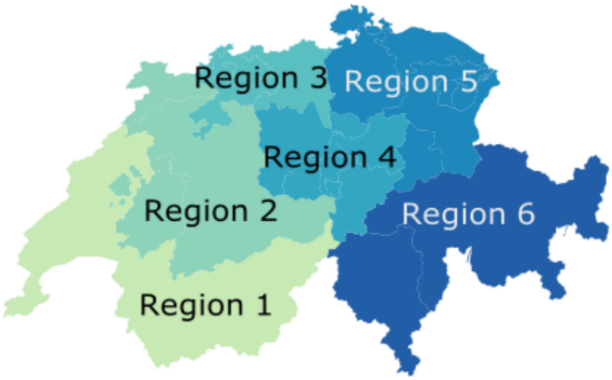
Data on BA.2.86 severity is lacking, but studies with pseudovirus indicate that it is less infective in certain cells types (Such as ACE2-293T cells), but not others (such as Calu-3 cells).

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 6 August to 27 August, the FOPH reported 1711 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 27% of this number. From 31 July to 27 August, the labs participating in the national surveillance program produced 526 positive tests (463 from 6 to 27 August). Along with the number of tests performed in the country, the number of positive tests continued to decrease in Switzerland during the month of July relative to June, and since the beginning of the year. Notably, the percent of positives sequenced within the program was 39.16%, which is higher than that of July (30.98%). The test positivity rate within the program for August was 13.9%, compared to 7.8% from July.

Although case ascertainment rates may be too low to identify meaningful trends, there has been a minor increase in the number of hospitalizations mostly among people with multiple comorbidities, and without severe pneumonia as in earlier during the pandemic. 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).

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 206 SARS-CoV-2 sequences have been declared to have been processed during this period. There are 217 sequences available on GISAID that were submitted during this period (and 255 collected during this period) as of 5 September 2023.

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
31	31 July - 6 August	72
32	7 August - 13 August	
33	14 August - 20 August	134
34	21 August - 27 August	
	Total	206

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 trend of declining numbers of SARS-CoV-2 sequences submitted each week reversed during the month of August 2023 (Calendar weeks 31 - 34). 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.

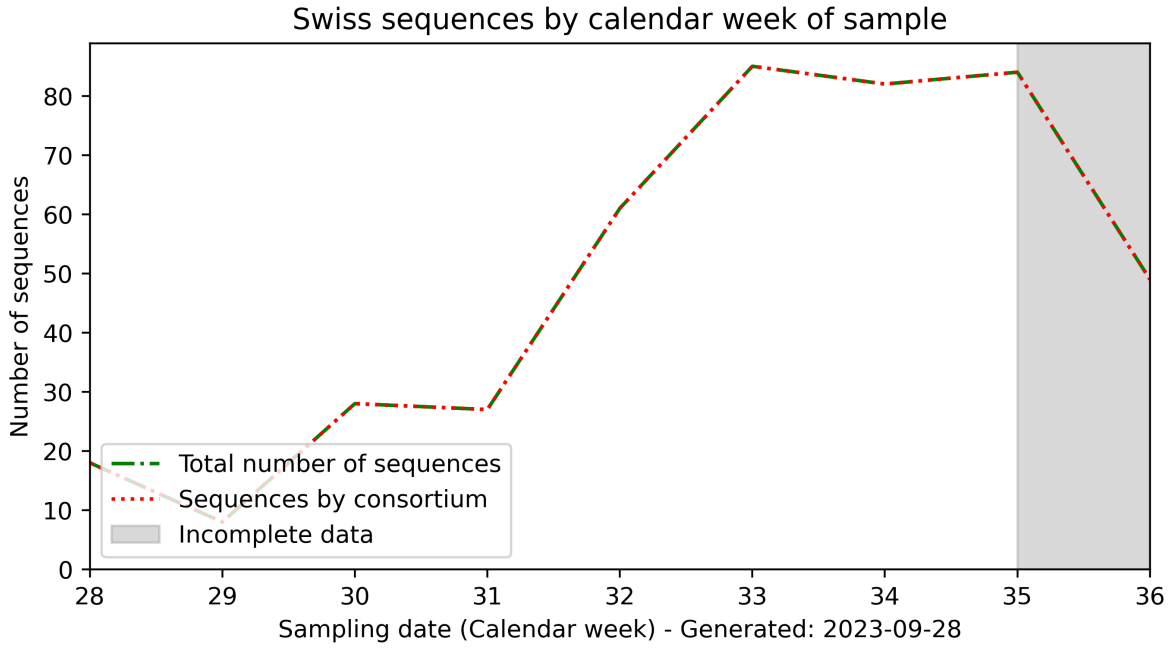


Figure 1: Number of SARS-CoV-2 sequences available for Switzerland (total available Swiss sequences in GISAID in green, Swiss sequences submitted through the program in dotted orange).

Figure 2 displays the number of SARS-CoV-2 cases sequenced for each Swiss region. Sequences remained low in all regions except region 1 and 2. The spike in region 1 sequencing was prompted by concern about the BA.2.86 variant, and correspondingly increased detection efforts. 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.

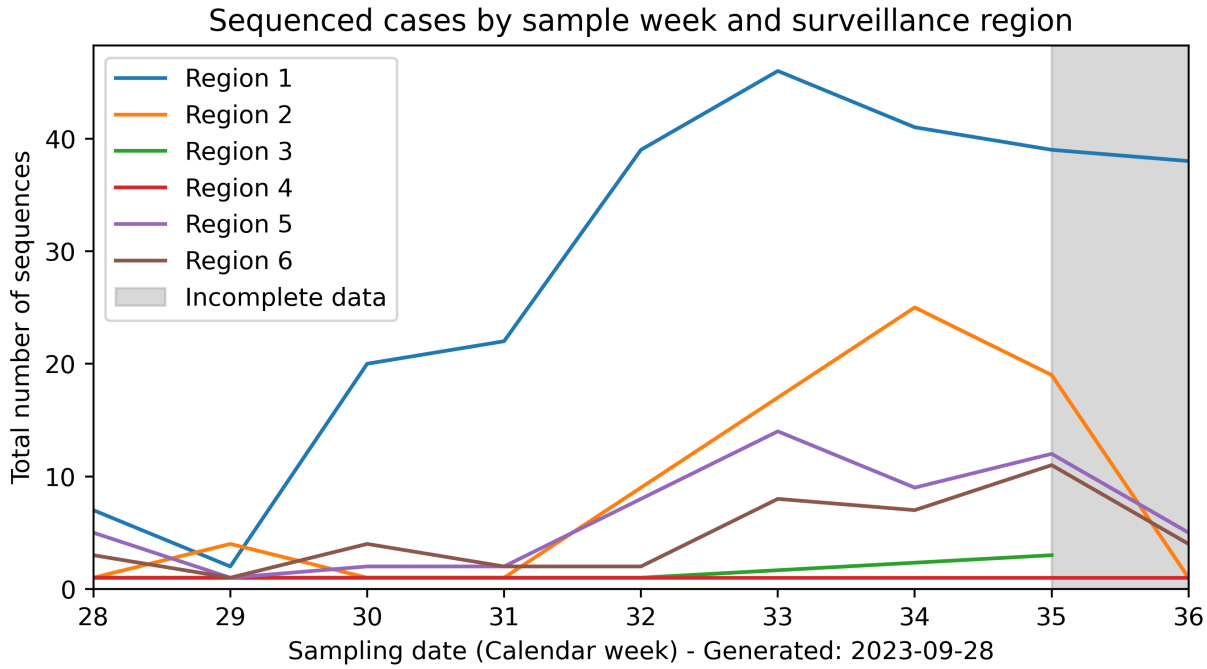


Figure 2: Sequencing coverage among the different Swiss regions per week, by number of sequences.

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).

The vast majority of circulating viruses are XBB sublineages now. XBB.1.9 continued its dominance over XBB.1.5. 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, 92 EG.5 sequences were detected during this period, amounting to 36% of the total sequences, a substantially increased proportion. Also noteworthy is the continued circulation of BA.2.75 derivatives, in particular nosocomial clusters of the BA.2.75 derivative DV.7 were detected in Geneva.

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	4	1	11	59	25	128	22	2	3	255
1	1	1	7	19	20	85	13	2	0	148
2	1	0	2	27	2	16	4	0	0	52
3	0	0	0	0	0	1	0	0	0	1
4	0	0	1	0	0	0	0	0	0	1
5	1	0	1	8	1	17	3	0	2	33
6	1	0	0	4	2	9	2	0	1	19

Table 2: number of sequences corresponding to selected variants in each region of Switzerland from July 31 to August 27, according to data received by 29 September, 2023.

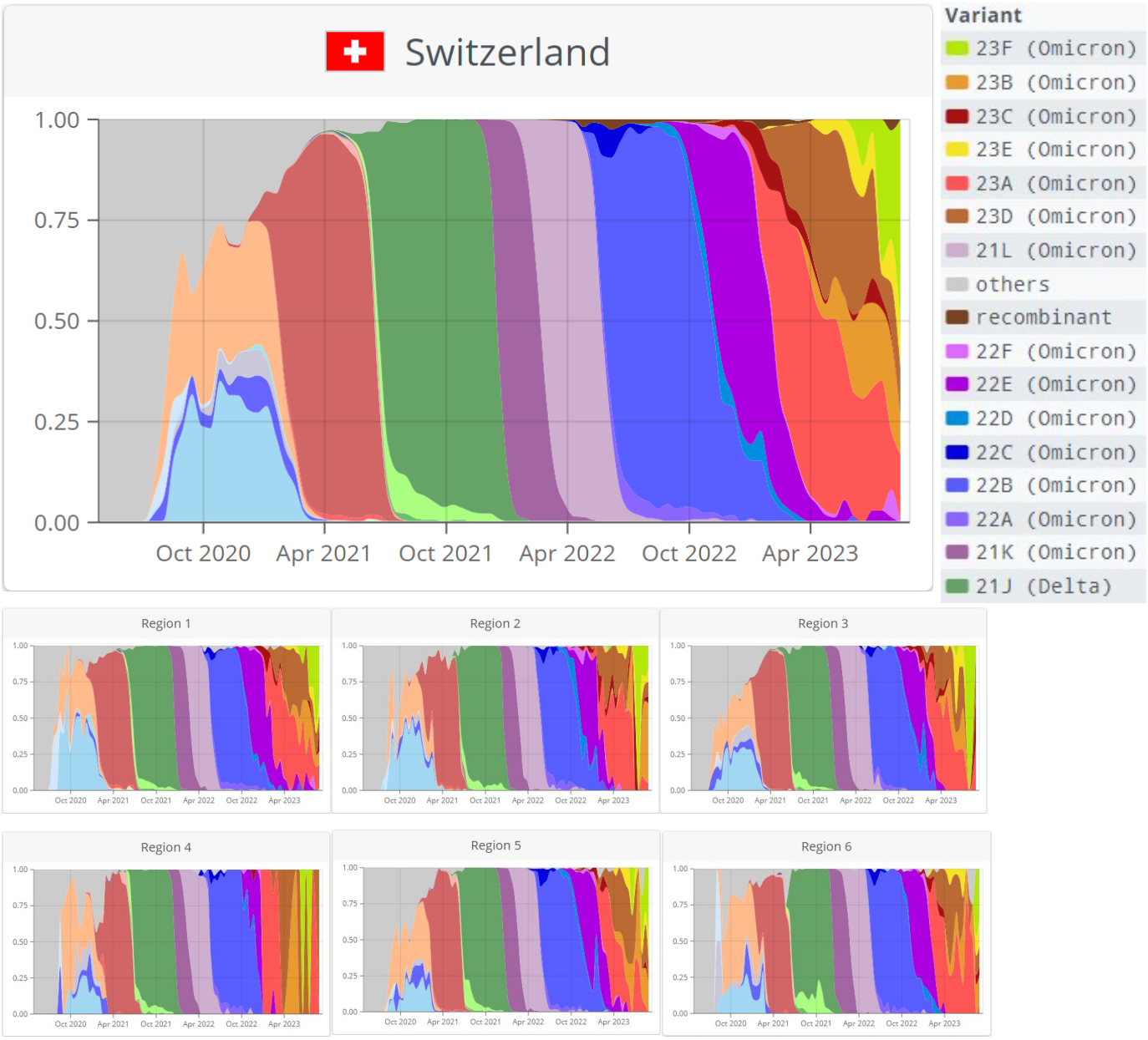


Figure 3: proportion of the total number of sequences (not cases), over time, that fall into defined variant groups, for Switzerland. Screenshot from CoVariants website. Dynamic navigation is available at https://covariants.org/per-country. Nexstrain lineage correspondence with pango lineages are as 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).

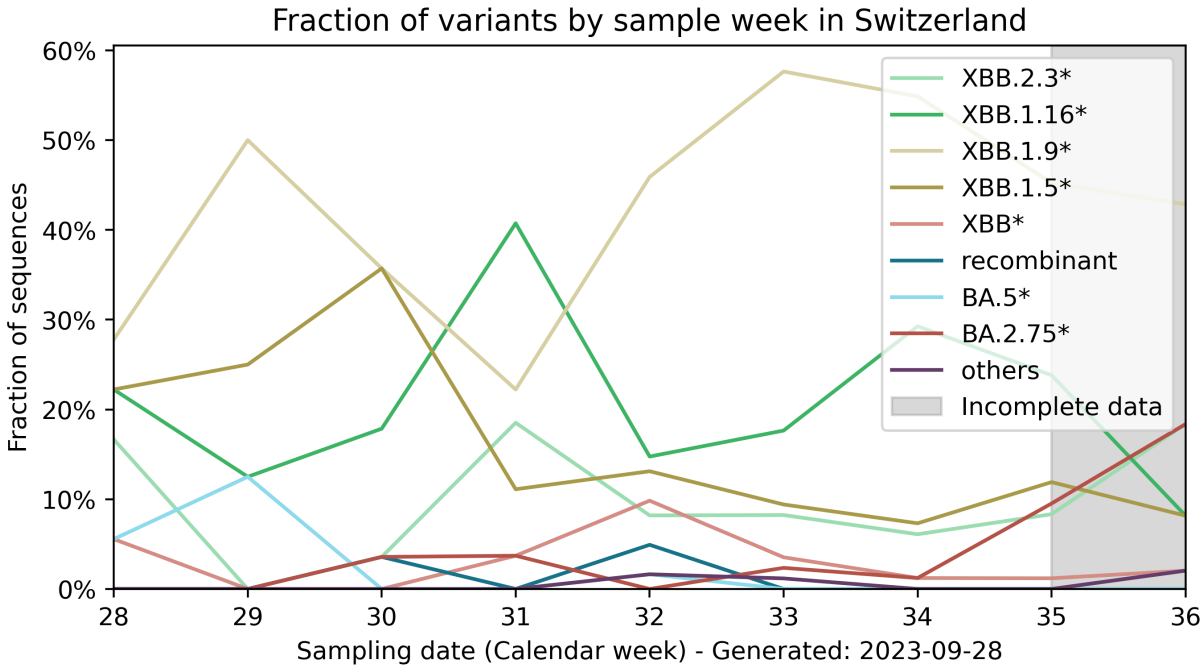


Figure 4: Percentage of circulating VOCs and VOIs in Switzerland by week, up to week 35 of 2023, according to the sequences from Switzerland that were successfully submitted. Note XBB.1.9 and its sublineages were the most common variants but did not account for much more than half of the sequences.

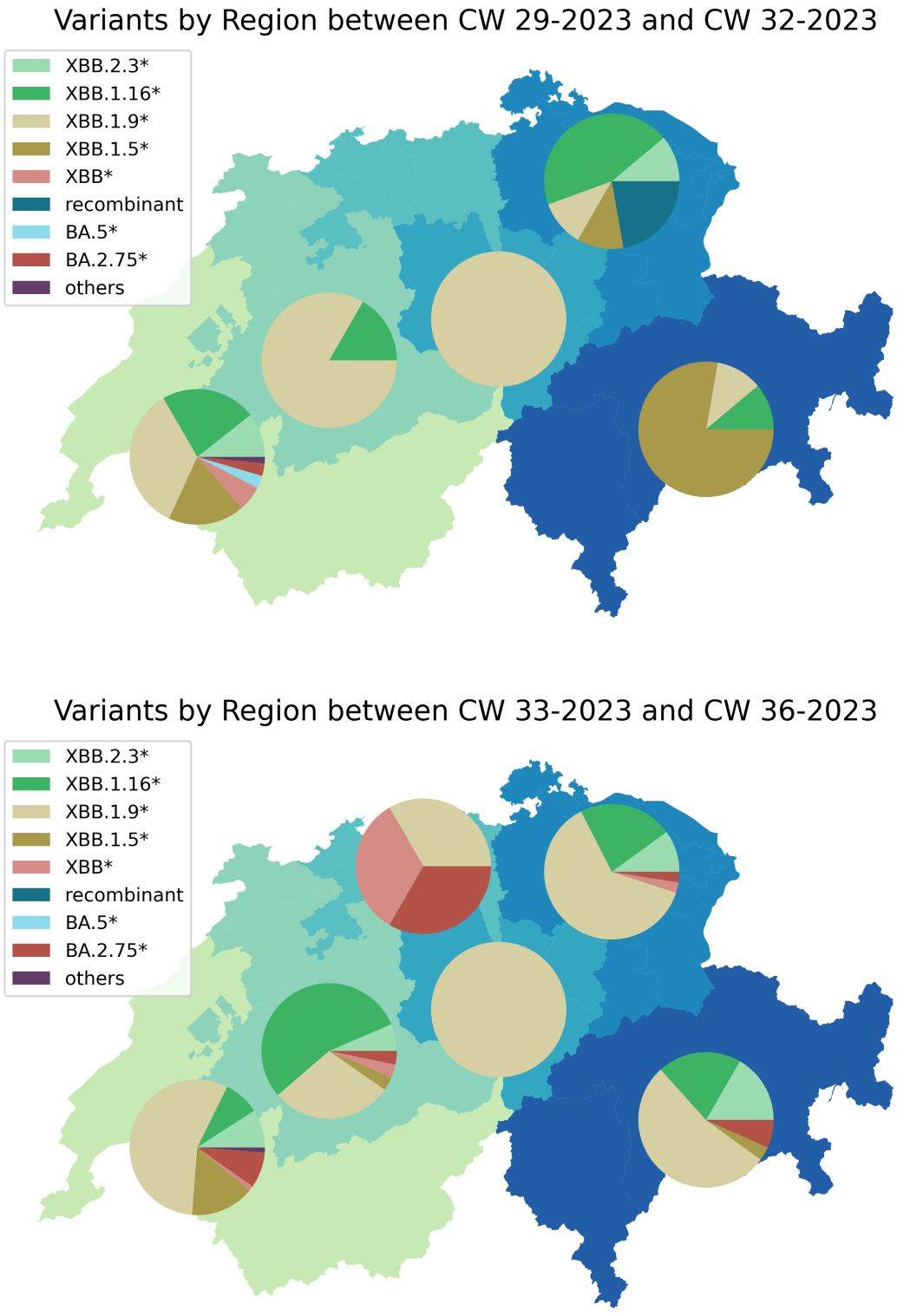


Figure 5: Distribution of variants per region, by Calendar Week (CW), for August 2023. Note the co-dominance of the XBB.1.5, XBB.1.9, and XBB.1.16 lineages. Region 4 was underrepresented and had just 2 samples of XBB.1.9.

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 multiple XBB* sublineages will compete with each other without achieving dominance. At a larger scale, XBB* (including all of its sublineages) will still be dominant. Data for BA.2.86 is unavailable, and represents a considerable unknown.

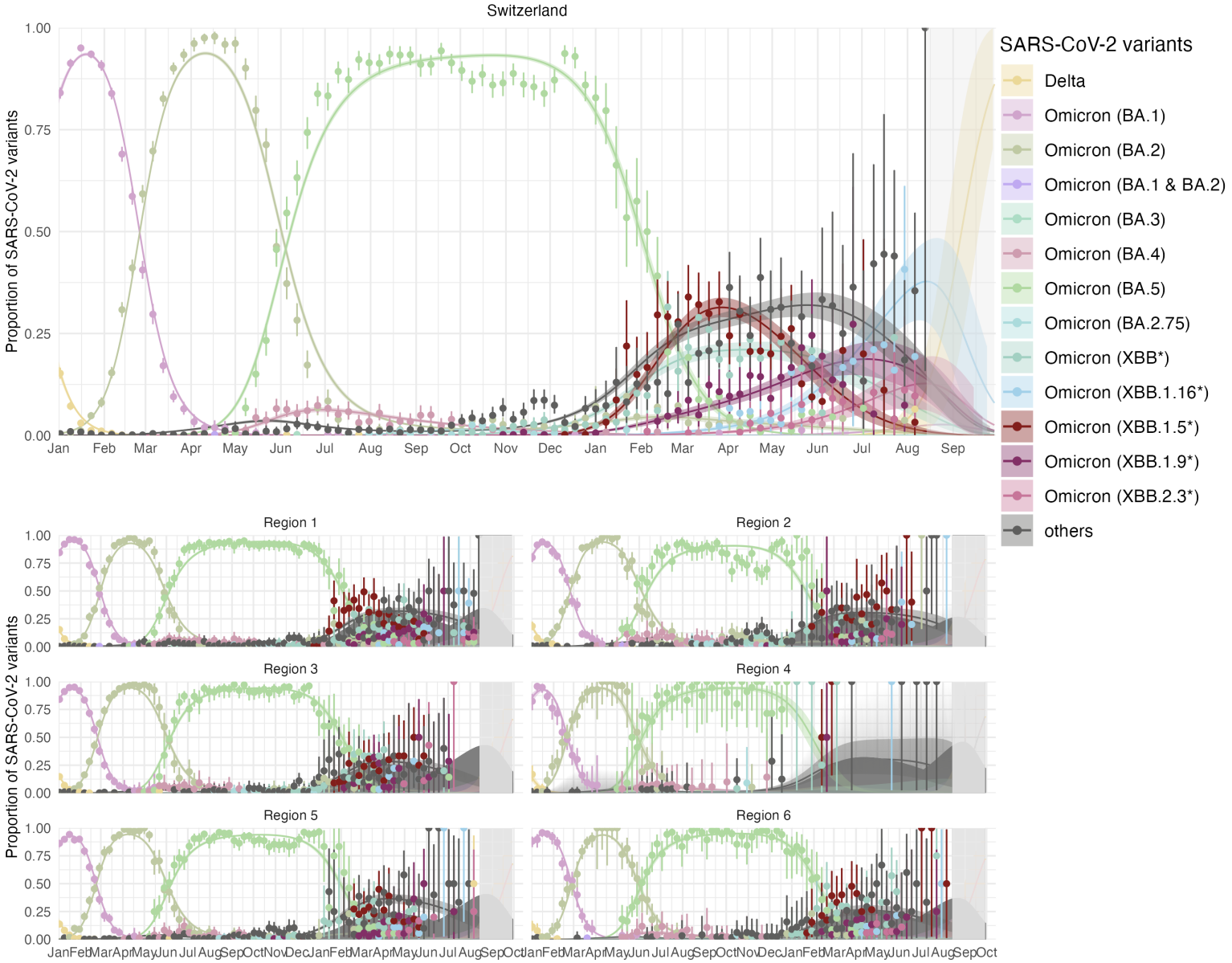


Figure 6: Observed and modeled proportion of SARS-CoV-2 variants over time in Switzerland. Since early 2021, multiple successive variants have been observed to displace all previous variants (often achieving a dominance of >99.9% of the circulation). Alpha was replaced by Delta, followed by Omicron BA.1, then BA.2, BA.5, BQ.1, XBB.1.5. After XBB.1.5, no lineage has been able to achieve strict dominance (>50% of all circulating viruses). 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

AA position	World	Europe	Switzerland
Sotrovimab (Spike mutations)			
337	0.03	0.01 (1)	0
340	0.06	0.08	0.36 (1)
356	0.98	1.14	1.45 (4)
371	92.68	91.92	99.64
377	0.02	0	0
449	0.00 (2)	0.01 (2)	0
476	0.03	0.02 (3)	0
494	1.35	1.95	1.82 (5)
Paxlovid® (Nsp5 mutations)			
15	0.00 (1)	0	0
48	0.06	0	0
49	0.00 (2)	0.01 (1)	0
140	0	0	0
143	0	0	0
144	0.00 (1)	0	0
165	0.00 (2)	0	0
166	0.00 (2)	0	0
167	0.00 (1)	0	0
168	0.00 (1)	0	0
172	0.00 (1)	0	0
173	0.00 (1)	0	0
186	0.01 (4)	0	0
188	0.01 (7)	0.01 (2)	0
189	0.00 (3)	0.01 (2)	0
192	0.01 (6)	0.02 (3)	0
194	0.05	0.13	0
248	0.00 (1)	0	0
252	0	0	0
304	0.00 (3)	0.01 (1)	0

Current data suggests that *in vitro* neutralization by sotrovimab of the currently circulating XBB variants is substantially reduced relative to the original virus, but to what extent is unclear due to conflicting experimental results. The 455F and 456L mutations together (the "FLip" mutations" have been shown to lead to increased resistance to sotrovimab (but not on their own). The new BA.2.86 variant appears to be completely resistant to neutralization by sotrovimab. The impact on clinical efficacy is however unclear, as some in vitro data also suggest an effector effect.

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 August 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 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.*

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 August, both in Switzerland and worldwide (Table 3).

7. Wastewater surveillance program

As of 2023, the wastewater surveillance program is funded by the FOPH separately from the rest of the national surveillance program. Wastewater data is presented weekly to the FOPH and will no longer be included in detail in this report. Data from the wastewater report is available here: (https://cov-spectrum.org/stories/wastewater-in-switzerland

Acknowledgements:

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

Erik Boehm, Marc Friedli, Pauline Vetter, Samuel Cordey, Richard Neher, Christian Althaus, Emma Hodcroft, Tanja Stadler, Philippe Lemercier, Ioannis Xenarios, Lorenzo Cerutti, Louis Du Plessis, Erik Studer, Laurent Kaiser, for the Swiss national SARS-CoV-2 genomic and variants surveillance program coordination committee.

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.

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Supplementary Table 1: Epidemiological data for Switzerland, its regions and cantons for Aug 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
31	31 July - 6 August	709	63	72	37.1
32	7 August - 13 August	963	131		
33	14 August - 20 August	1 010	147	134	40.4
34	21 August - 27 August	1 107	185		
	Total	3 789	526	206	39.2

Supplementary Table 2: Total number of tests performed by the laboratories participating in the surveillance program from 31 July to 27 August 2023.

week	Date	HUG	CHUV	ICH-VS	IFIK	UZH IMV	USB	EOC	All
31	31 July - 6 August	11	14	0	0	0	21	4	72
32	7 August - 13 August		22						
33	14 August - 20 August	42	17	0	6	10	16	12	134
34	21 August - 27 August		31						
	Total	53	84	0	6	10	37	16	206

Supplementary Table 3: number of sequences submitted to GISAID by each laboratory during the surveilled period (31 July to 27 August21 2023).

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