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

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1. Summary

During the month of December 2023, the number of positive SARS-CoV-2 tests per week increased modestly in Switzerland, (1'044 vs. 944 for November). Meanwhile, the test **positivity rate within the program decreased slightly** (29% vs Novembers 31%). Testing rates continued to rise (3'614 per week vs 3'026 for November. **The number of hospitalizations due to COVID-19 steadily decreased after a peak in late November/early December**.

The 4'175 positive tests processed by laboratories participating to the program constituted about 1/3rd(33.6%) of the reported positive tests in Switzerland.

A total of 775 new sequences were submitted (729 collected) to GISAID during the reporting period, covering the month of December (4 December to 31 December), which represents around 19% of the program's positive tests, and about 5% 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 December, the **JN.1** sublineage of the BA.2.86 clade**, designated a variant of interest by the WHO on December 13, 2023, took over as the prevalent strain in Switzerland,** surpassing the previously widespread EG.5. By the end of December, JN.1 represented more than 70% of the sequences across all Swiss regions, indicating its dominance. The data from wastewater surveillance during November showed that **JN.1 became the dominant strain, coinciding with the highest amount of RNA detected in wastewater since the start of surveillance and a significant increase in SARS-CoV-2 positivity rates in the Sentinella system, hinting at an unparalleled community transmission wave.** Despite this surge, **hospitalization rates remained relatively low in comparison to previous years. There is no current evidence to suggest that these BA.2.86 subvariants are more severe.** It's noteworthy that **the neutralizing response against JN.1** and other BA.2.86 derivatives **by the mRNA vaccines currently used in Switzerland is comparable to that against the XBB derivative EG.5.**

Additionally, the prevalence of sequences featuring the "FLip" mutation pair, which provides a significant advantage in the XBB lineage by enhancing immune evasion, saw a sharp decline during this period, along with other XBB sublineages carrying these mutations.

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 has been renewed for 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 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 4 December to 31 December 2023 (weeks 49-52). 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 JN.1 sublineage of BA.2.86, and lingering XBB sublineages. During December 2023 in Switzerland, JN.1 progressively increased from 48.2% of sequences to a high of 82.3% of sequences in week 52 of 2023 (the last week of this reporting period). All BA.2.86 sequences together reached a high of 88.4% during the last week of 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.

The 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. Neutralization of BA.2.86 after an XBB.1.5 monovalent booster is comparable to the neutralization against various XBB subvariants, which suggests that vaccination efficacy has not been negatively affected to a substantial degree by the replacement of EG.5 by JN.1. 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. Data suggests that there is no loss of efficacy against other antivirals, such as protease inhibitors.

Severity

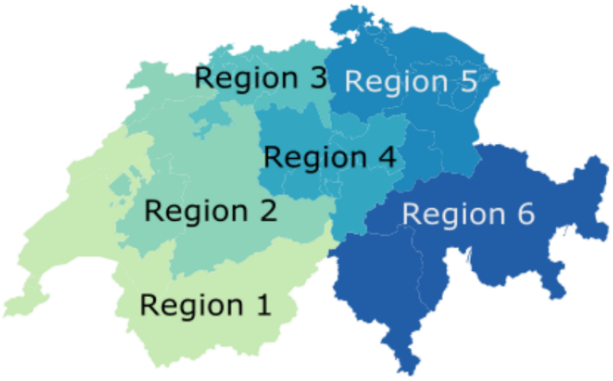
There is currently no evidence that the severity of the new subvariants has significantly changed. Indeed, some studies, including animal studies provide evidence that XBB sublineages including EG.5 and BA.2.86 are not more severe.

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 4 December to 31 December, the FOPH reported 12'417 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 (4'175 positive tests). Along with the number of tests performed in the country, the number of positive tests/week increased slightly in Switzerland during the reporting period of November relative to that of October (1044 vs 944/week). Notably, within the program, the percent of positives sequenced within the program remained similar 22.8% in December vs 20.3% in November. The test positivity rate within the program for December was 28.9%, compared to 31.0% from November. Overall, about 5% 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. This trend appears to have peaked in November, and December saw a decline in hospitalizations. For more information, please refer to the BAG dashboard (https://idd.bag.admin.ch/).

. 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 1.

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

A total of 952 SARS-CoV-2 sequences have been declared to have been processed during this period. There are 775 sequences available on GISAID that were submitted during this period (and 729 collected during this period) as of 30 January 2024.

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
Dec 4 to 10	Dec 4 to 10	441
Dec 11 to 17	Dec 11 to 17	
Dec 18 to 24	Dec 18 to 24	511
Dec 25 to 31	Dec 25 to 31	
	Total	952

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 2 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 decreased during the December reporting period 2023 (Calendar weeks 49 - 52).

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.

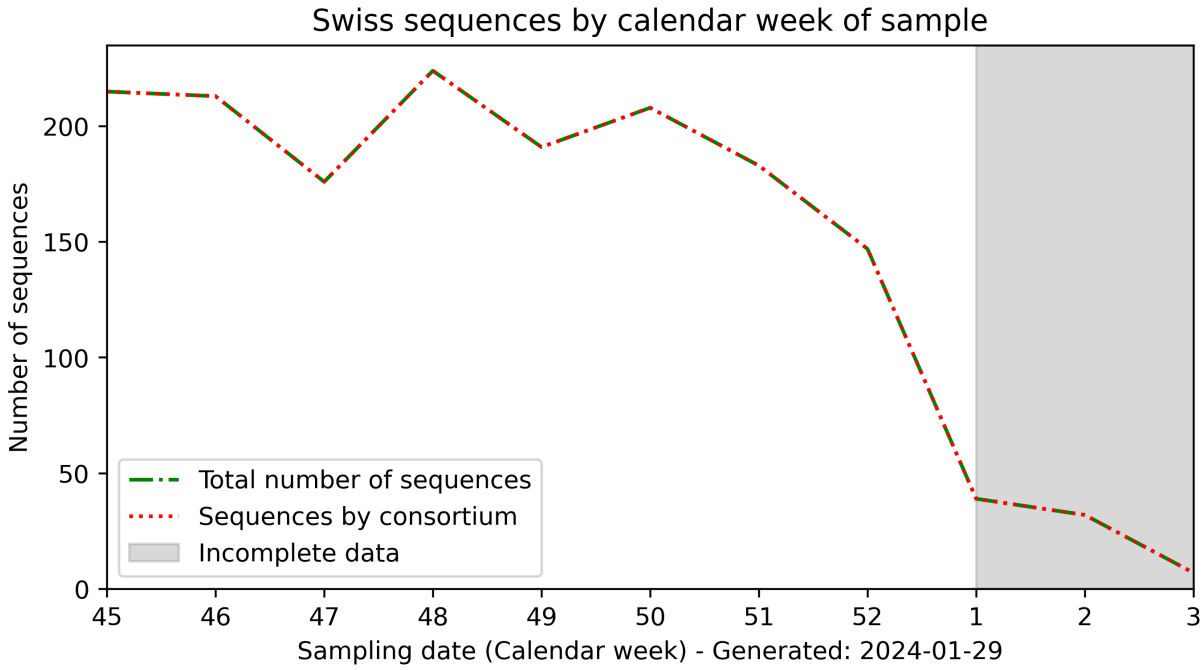


Figure 1: Number of SARS-CoV-2 sequences available for Switzerland (total available Swiss sequences in GISAID in green, Swiss sequences submitted through the program in dotted orange).

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.

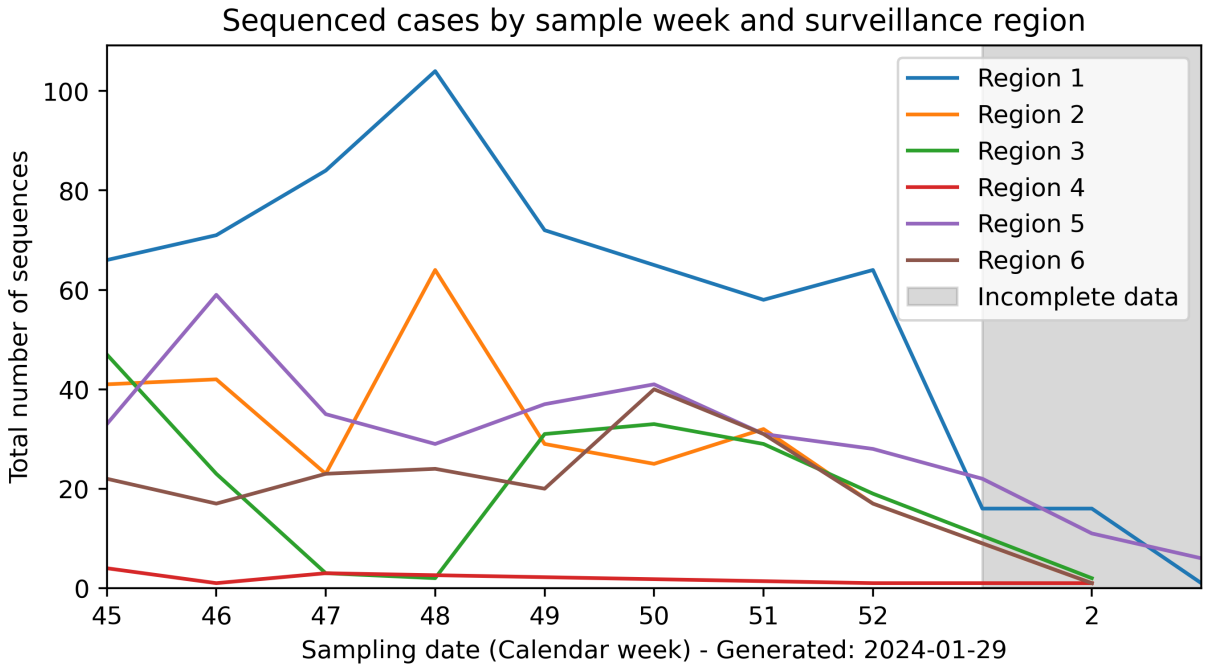


Figure 2: Sequencing coverage among the different Swiss regions per week, by number of sequences. Note that region 1 is over-represented, with 3/7 sequencing centers.

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 JN.1 sublineages now. During the November reporting period, the XBB.1.9 sublineage lost its dominance as the BA.2.86 sublineage JN.1 rose significantly, and it has remained dominant in December. Overall, 118 EG.5 sequences were detected during this period, amounting to 16.2% of the total sequences, in contrast there were 539 BA.2.86 sequences (473 were JN.1*) accounting for 73.9% of December's sequences. Circulation of BA.2.75 derivatives was not detected in December (4 sequences of the DV.7.1 sublineage were detected in November. No BA.5 sequence was detected during this reporting period, and none have been detected since a single detection in week 39 of 2023.

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.2.86*	EG.5.1*	JN.1*	XBB*	others	Recombinant	Sequences
All	7	118	534	58	2	12	731
1	2	39	189	22	2	7	261
2	3	17	78	3	0	2	103
3	0	14	87	11	0	0	112
4	0	1	0	0	0	0	1
5	1	26	96	12	0	2	137
6	1	20	77	9	0	1	108

Table 2: number of sequences corresponding to selected variants in Switzerland from 4 December to 31 December, by region, according to data received by 31 January 2024.

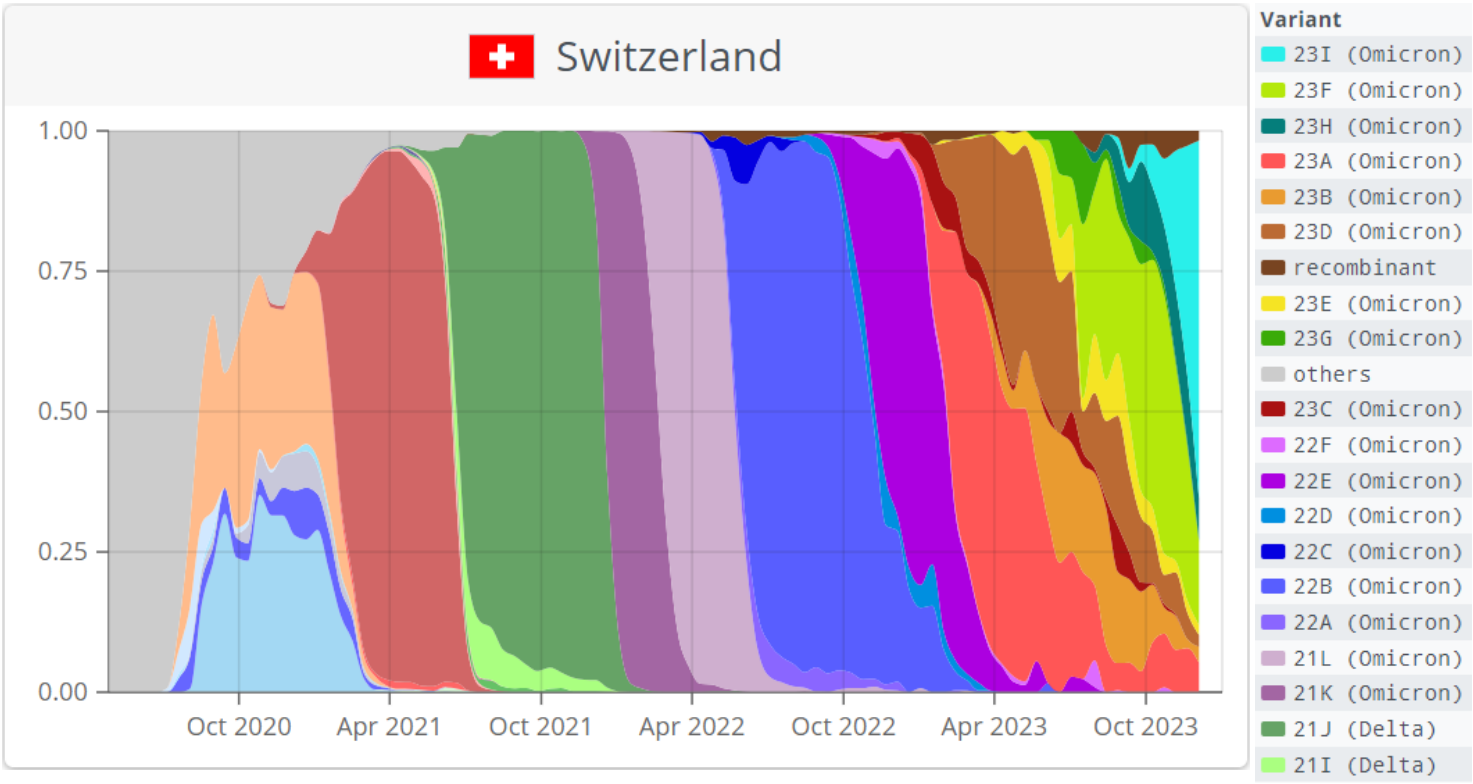


Figure 3: proportion of sequences over time that fall into defined variant groups, for Switzerland. Dynamic navigation is available at https://covariants.org/per-country. Selected Nexstrain lineage correspondence with pango lineages are as follows: 21 J- B.1.617.2 (Delta); 21K- BA.1; 21L- BA.2; 22B- BA.5; 22E- BQ.1; 22F- XBB; 23A- XBB.1.5 (red); 23D- XBB.1.9 (brown); 23E- XBB.2.3 (yellow); 23F- EG.5.1 (light green); 23G- XBB.1.5.70 (dark green); 23H- HK.3 (blue-green); and 23I- BA.2.86 (cyan). Note that the 23I (BA.2.86) primarily increased due to the JN.1 subvariant

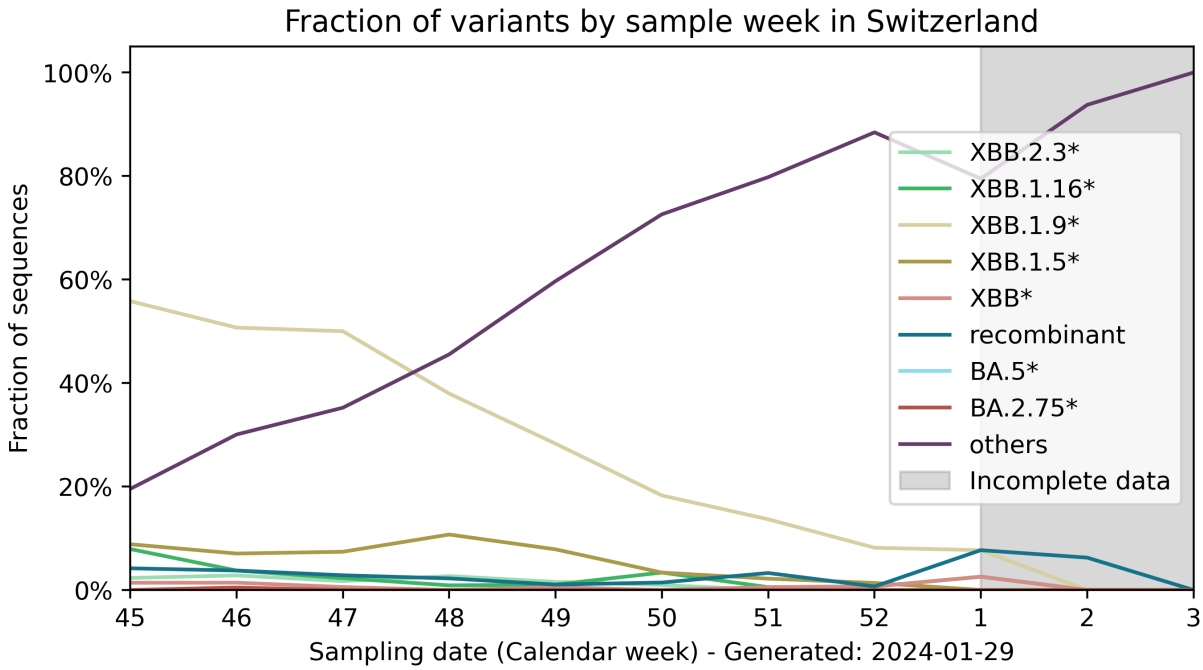


Figure 4: Percentage of circulating VOCs and VOIs in Switzerland by week, up to week 52 of 2023, according to the sequences from Switzerland that were successfully submitted. Note the BA.2.86 sublineage JN.1, included here among the "others", was the most common variant, accounting for more nearly two thirds of the sequences (and climbing).

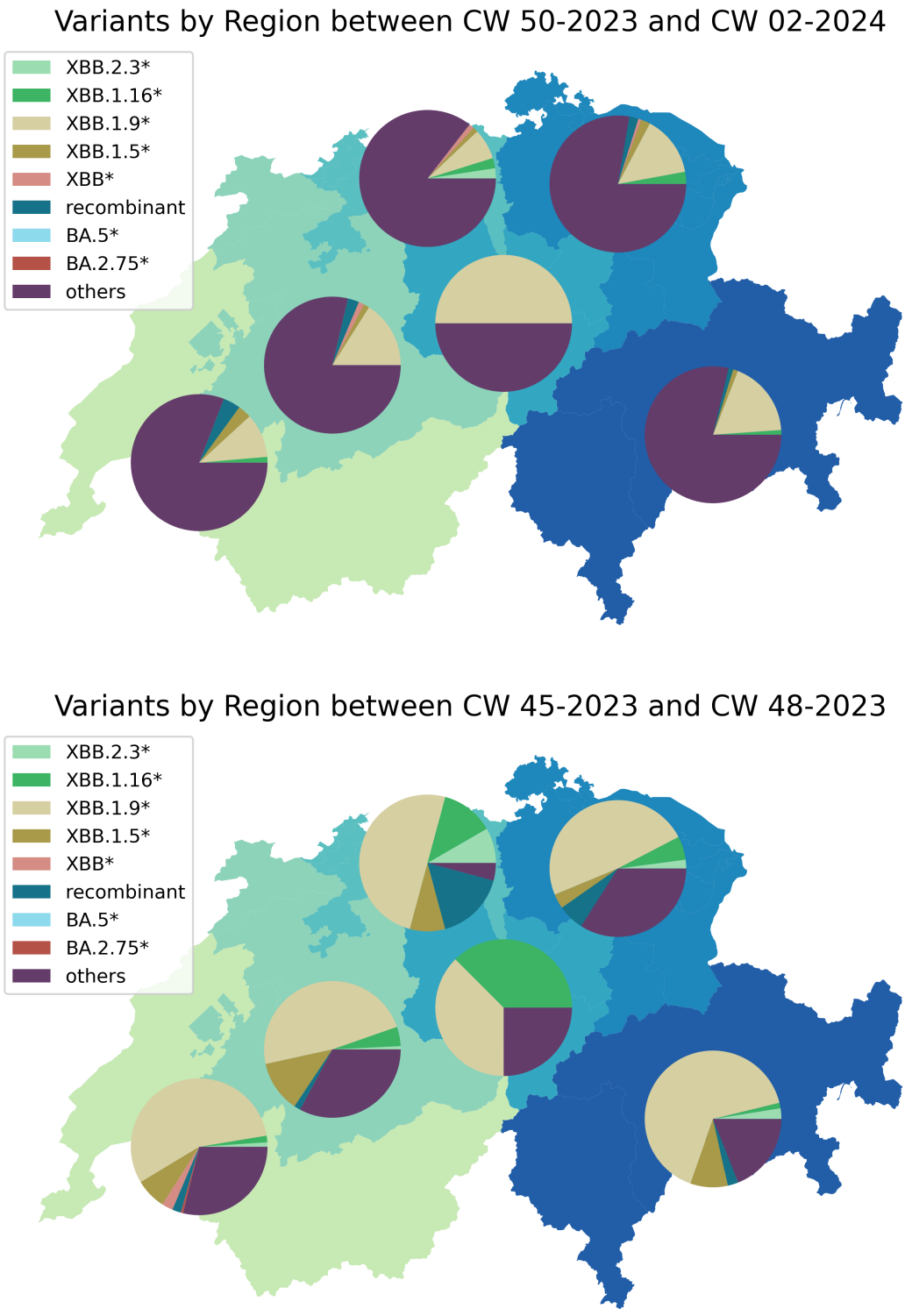


Figure 5: Distribution of variants per region, by Calendar Week (CW), for early vs late November 2023. Note the large increase of the BA.2.86 sublineages (primarily JN.1), included here among "others", in every region.

5. 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	0	0
340	0.04	0.05	0.14 (1)
356	53.2	67.7	74.1
371	93.2	93.1	98.9
377	0.00 (3)	0.01 (2)	0
449	0.01 (5)	0.02 (5)	0
476	0.04	0.04	0
494	0.32	0.26	0.27 (2)
Paxlovid® (Nsp5 mutations)			
15	0.00 (1)	0	0
48	0.01 (8)	0	0
49	0.01 (6)	0.01 (4)	0
140	0.00 (2)	0	0
143	0.00 (1)	0	0
144	0.00 (1)	0	0
165	0.00 (2)	0.00 (1)	0
166	0.00 (3)	0.00 (1)	0
167	0.00 (1)	0	0
168	0.00 (2)	0	0
172	0.00 (1)	0	0
173	0.01 (5)	0	0
186	0.01 (11)	0.02 (7)	0
188	0.01 (5)	0.01 (4)	0
189	0.01 (6)	0.01 (3)	0
192	0.01 (8)	0.01 (3)	0
194	0.03 (23)	0.04 (14)	0
248	0.00 (2)	0.00 (1)	0
252	0.00 (3)	0.01 (2)	0
304	0.00 (2)	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 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 December 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 rare worldwide (less than 0.1%) in December, with Nsp5:194 mutations being the most common worldwide(0.03%, as in November). No sequences with a known Paxlovid resistance mutation were detected in Switzerland (Table 3).

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://idd.bag.admin.ch/) and sequence data submitted to GISAID to provide a summary of the SARS-CoV-2 epidemiology in Switzerland.

week	date	Total PCR tests	Positive tests	Sequenced	% positives sequenced
49	Dec 4 to 10	3'721	1'241	441	17.8
50	Dec 11 to 17	3'979	1'243		
51	Dec 18 to 24	3'724	1'014	511	30.2
52	Dec 25 to 31	3'032	677		
	Total	14'456	4'175	952	22.8

Supplementary Table 1: Total number of tests performed by the laboratories participating in the surveillance program from 4 December 2023 to 31 December 2023.

week	Date	HUG	CHUV	ICH-VS	IFIK	UZH IMV	USB	EOC	All
49	Dec 4 to 10	91	18	48	77	78	59	40	441
50	Dec 11 to 17		30						
51	Dec 18 to 24	53	14	66	144	73	59	80	511
52	Dec 25 to 31		22						
	Total	144	84	114	221	151	118	120	952

Supplementary Table 2: number of sequences submitted to GISAID by each laboratory during the surveilled period (from 4 December 2023 to 31 December 2023).

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