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

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1. Summary

During the month of October, the number of positive SARS-CoV-2 tests increased in Switzerland, and the test positivity rate within the program increased to 19.6% from September's 16.9%. Notably, testing rates have increased over 90% (8'493 tests for October vs 7'218 tests for September and the lowest value of 3'252 from July 2023). The number of hospitalizations due to COVID-19 continues to be low, but continued to modestly increase in October.

The 1'663 positive tests processed by laboratories participating to the program constituted about 1/3 of the reported positive tests in Switzerland and was substantially more than September's number (1'222, which was over August's number).

A total of 570 new sequences were submitted to GISAID during the reporting period, covering the month of October (25 September to 22 October), which represents around 34% of the program's positive tests, and about 12% of all positive tests. Note that since the beginning of 2023, the program has been adapted to focus on samples originating from hospitalized patients.

In October, the majority of the sequences in Switzerland still belonged to the XBB 1.9 sublineage (particularly EG.5). The percentage of the EG.5 subvariant (now designated as a VOI by the WHO) in Switzerland increased again in October, after a slight decline in September. It accounts for 54.9% of the sequences detected in October. Sublineages with the "FLip" pair of mutations, which are apparently beneficial and lead to increased immune escape, accounted for only 19% of October's sequences, a decrease from September's 31%.

The new subvariant of BA.2.86, dubbed JN.1, which appears to be growing worldwide, was first detected in Switzerland in patient samples, during the week of 2.10.2023, and represented up to 15 % of the sequences in some regions of Switzerland, at the time of writing of this report. All BA.2.86 sublineages, including JN.1 were designated as a variant under monitoring by WHO on 21 November 2023. Wastewater data suggest that its proportion is progressively increasing over time. Current data does not suggest that any of these BA.2.86 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/).

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 2022and 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 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 25 September to 22 October, 2023 (weeks 39-42). 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, EG.5, and BA.2.86. Currently circulating VUMs consist of BA.2.75, CH.1.1, XBB*, XBB.1.9.1, XBB.1.9.2, and XBB.2.3.

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.

Worldwide, Omicron circulates mainly in the form of XBB sublineages, BA.2.75 sublineages, and BA.2.86 sublineages. In Switzerland, EG.5 started overtaking other lineages, and its rise briefly paused before increasing again in October, accounting for a high of 58% of sequences in week 41, although week 42 was slightly less.

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.

A new BA.2.86.1 sublineage, JN.1, carrying a spike mutation (L455S) appears to be the most competitive of the BA.2.86 sublineages. Its immune escape has not been characterized yet, but the residue is at the same site as other known immune escape mutations.

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.

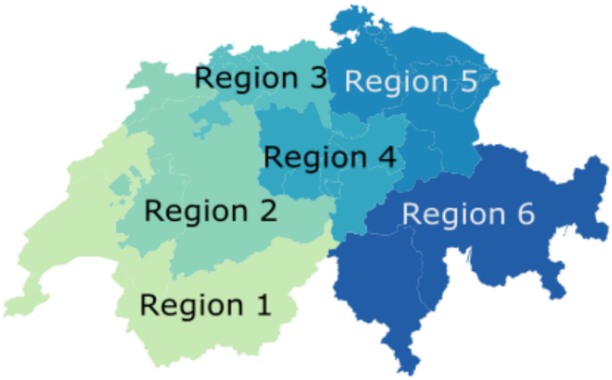
Data on BA.2.86 severity is lacking, but studies with pseudovirus indicate that it is less infective in certain cells types (Such as ACE2-293T cells), but not others (such as Calu-3 cells).

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 8 October to 29 October, the FOPH reported 4'864 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 over 34% of this number (1'663 positive tests). Along with the number of tests performed in the country, the number of positive tests increased by more than a third in Switzerland during the month of October relative to September (1'663 vs 1'222 positive). This percentage has been increasing since July. Notably, the percent of positives sequenced within the program was 34.3%, which is slightly higher than that of September (33.1%). The test positivity rate within the program for October was 16.9%, compared to 16.9% from September. Overall, about 12% of positive cases were sequenced.

Although case ascertainment rates may be too low to identify meaningful trends, there has been a trend during the month of September of minor increases 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 570 SARS-CoV-2 sequences have been declared to have been processed during this period. There are 558 sequences available on GISAID that were submitted during this period (and 541 collected during this period) as of 1 December 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
39	September 25 - October 1	285
40	October 2 to October 8	
41	October 9 to October 15	285
42	October 16 to October 22	
	Total	570

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, numbers of SARS-CoV-2 sequences submitted each week remained stable during the month of October 2023 (Calendar weeks 39 - 42). 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.

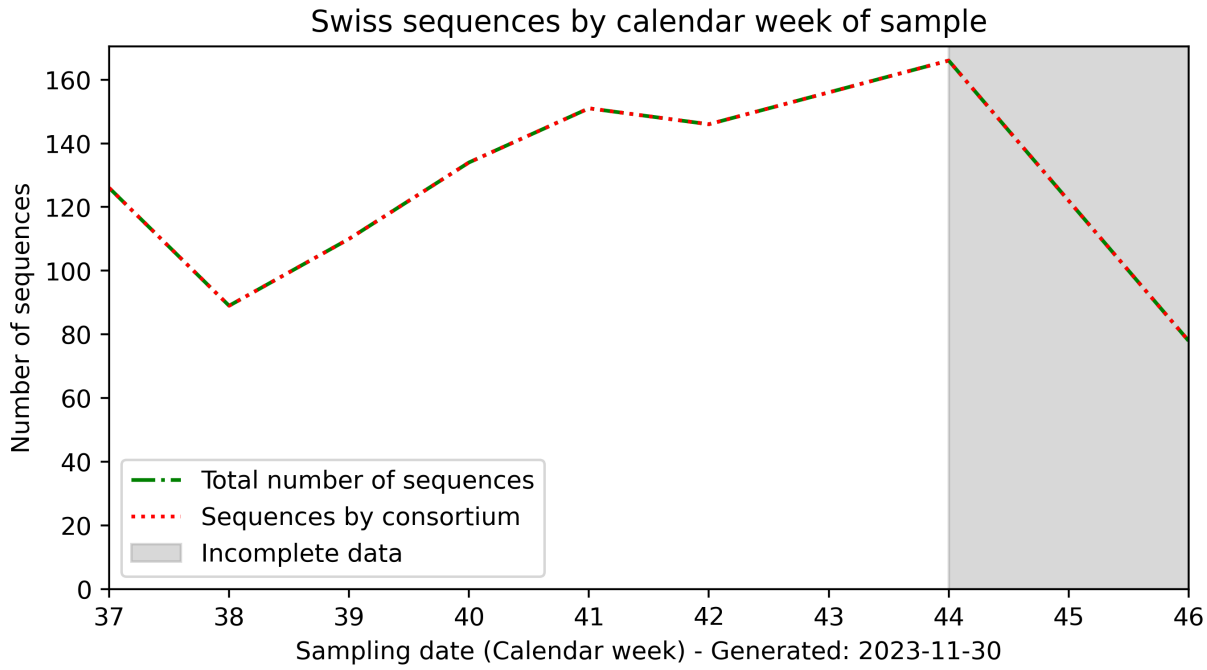


Figure 1: Number of SARS-CoV-2 sequences available for Switzerland (total available Swiss sequences in GISAID in green, Swiss sequences submitted through the program in dotted orange).

Figure 2 displays the number of SARS-CoV-2 cases sequenced for each Swiss region. Sequences remained low in all regions except region 1. Notably, region 4 (Luzern, Unterwalden, Uri, Zug and Schwyz) is still not effectively represented due to the absence of a laboratory participating in the program in this region, after the switch to surveillance of hospitalized cases.

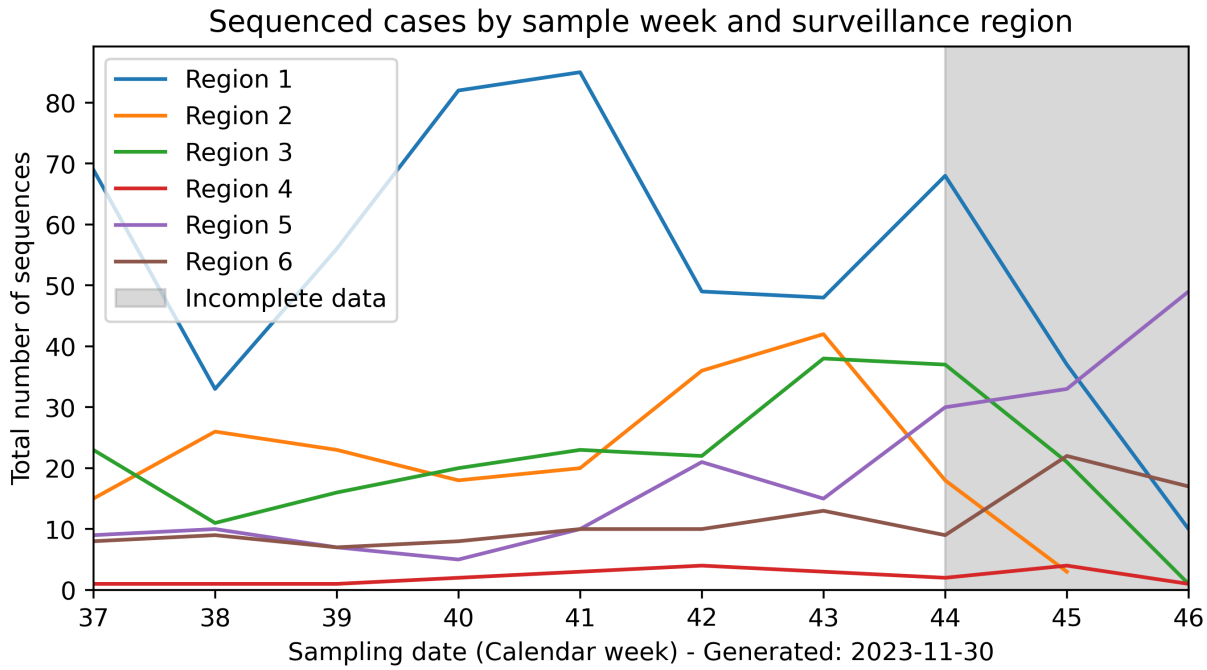


Figure 2: Sequencing coverage among the different Swiss regions per week, by number of sequences. Note that region 1 is over-represented, with 3/7 sequencing centers.

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. During the month of October, XBB.1.9 and its sublineages continued its dominance, comprising 65% of the sequences (Tables 2 and figures 2 and 3). Notably, 297 EG.5 sequences were detected during this period, amounting to 54.9 of the total sequences, a substantially increased proportion. Also noteworthy is the continued circulation of BA.2.75 derivatives, which persisted in October, in particular 5 sequences of the BA.2.75 derivative DV.7 were detected in Switzerland. Thirty BA.2.86 sequences (5.6% of sequences) were detected in Switzerland during this reporting period, of which 9 were JN.1 (1.7%). Notably 1 BA.5 sequence was detected (the first since week 32 of August). Since the beginning of November (data will be included in the next report), BA.2.86 derivatives have been progressively increasing in proportion.

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	5	1	12	64	38	351	25	30	15	541
1	2	1	5	21	17	187	15	18	6	272
2	3	0	2	17	4	66	2	2	1	97
3	0	0	1	14	7	49	3	6	1	81
4	0	0	1	1	1	5	0	0	0	8
5	0	0	2	9	5	19	2	3	3	43
6	0	0	1	2	3	24	2	0	3	35

Table 2: number of sequences corresponding to selected variants in each region of Switzerland from 28 August to 24 September, according to data received by 01 November, 2023. Note: recombinants denote recombinations between identified lineages, which may be recombinates themselves (ie: the XBB lineages)

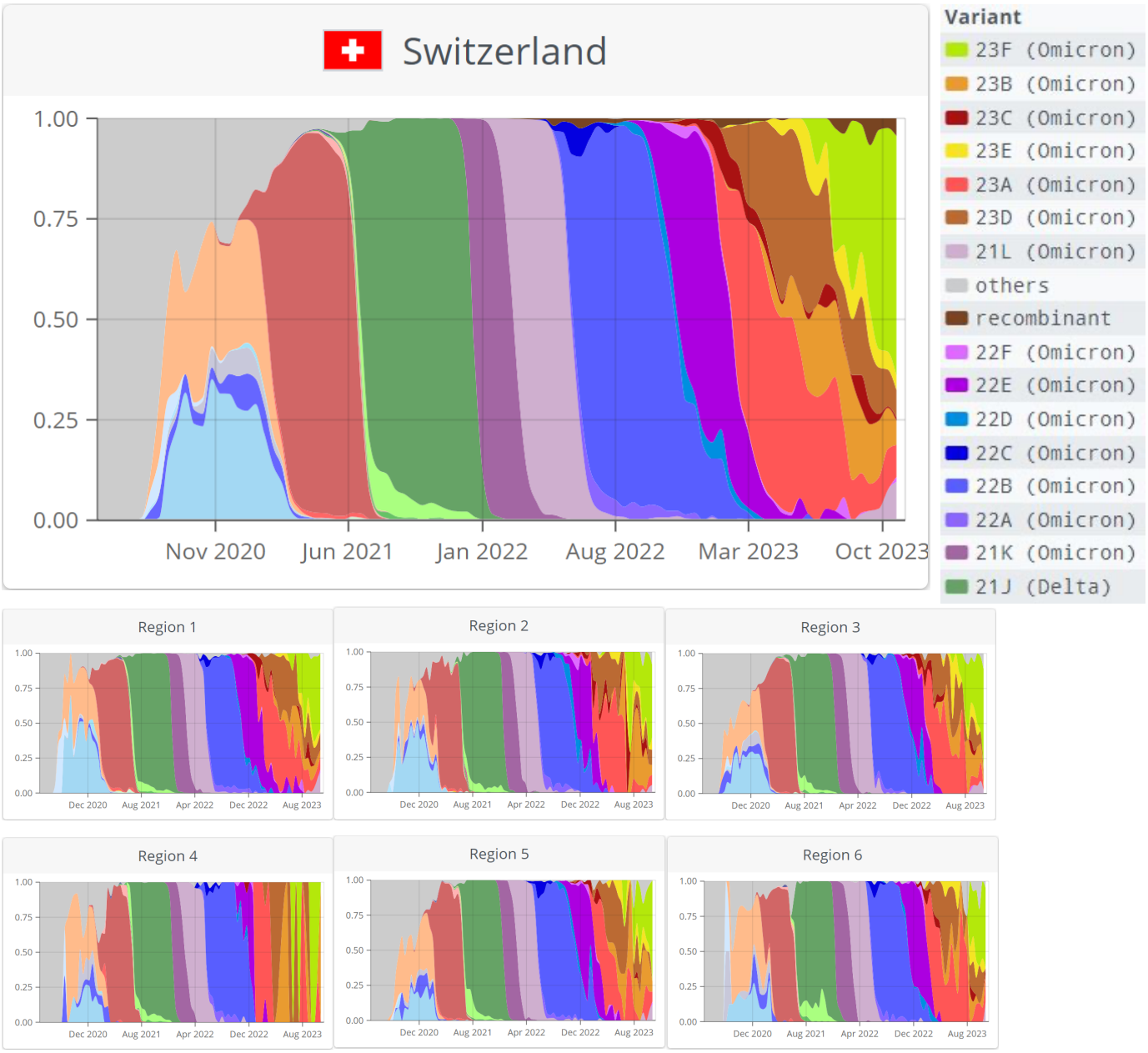


Figure 3: proportion of the total number of sequences (not cases), over time, that fall into defined variant groups, for Switzerland. Screenshot from CoVariants website. Dynamic navigation is available at https://covariants.org/per-country. Nexstrain lineage correspondence with pango lineages are as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

Note that the 21L variants progressively increased in proportion over the last month. BA.2.86 has not been given its own Nexstrain designation yet, and is still grouped with basal BA.2 in these graphs. Basal BA.2 is not resurging.

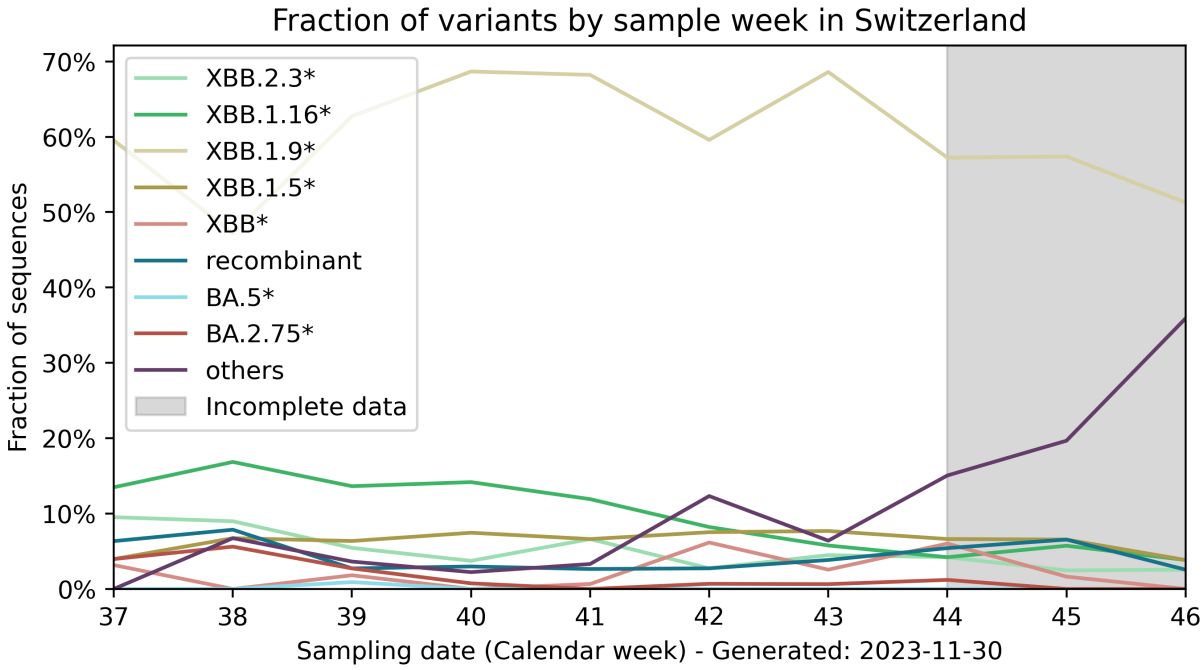


Figure 4: Percentage of circulating VOCs and VOIs in Switzerland by week, up to week 44 of 2023, according to the sequences from Switzerland that were successfully submitted. Note XBB.1.9 and its sublineages were the most common variants, accounting for more than half of the sequences. Not the increase in other lineages.

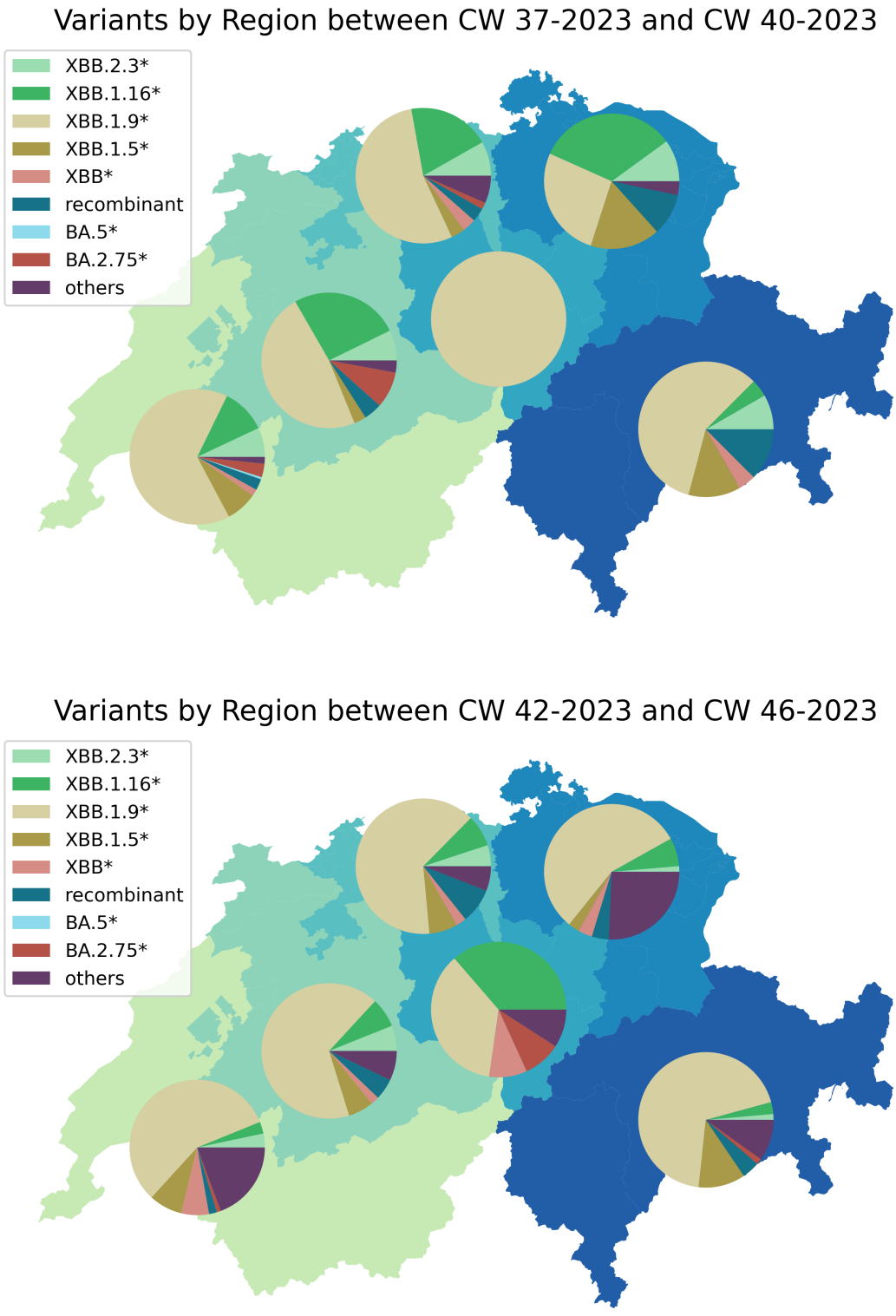


Figure 5: Distribution of variants per region, by Calendar Week (CW), for early October vs early November 2023. Note the continued dominance of XBB.1.9 and its sublineages.

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.

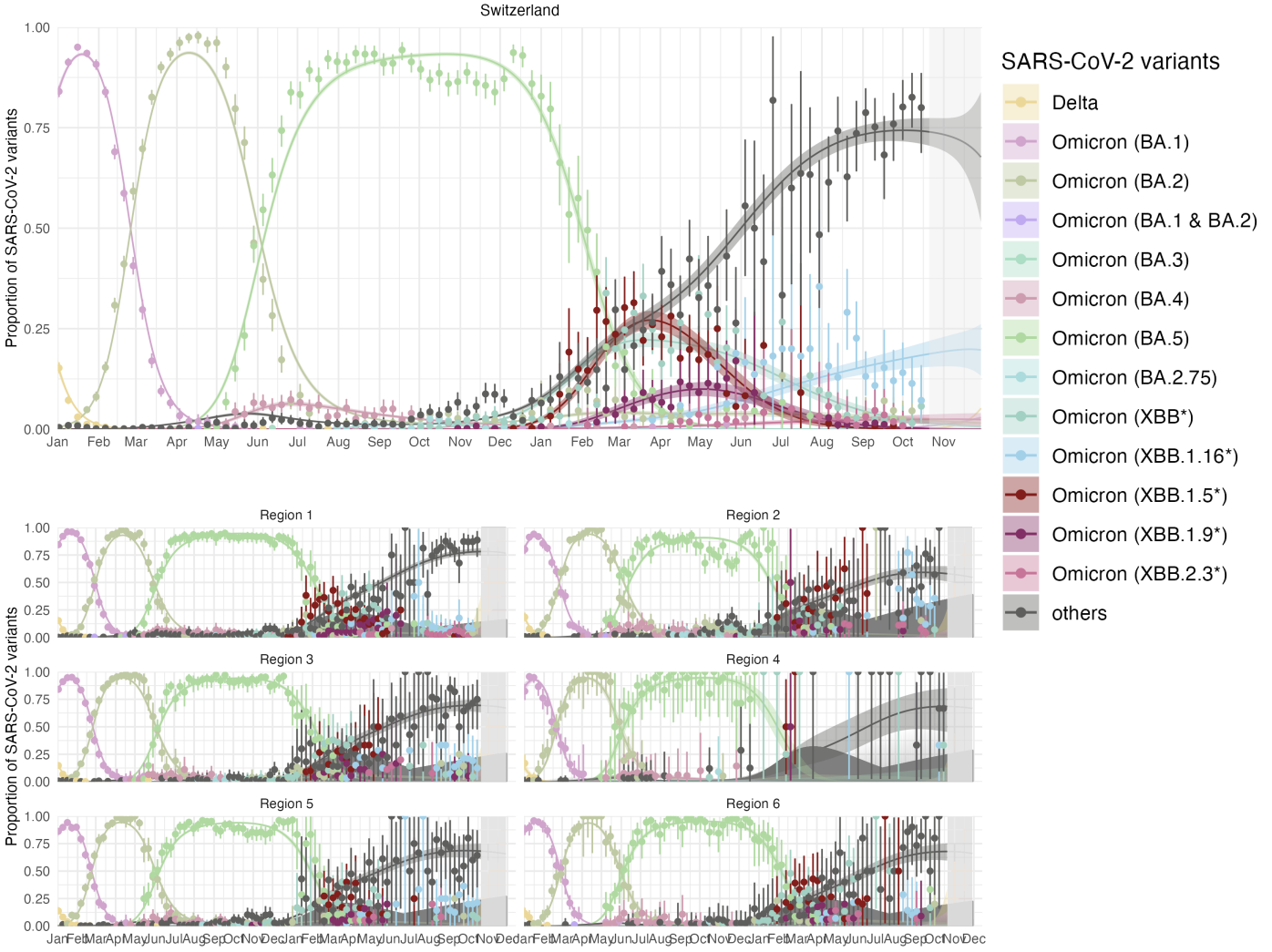


Figure 6: Observed and modeled proportion of SARS-CoV-2 variants over time in Switzerland. Since early 2021, multiple successive variants have been observed to displace all previous variants (often achieving a dominance of >99.9% of the circulation). Alpha was replaced by Delta, followed by Omicron BA.1, 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	0.01	0.02 (6)	0
340	0.05	0.06	0.37 (2)
356	2.94	4.49	6.65
371	94.36	93.07	99.63
377	0.00 (3)	0.01 (2)	0
449	0.01 (5)	0.02 (5)	0
476	0.02	0.03 (8)	0.18 (1)
494	1.45	1.70	1.11 (6)
Paxlovid®	(Nsp5 mutations)		
15	0.00 (2)	0	0
48	0.05	0.01 (4)	0
49	0.01 (8)	0.01 (3)	0
140	0.00 (2)	0	0
143	0.00 (2)	0	0
144	0.00 (3)	0.00 (1)	0
165	0.00 (2)	0	0
166	0.00 (3)	0.00 (1)	0
167	0.00 (2)	0	0
168	0.00 (2)	0	0
172	0.00 (2)	0	0
173	0.01 (10)	0.01 (3)	0
186	0.01 (5)	0.01 (2)	0
188	0.01 (5)	0.01 (3)	0
189	0.01 (7)	0.02 (5)	0
192	0.01 (5)	0.01 (2)	0
194	0.04	0.08	0
248	0.01 (5)	0	0
252	0.01 (5)	0.00 (1)	0.18 (1)
304	0.00 (3)	0	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 September 2023 (Table 3). Notably, the proportion of sequences bearing S:356 mutations has increased, and this mutation is found in BA.2.86 lineages

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 December, 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 worldwide in October, with Nsp5:194 mutations being the most common (but less than 0.1%). One single sequence with a Paxlovid resistance mutation (Nsp5:252) was detected in Switzerland (Table 3).

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.

sup_table_overview_Oct.xlsx

Supplementary Table 1: Epidemiological data for Switzerland, its regions and cantons for September 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
39	Sept 25 - Oct 1	1'845	326	285	39.6
40	Oct 2 to Oct 8	2'031	394		
41	Oct 9 to Oct 15	2'211	434	285	30.2
42	Oct 16 to Oct 22	2'406	509		
	Total	8'493	1'663	570	34.3

Supplementary Table 2: Total number of tests performed by the laboratories participating in the surveillance program from 25 September to 22 October 2023.

week	Date	HUG	CHUV	ICH-VS	IFIK	UZH IMV	USB	EOC	All
39	Sept 25 - Oct 1	44	19	48	20	18	71	39	285
40	Oct 2 to Oct 8		26						
41	Oct 9 to Oct 15	91	27	47	41	14	40	0	285
42	Oct 16 to Oct 22		25						
	Total	135	97	95	61	32	111	39	570

Supplementary Table 3: number of sequences submitted to GISAID by each laboratory during the surveilled period (25 September to 22 October 2023).

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