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

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1. Summary

During the month of November, the number of positive SARS-CoV-2 tests dramatically increased in Switzerland, with the weekly rate being over double that of October. Similarly, the test positivity rate within the program increased to 31%% from October's 19.6%. Notably, testing rates have increased approximately 50% (2'123 test/week for the October reporting period vs 3'026 test/weeks for November). The number of hospitalizations due to COVID-19 continued to modestly but steadily increase in November.

The 5'629 positive tests processed by laboratories participating to the program constituted about 1/3rd of the reported positive tests in Switzerland and was substantially more than October's number.

A total of 1'141 new sequences were submitted to GISAID during the reporting period, mainly covering the month of November (23 October to 3 December), which represents around 20% of the program's positive tests, and about 7% 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 November, the majority of the sequences in Switzerland still belonged to the XBB clade (particularly EG.5), but the percent of sequences belonging to this clade steadily declined during this period as BA.2.86 and its sublineages grew. The percent of sequences with the "FLip" pair of mutations, which are apparently beneficial in the XBB background (and lead to increased immune escape), was relatively stable during this reporting period, at about 30%.

On 13 December 2023, the WHO designated the BA.2.86 sublineage JN.1 as a Variant of Interest (VOI). JN.1 accounts for the majority of the BA.2.86 sublineages in Switzerland, and is now dominant in all regions of Switzerland as of the writing of this report. Wastewater data shows that JN.1 achieved dominance during the November reporting period. 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. It will be reconducted during 2024.

Because greater transmissibility and/or immune escape potential of the different Variants of Concern (VOCs) and Variants of Interest (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 2022 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 Römerand 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 23 October to 3 December 2023 (weeks 43-48). 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, BA.2.86, and JN.1. 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 lineages that resulted from recombination within Omicron, please refer to previous reports.

Worldwide, Omicron circulates mainly in the form of the EG.5 sublineage of XBB.1.9, and the JN.1 sublineage of BA.2.86. In Switzerland, EG.5 reached a high of 62% of sequences in week 43 of October (first week of this reporting period), and progressively declined to 37% by week 48 (the last week of the reporting period). JN.1 accounted for 4.3% of patient sequences at week 43, and 28.8% at week 48. All BA.2.86 sequences together reached a high of 33.8% during this reporting period.

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 the XBB lineages do not display it, whereas BA.2.86 and its sublineages do. BA.2.86 specific PCRs are being validated to confirm detection of probable BA.2.86 samples identified by SGTF assay.

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 studies 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 recently been characterized, and JN.1 shows roughly a 2-3 fold reduction in neutralization, relative to its parental BA.2.86, by patient sera following an XBB breakthrough infection. Note that neutralization of JN.1 is still very low after an EG.5 breakthrough infection. JN.1’s neutralization escape against sotrovimab is roughly 3x higher than that of EG.5.

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

Severity

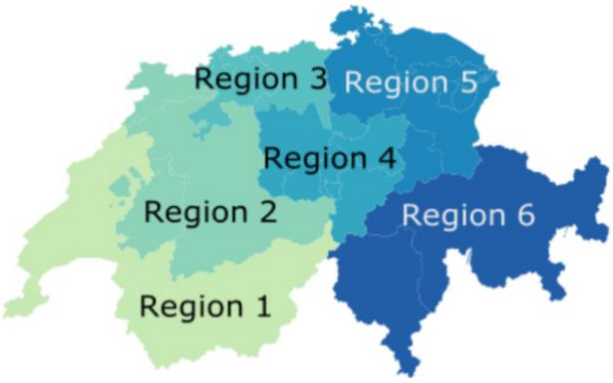
There is currently no evidence that the severity of the new subvariants has significantly changed. Indeed, some studies, including animal studies provide evidence that XBB sublineages including EG.5 and BA.2.86 are not more severe.

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 23 October to 3 December, the FOPH reported 13'858 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 33% of this number (5'629 positive tests). Along with the number of tests performed in the country, the number of positive tests/week more than doubled in Switzerland during the reporting period of November relative to that of October (938 vs 416 /week). Notably, within the program, the percent of positives sequenced within the program dropped from 34.3% in October's reporting period to 20.3 in Novembers' despite the increased number of sequences, due to the large increase in positive tests. The test positivity rate within the program for November was 31.0%, compared to 19.6% from October. Overall, about 7% of ascertained positive cases were sequenced.

Although case ascertainment rates may be too low to identify meaningful trends, there had been a trend during the months of October and November towards 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 1'141 SARS-CoV-2 sequences have been declared to have been processed during this period. There are 973 sequences available on GISAID that were submitted during this period (and 1'048) 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
43	October 23 to 29	348
44	October 30 to November 5	
45	November 6 to 12	382
46	November 13 to 19	
47	November 20 to 26	411
48	November 27 to December 3	
	Total	1'141

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 generally increased during the November reporting period 2023 (Calendar weeks 43 - 48).

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.

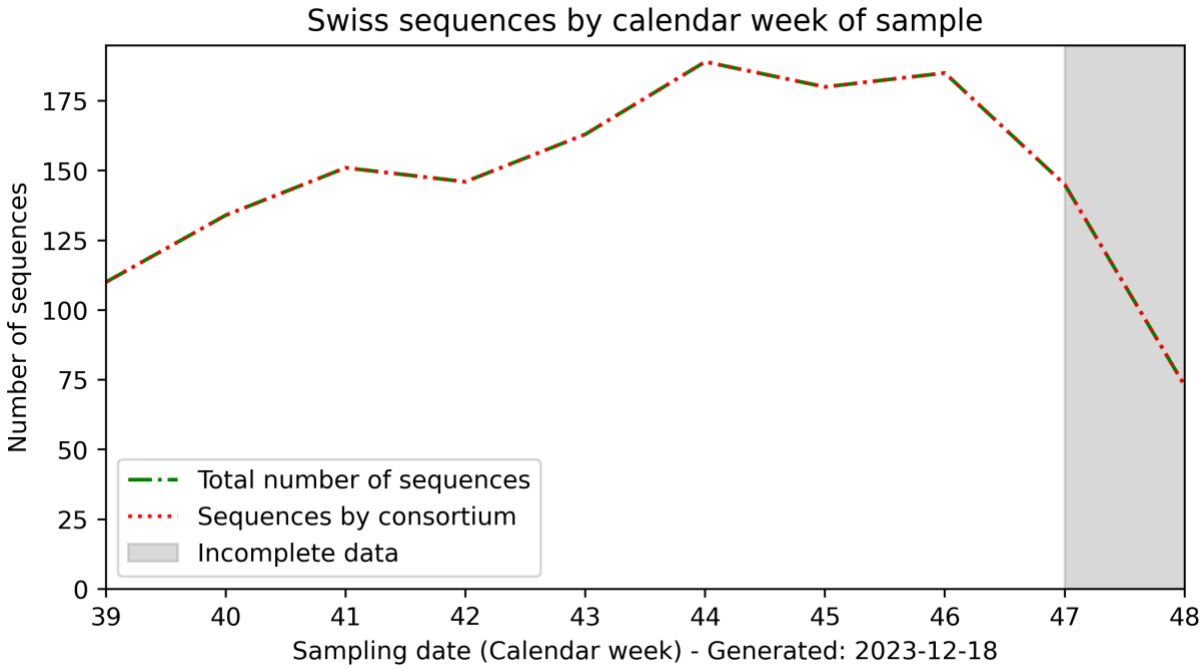


Figure 1: Number of SARS-CoV-2 sequences available for Switzerland (total available Swiss sequences in GISAID in green, Swiss sequences submitted through the program in dotted orange).

Figure 2 displays the number of SARS-CoV-2 cases sequenced for each Swiss region. Region 1 continued to have the highest number of sequences. 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.

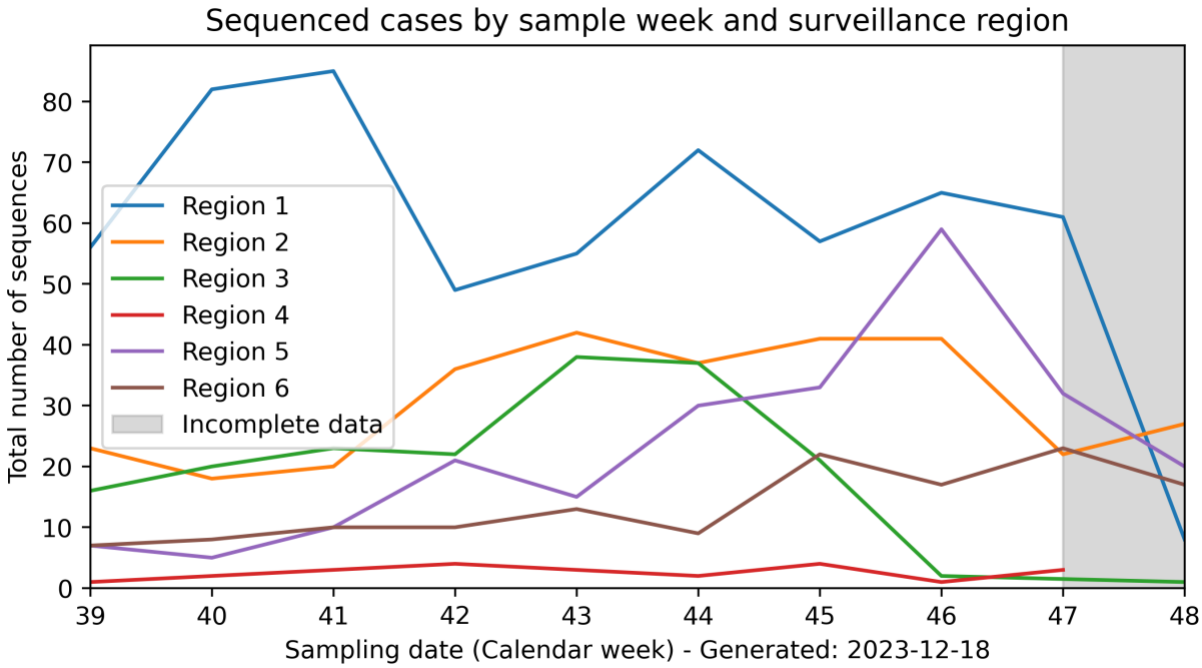


Figure 2: Sequencing coverage among the different Swiss regions per week, by number of sequences. Note that region 1 is over-represented, with 3/7 sequencing centers.

4. Recently circulating variants in Switzerland

Determination of the proportion of total number of sequences over time falling into defined variant groups is 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 EG.5 or JN.1 now. During the November reporting period, the XBB.1.9 sublineage lost its dominance as the BA.2.86 sublineage JN.1 rose significantly. Overall, 455 EG.5 sequences were detected during this period, amounting to 48.7& of the total sequences, in contrast there were 208 BA.2.86 sequences (122 JN.1) accounting for 22.3% of sequences. Circulation of BA.2.75 derivatives was very low in November's reporting period, with just 4 sequences (all of the DV.7.1 sublineage). No BA.5 sequence was detected during this reporting period (1 was detected in week 39, which was the first since week 32).

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	0	20	40	70	522	26	214	39	935
1	2	0	14	7	23	182	7	76	7	318
2	0	0	1	10	23	108	7	52	9	210
3	0	0	2	7	6	63	6	4	11	99
4	1	0	0	4	0	3	0	2	0	10
5	0	0	3	11	6	101	4	55	9	189
6	1	0	0	1	11	65	2	18	3	101

Table 2: number of sequences corresponding to selected variants in each region of Switzerland from 23 October to 3 December, according to data received by 19 December, 2023. Note: recombinants denote recombinations between identified lineages, which may be recombinates themselves (ie: the XBB lineages)

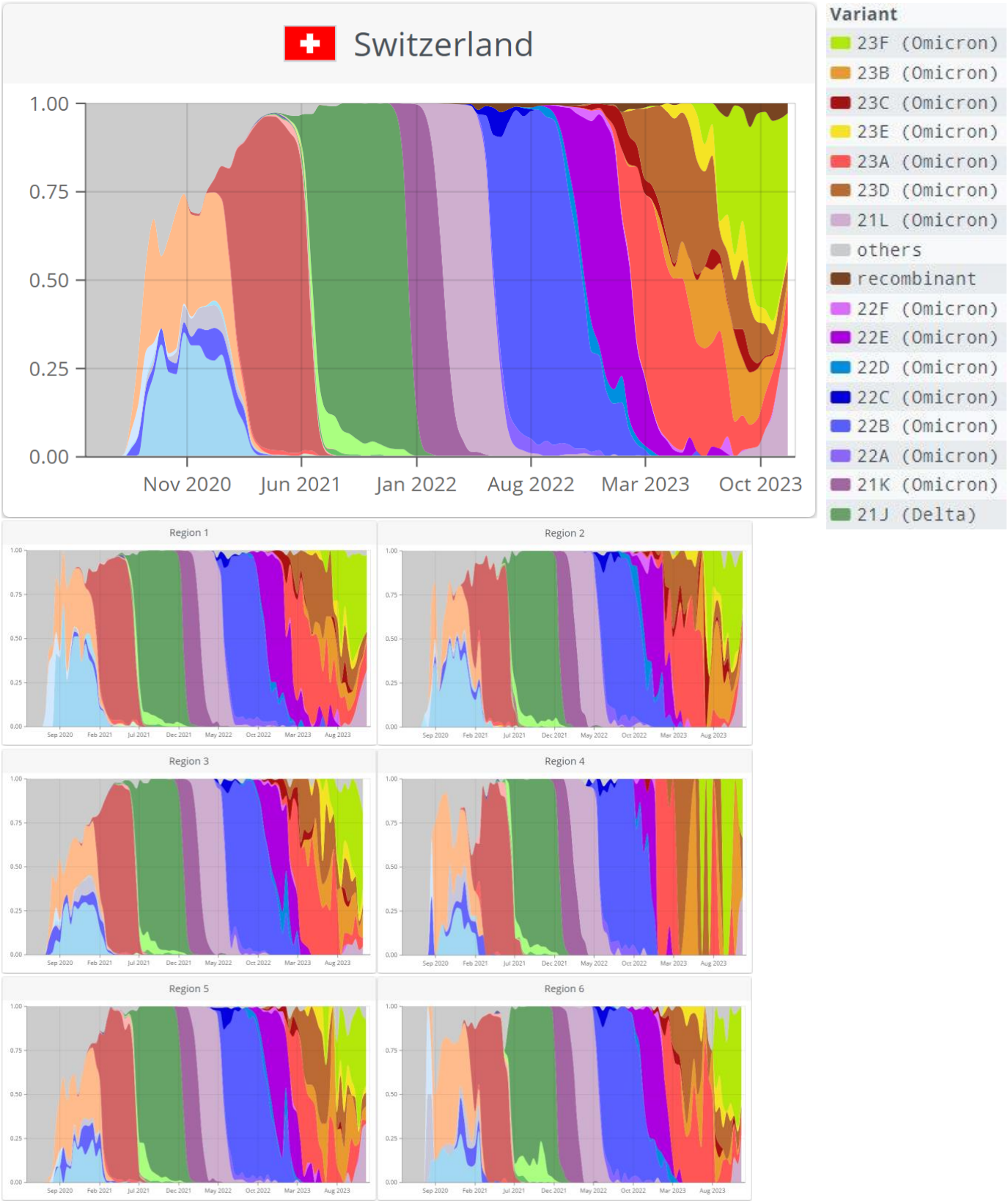


Figure 3: proportion of sequences over time that fall into defined variant groups, for Switzerland. Dynamic navigation is available at https://covariants.org/per-country. Selected Nexstrain lineage correspondence with pango lineages are as follows: 21 J- B.1.617.2 (Delta); 21K- BA.1; 21L- BA.2; 22B- BA.5; 22E- BQ.1; 22F- XBB; 23A- XBB.1.5; 23D- XBB.1.9; 22E- XBB.2.3; and 23F- EG.5.1. 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.

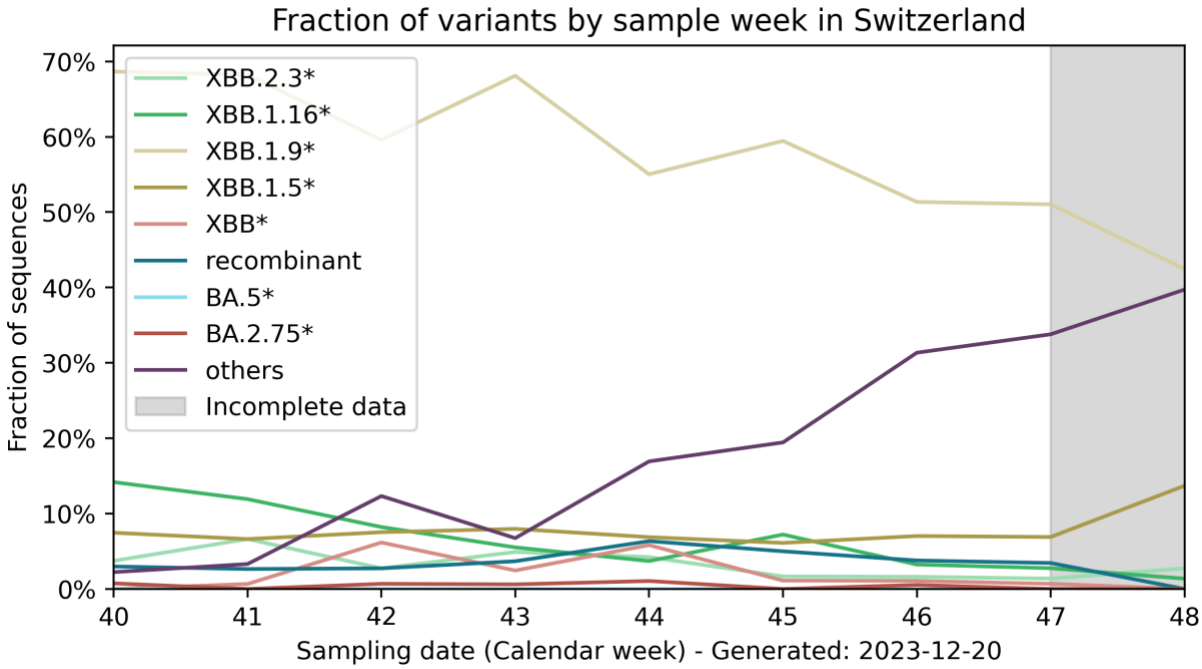


Figure 4: Percentage of circulating VOCs and VOIs in Switzerland by week, up to week 48 of 2023, according to the sequences from Switzerland that were successfully submitted. Note XBB.1.9 and its sublineages were the most common variants, accounting for more than half of the sequences, but were in decline. Note the increase in other lineages, primarily BA.2.86 and its sublineages (grouped into "others") which nearly surpassed XBB.1.9 and its sublineages (primarily EG.5) in clinical samples by the end of the reporting period.

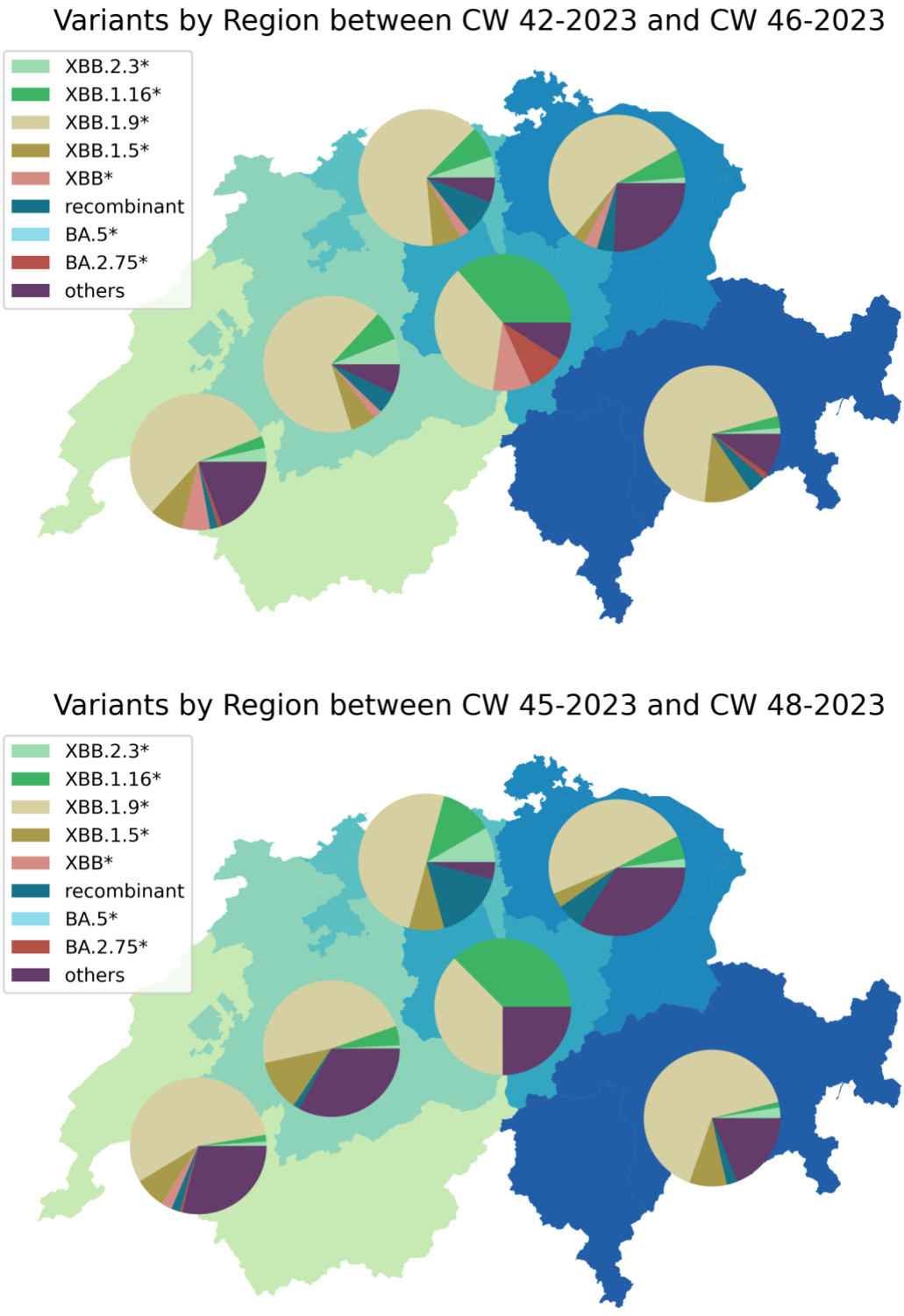


Figure 5: Distribution of variants per region, by Calendar Week (CW), for early vs late November 2023.

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 sublineages (of XBB and BA.2.86) and will compete with each other with substantial co-circulation. Data for BA.2.86 is currently aggregated under "other" in these model predictions.

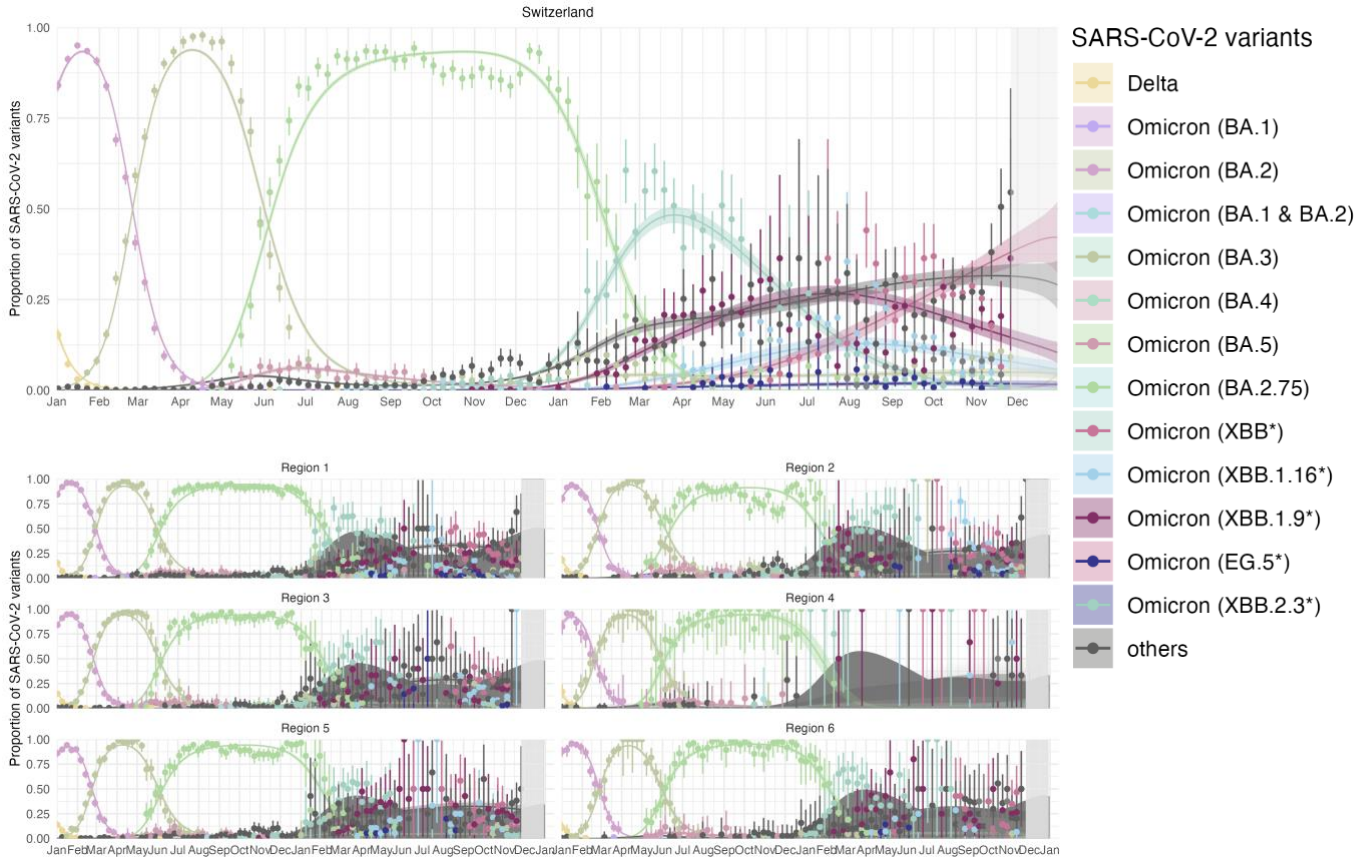


Figure 6: Observed and modeled proportion of SARS-CoV-2 variants over time in Switzerland. Since early 2021, multiple successive variants have been observed to displace all previous variants (often achieving a dominance of >99.9% of the circulation). Alpha was replaced by Delta, followed by Omicron BA.1, then BA.2, BA.5, BQ.1, XBB.1.5. After XBB.1.5, no lineage has been predicted achieve strict dominance (>50% of all circulating viruses) – although the XBB.1.9 sublineage EG.5 did achieve such dominance for a short time. 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	0.02	0.03	0
340	0.05	0.08	0.11(1)
356	15.50	24.52	23.85
371	93.57	91.88	98.07
377	0	0	0
449	0.01 (6)	0.01 (2)	0
476	0.04	0.05	0.18 (1)
494	0.93	1.16	0.75 (7)
Paxlovid®	(Nsp5 mutations)		
15	0	0	0
48	0.03	0.00 (1)	0
49	0.02	0.02 (7)	0
140	0.00 (1)	0	0
143	0	0	0
144	0	0	0
165	0	0	0
166	0.01 (10)	0.01 (1)	0
167	0	0	0
168	0.00 (1)	0.00 (1)	0
172	0	0	0
173	0.01 (5)	0.01 (3)	0
186	0.01 (9)	0.01 (4)	0.21 (2)
188	0.00 (3)	0.00 (1)	0
189	0	0	0
192	0.00 (1)	0.00 (1)	0
194	0.04	0.08	0
248	0.00 (2)	0	0
252	0.00 (1)	0	0
304	0.00 (3)	0.01 (3)	0.11 (1)

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 very resistant to neutralization by sotrovimab. JN.1 (a BA.2.86 sublineage) appears to have even greater resistance to neutralization by sotrovimab, and is now the dominant variant as of the time of this report.

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.2.86 and XBB) sotrovimab escape mutations remained rare in Switzerland and worldwide during November 2023 (Table 3). Notably, the proportion of sequences bearing S:356 mutations has increased, as 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, BA.2 and its sublineages (including XBB and BA2.86*) contain the spike S371F mutation leading to partial sotrovimab resistance. Also note: BA.2.86 is mutated at spike position 356.*

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 the November reporting period, with Nsp5:194 mutations being the most common worldwide(but less than 0.1%). Three sequences with a Paxlovid resistance mutation (2x Nsp5:186, 1x Nsp5:304) were 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_Nov.xlsx

Supplementary Table 1: Epidemiological data for Switzerland, its regions and cantons for November 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
43	October 23 to 29	2'535	615	348	25.3
44	Oct. 30 to Nov. 5	2'691	759		
45	November 6 to 12	2'989	846	382	20.0
46	November 13 to 19	3'218	1'066		
47	November 20 to 26	3'316	1'163	411	17.5
48	Nov. 27 to Dec. 3	3'409	1'180		
	Total	18'158	5'629	1'141	20.3

Supplementary Table 2: Total number of tests performed by the laboratories participating in the surveillance program from 23 October to 3 December 2023.

week	Date	HUG	CHUV	ICH-VS	IFIK	UZH IMV	USB	EOC	All
43	October 23 to 29	80	21	0	39	53	54	40	348
44	Oct. 30 to Nov. 5		26		35				
45	November 6 to 12	85	31	0	30	88	59	39	382
46	November 13 to 19		15		35				
47	November 20 to 26	69	25	46	74	74	58	40	411
48	Nov. 27 to Dec. 3		25						
	Total	234	143	46	213	215	171	119	1'141

Supplementary Table 3: number of sequences submitted to GISAID by each laboratory during the surveilled period (from 23 October to 3 December 2023).

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