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Swiss national SARS-CoV-2 genomic and variants surveillance program: report of the month of November and Preliminary Data of Omicron for the month of December

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1. Summary

Approximately 6% of the total number of cases identified in Switzerland in November were sequenced by the Surveillance program, yielding over 11900 sequences.

In November, COVID-19 cases numbers increased dramatically in Switzerland, and were due almost exclusively to the B.1.617.2 (Delta) variant or its sub-lineages. There are a large variety of Delta sub-lineages have, but no strong sign in Switzerland of any specific sub-lineage outcompeting others.

No important geographical breakdown of a particular sub-lineage has been noticed.

Unsurprisingly, B.1.617.2 (Delta or its sub-lineages) was also the most frequent variant detected in wastewater during the month of November.

Circulation of all other variants had essentially stopped in November. However in late November the new B.1.1.529/"Omicron" variant of concern, was detected in Switzerland. This variant is believed to have originated in southern Africa, and the first confirmed case in Switzerland was collected on November 21, 2021 in Basel-Land, and shortly thereafter another case was confirmed in Geneva. Since then, and following other importation events, it has become clear that Omicron has established community transmission chains within Switzerland. AS of December 21, 2021, 160 Omicron sequences have been retrieved in Switzerland. Of note, because of the inherent delay of sequencing, the number of cases are very significant, as seen by the increase in Omicron-specific mutations detected in different parts of Switzerland.

This new Omicron variant of concern has more spike mutations than any other known variant. This variant Omicron has a significant growth advantage relative to Delta. Early data demonstrates that it is able to evade neutralizing antibodies raised against previous variants or after 2 doses of vaccine, and as a result the vaccine breakthrough and reinfection rates are much higher, although 3 doses partially restores protection. Additionally many clinically used therapeutic antibodies are unable to neutralize it, with Sotrovimab being the only antibody available in Switzerland that retains substantial activity.

It has already split into 3 sublineages: BA.1-3. BA.1 is currently the most common variant. All sub-lineages are still detected by RT-PCR tests, but S-gene target failure in some assays can be used as a proxy for BA.1 and BA.3 prior to sequencing, as previously seen with VOC Alpha.

The relative severity of Omicron infections is currently unknown, but in the context of a winter with a severe wave caused by Delta, the arrival of Omicron is cause for grave concern. Preliminary data from the UK indicates that there is no significant intrinsic difference in severity relative to previous variants, and early reports of mild disease were likely due to very high levels of previous exposure in the reporting communities.

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.

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.

Currently, 13 diagnostic laboratories are participating in the program, including university hospital centres in Switzerland (Geneva, Lausanne, Bern, Basel, Zurich, St-Gall, Ticino), in addition to private laboratories (Viollier; Medisupport including Dianalabs, Polyanalytic, Dianalabs Valais, Proxilab and Bioanalytica; Labor Team W, Risch), cantonal-based laboratories (Hôpital du Valais – Institut Central), Spital Region Oberaargau (Bern, Solothurn, Aargau, Luzern), and 3 high-throughput sequencing platforms (Health 2030 Genome Centre in Geneva, Functional Genomics Centre Zurich run by ETH Zürich and University of Zürich, Genomics Facility Basel run by ETH Zürich and University of Basel).

Processed sequencing data are shared openly within 14 days from positive PCR result 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 National COVID-19 Science Task Force and the Swiss Institute of Bioinformatics (SIB).

In order to complement the genomic surveillance based on patient samples, sequencing of SARS-CoV-2 in wastewater samples is also performed, initially funded for 6 months. Samples are collected daily in six wastewater treatment plants (WWTP), under the coordination of Eawag. Up to 50 samples per week over the first 26 weeks have been performed. The sequencing and analysis of these samples, including detection of variants, is done under the coordination of Prof Niko Beerenwinkel. It started in December 2020 for Lausanne and Zurich, and in February 2021 for all six WWTP (https://bsse.ethz.ch/cbg/research/computational-virology/sarscov2-variants-wastewater-surveillance.html). The analysis of wastewater samples is envisaged to run until the end of the surveillance program on 31.3.2022.

Immunological characterization of the variants within the surveillance program is 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, Niko Beerenwinkel, David Dreifuss, Chaoran Chen, Tanja Stadler, Priscilla Turelli, Didier Trono, Emma Hodcroft, Nadja Wipf, Damir Perisa, 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 November 1 to December 5 (weeks 44, 45, 46, 47, 48). All data presented in this report are based on the sampling date.

Because of the current situation, first data of the month of December will also be included in this report, in order to discuss Omicron.

3. Variants of concern (VOCs), variant of interest (VOI) and other surveilled variants: brief summary and special focus

Five variants and their sub-lineages are considered VOCs by the WHO, B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta), and B.1.1.529 (Omicron). While still a VOC for WHO, the European Centre for Disease Prevention and Control de-escalated Alpha as a VOC.

A new VOC, Omicron

Most concerningly, a new B.1.1.529 variant of concern (Omicron) was first identified in South-Africa and Botswana during November 2021, and has already spread worldwide. It carries an unprecedented number of mutations on the genome (>50), with most being on the gene coding for the Spike protein (>30) and in particular within the receptor binding domain (15). These mutations are associated with both immune escape and/or increased transmissibility, conferring this variant a growth advantage. It has already split into 3 sublineages: BA.1-3, with BA.1 being, by far, the most common variant. This variant has established itself in Switzerland, although as of early December, at most it only accounted for a few percent of cases. In other European countries, it has been observed to have a rapid doubling time and as of the time of writing of this report, it is the dominant variant in the UK; its spread in Switzerland will be scrutinized closely over the next weeks.

Detection

All sub-lineages are still detected by RT-PCR tests, but BA.1 and BA.3 (but not BA.2) exhibits S-gene target failure with some assays that can be used as a proxy prior to sequencing, as seen with VOC Alpha (and due to the same deletion as found in Alpha). There are only 3 mutations of Omicron are on the N-gene, of which 2 (positions 203 and 204) were already known in multiple other variants, thus antigenic test performance is unlikely to be affected. Preliminary data from PHE showed that the 5 different lateral flow assays that they tested maintain their diagnostic accuracy.

Immune escape

Preliminary in vitro and epidemiological data suggests that Omicron has a significant growth advantage relative to Delta. Early in vitro data demonstrates that it is able to evade neutralizing antibodies raised against previous variants or after 2 doses of vaccine, although 3rd vaccine doses or a combination of previous infection and 2 vaccine doses retained substantial neutralization. In light of this data, it is unsurprising that observed vaccine breakthrough and reinfection rates are much higher. Of note, a clusters of recently boosted triple-vaccinated individuals in their 20s and 30s have been reported. This escape from neutralizing antibodies extends to most clinically-used therapeutic antibodies. Notably, this includes the combination of casirivimab/imdevimab (REGN-CoV2), one of the most used monoclonal antibody treatments in Switzerland, losing their ability to neutralize Omicron. Sotrovimab is currently the only antibody available in Switzerland that retains substantial neutralizing activity.

While Omicron largely escape humoral immunity/neutralizing antibodies, the good news is that cell mediated immunity appears to remain largely intact and thus vaccines or previous exposure should still confer substantial protection against severe outcomes.

Severity

Data on severity is still unclear. Early reports of mild cases do not suggest that Omicron is intrinsically less severe, as the early reports were from a young population with high rates of previous exposure, in which other variants would also be expected to produce mild cases.

Note: The Health 2030 Genome Center highlighted a potential issue in a genomic region of the SARS-CoV-2, which may cause sequencing errors of Omicron. A set of amplicons at the position 22200 will amplify Omicron sequences without showing the insertion present in Omicron at that spot. Attempts are currently being made to solve this issue through with two approaches: (1) a longer read (2) a new version of kit, namely COVIDSeq V4.

The VOC currently driving the pandemic, Delta

Delta is currently still the main driver of the pandemic in Switzerland and most of the world. The proportion of the Delta sub-lineage AY.4.2, considered a Variant under monitoring by both the ECDC and Public Health England, slowly increased in Switzerland during November. It may have a transmission advantage of 10 - 15%, although this is still unclear due to a small dataset. A report from the UK noted no difference in hospitalization rate, severity, or vaccine efficacy compared to the original B.1.617.2 variant. For detailed characteristics of the mutations carried in the AY.4.2 sub-lineage and other Delta lineages, please refer to the reports from the months of September and October.

Vaccines effectiveness:

In large populations, protection against severe disease seems to be maintained against the Delta variant, although complete protection against infection is not. However, this protection shows signs of decreasing over time. Multiple studies have showed significant reductions in vaccine efficacy several months after the second dose, in a context where Delta was the dominant variant. It is not clear how much of this is a result of decreasing immunity against all variants, and how much was due to partial immune escape by Delta. Regardless, this data justifies the approval of a 3rd dose/booster dose to protect against Delta, and a booster dose is also clearly needed to protect against Omicron.

While the viral shedding in vaccine-breakthrough infections caused by the Delta variant seems to be shortened, data regarding the length of infectiousness and transmissibility are still scarce and conflicting. Similar data are currently absent for Omicron.

Therapeutic intervention effectiveness

Numerous mutations have been reported to substantially reduce the therapeutic effectiveness of mAbs currently used to treat COVID-19, as well as those under development (Table 1). Notably, the Delta variant retains susceptibility to all mAbs approved for use in Switzerland, while Omicron escapes all except Sotrovimab. Delta is resistant to Bamlanivimab (not in use in CH), and displays weak resistance to Imdevimab, but the combination of Imdevimab and Casirivimab (which is the standard combination) remains highly effective *in vitro*. Delta sub-lineages with the K417N mutation are resistant to Casirivimab, but the combination of Imdevimab and Casirivimab still remains highly effective. Some point mutations may annihilate the *in vitro* neutralizing effect of the sotrovimab.

AA position	CAS	IMD	CAS&IMD	SOT
337		*L*		R/L/H/T
340				K/A/G
356				T
406	*D/W*	*W*	*W*	
417	*E/N/R*			
439		*K/V*		
440		*K*		
444		*N/Q/T/L/M/x*	*T*	
445	*T*	*A*	*A*	
446		*V/x*		
450		*D*		
453	*F*			
455	*F*			
476	*S*		*D (weak, 4x)*	
484	*K/Q*			
485	*D*			
486	*V/L/S/X*			
493	*K/E/R*	*R*		
494	*P*			
498		*H*		
499		*S*		

Table 1: resistance mutations to mAbs used to treat COVID-19 in Switzerland causing 5 fold or greater reduction in neutralization, except for 476 D which causes only a weaker 4 fold reduction. CAS = Casirivimab, IMD = Imdevimab, SOT = sotrovimab

In addition to mAbs, there are a number of other antiviral treatments under development, such as protease inhibitors (either targeting host cell proteases such as TMPRSS2, or virally encoded ones such as 3CL like proteases) like Paxlovid® (PF-07321332) or RNA nucleotide analogues (which interfere with replication of the viral genome such as Molnupiravir). No data is available regarding mutations enabling escape from these proteases (and there are unlikely to be any for treatments targeting host cell proteases). In contrast, serial passage of virus in the presence of Molnupiravir lead to the accumulation of mutations that increased viral resistance to Molnupiravir. Despite this, the mutations conferring resistance to Molnupiravir significantly reduced overall viral fitness, and were thus detrimental to the virus when Molnupiravir was not present. Preliminary data confirms that Molnupiravir, Paxlovid, and Remdesivir all retain full *in vitro* efficacy again Omicron.

The circulation of specific mutations leading to decreased effectiveness of known therapeutics available for clinical use in Switzerland will be surveilled (see Section 6 below).

Considering potential transmissibility, immune escape, and diagnostic issues, the variants presented below will be particularly surveilled:

- variants classified as VOCs: B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta), B.1.1.529 (Omicron) – and their sub-lineages
- variants that include E484K + N501Y: higher transmissibility, immune escape risk, resistance to mAbs – until sufficient monitoring suggests they do not have a replicative/escape advantage) such as B.1.621 (Mu).
- variants that include L452R: increased transmissibility, resistance to mAbs, such as: B.1.617.2 (Delta) and C.37 (Lambda)
- Any Delta or Omicron sub-lineage with a transmissibility advantage, enhanced immune escape or increased severity.

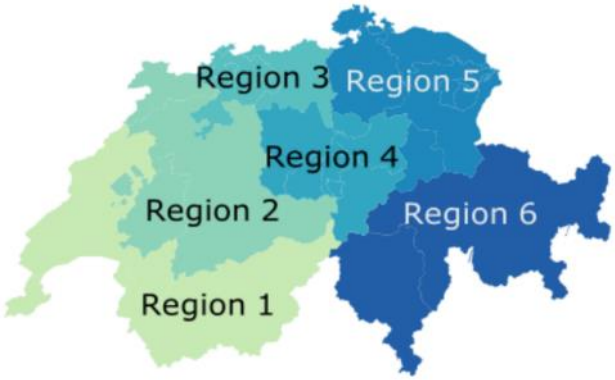
4. Epidemiology in Switzerland and number and origin of sequences produced through the program during the surveilled period

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.

The number and origin of sequences submitted to GISAID by each laboratory during January and February, 2021, prior to the start of the surveillance program can be found in the first report covering the months of March and April 2021.

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

Due to the need to prepare this report early and incorporate data from early December, data for the latter part of this report is incomplete.

Number of cases processed by the laboratories participating in the surveillance program

During November, the FOPH reported a total of over 194,107 confirmed SARS-CoV-2 cases in Switzerland. 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.

As of the writing of this report, the laboratories participating in this program reported 60,159 positive tests during the surveilled program, which represents over 30% of the total number of cases reported in Switzerland (including both PCR and antigen-based tests). Because of reporting delays, this number may be underestimated. 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 appendix Table 3.

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

A total number of 11,950 SARS-CoV-2 sequences have been declared to have been submitted to GISAID during this period. More than 15,000 sequences are available for this period on GISAID, and the difference may be explained by reporting delays.

This represents around 6% of all cases detected in Switzerland during the surveilled period (see Supplementary Table 2 and 3 in the Appendix for details). Of note, this number includes sequences from samples received from other laboratories in order to ensure sequencing of post-vaccination infections.

Table 2 shows the number of sequences successfully submitted to GISAID through the surveillance program during the surveilled period by calendar week (data is incomplete).

Week	Date	Number of sequences declared and successfully submitted to GISAID during the surveilled period, by all laboratories in the program
44	Nov 1 to Nov 7	2 917
45	Nov 8 to Nov 14	2 572
46	Nov 15 to Nov 21	2 991
47	Nov 22 to Nov 28	2 769
48	Nov 29 to Dec 5	701
	Total	11 950

Table 2: 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. Data are incomplete due to late reporting by one laboratory

The total number of SARS-CoV-2 sequences declared and submitted to GISAID by each laboratory during the month of November is available in Supplementary Table 3 in the appendix.

Covering of sequencing in Switzerland and contribution of the national SARS-CoV-2 surveillance sequencing program

As shown in Figure 1, the total number of SARS-CoV-2 sequences submitted per week generally increased towards the end of October (weeks 40 to 43), reflecting the increase in cases within Switzerland in the latter half of October. Almost all of the sequences available in GISAID (green curve) and those on which the surveillance is conducted, come from the national surveillance program. Note that number of sequencing available for the month of December (weeks 49 and 50) are limited due to the inherent delay of sequencing.

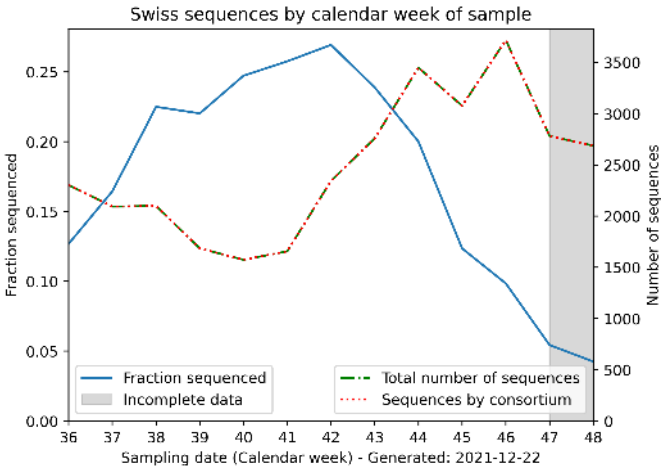


Figure 1: Number of SARS-CoV-2 sequences available for Switzerland (total available Swiss sequences in GISAID in green, Swiss sequences submitted through the program in dotted orange) and fraction of the total number of positive cases declared to the FOPH that have been sequenced (blue curve).

During the surveilled period, the total proportion of positive sequenced cases dropped below the 10% aim of the program due to a rapid rise in case numbers, not a decline in sequencing.

Figure 2 displays the number and fraction of SARS-CoV-2 cases sequenced for each Swiss region. Region 6 continued to have the lowest total number of sequences, while regions 4 and 5 continued to have the lowest fraction of cases sequenced.

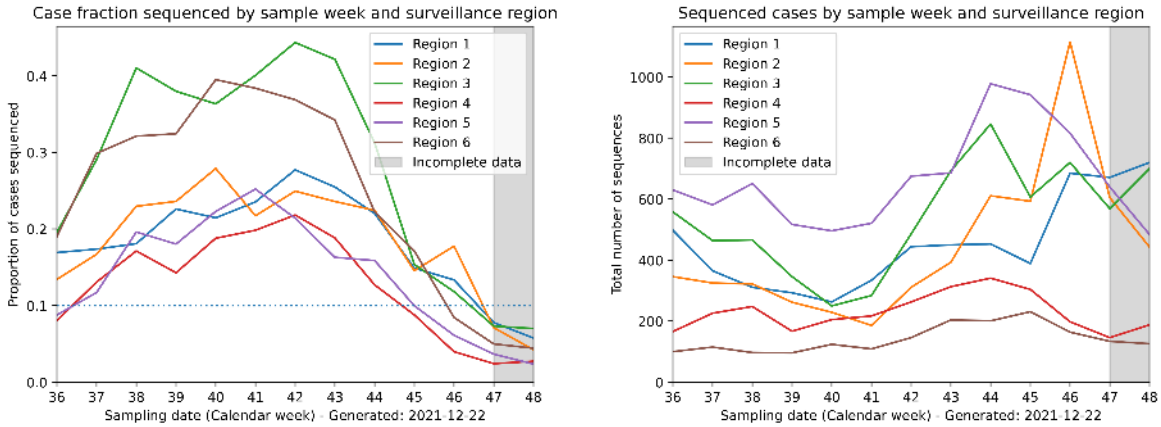


Figure 2: Sequencing coverage among the different Swiss regions per week, presented by fraction of cases sequenced (left) and by number of sequences (right).

5. Variants circulating in Switzerland since January 2021, with a focus on the surveilled period

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 B.1.617.2 Delta variant (in green in Figure 4) and its sub-lineages were the most commonly retrieved lineages during the month of November and early December all over Switzerland, followed by Omicron (Table 3, also Figures 5 and 6). Data for the first half of December is incomplete and may be compromised by sampling bias, but indicates continued Omicron growth. Neither Mu nor Lambda have been retrieved at all in Switzerland since September (table 3).

Region	Delta	None	Omicron	Alpha	Others	sequences	cases	% sequenced
All	15507	90	104	1	9	15711	194107	8.1
1	2891	15	9	1	2	2918	30919	9.4
2	3339	18	7	0	3	3367	32038	10.5
3	3368	37	34	0	3	3442	30510	11.3
4	1168	5	4	0	0	1177	24050	4.9
5	3798	14	47	0	1	3860	66867	5.8
6	852	1	3	0	0	856	9723	8.8

Table 3: number of sequences corresponding to selected variants in each region of Switzerland from 1 November to 5 December 2021. No Beta, Gamma, Lambda, Mu, etc. were identified, according to data received by December 21.

Many Delta sequences are assigned to AY* lineages, which are Delta sub-lineages. AY.43 remains the most common sub-lineage in Switzerland. Within Delta-sub-lineages, AY.4.2 remained rare during the month of November in Switzerland: among 15507 Delta sequences retrieved November, 131 were AY 4.2. Despite this rarity, it has none the less increased in proportion, representing 1.5% of the cases in week 48 at the end of November, compared to 0.5% in week 44 at the beginning of November.

Much more concerning is the increase in Omicron cases following its first detection, and its estimated transmission advantage over over 100% relative to Delta (Figure 3).

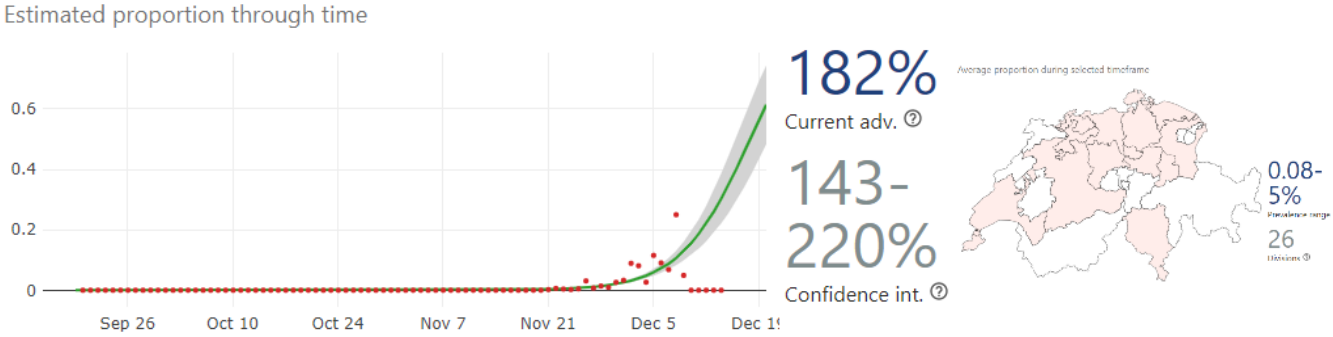


Figure 3: B.1.1.529 (Omicron) estimated transmission advantage over time compared to co-circulating strains (left) and geographic distribution across Switzerland and average proportion during the surveilled period (right), as of 20 December 2021. Dynamic navigation available at https://cov-spectrum.ethz.ch/explore/Switzerland.

Among other sequences identified in Switzerland during the surveilled period, very few other lineages were recorded as of data received by December 22. Only 9 samples with identifiable non-Delta and non-Omicron lineages were detected.

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.

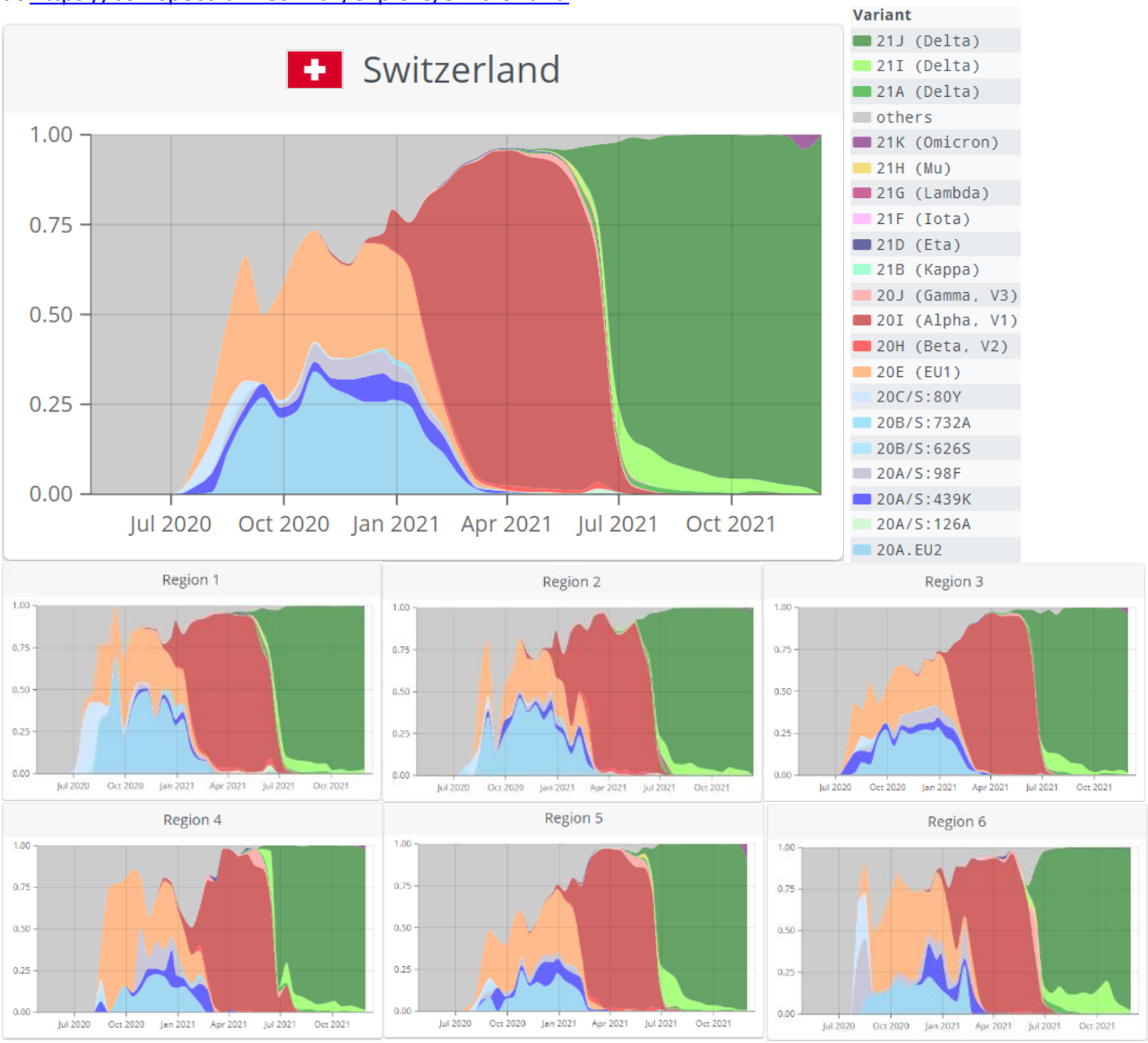


Figure 4: proportion of the total number of sequences (not cases), over time, that fall into defined variant groups, for Switzerland. Screenshot from CoVariant website. Dynamic navigation is available at https://covariants.org/per-country. Dark green indicates the currently dominant B.1.617.2 (Delta) lineage or its sub-lineages. Dark Red indicates B.1.1.7 (Alpha), the previously dominant lineage in Switzerland. Purple indicates.1.1.529 (Omicron).

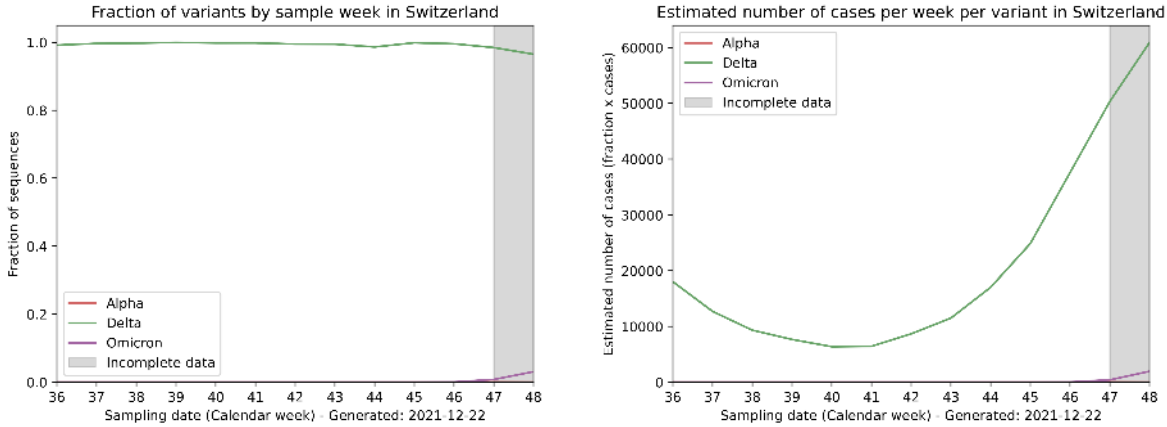


Figure 5: (Left): Percentage of circulating VOCs and VOIs in Switzerland by week, over the 49 first weeks of 2021 (total number of B.1.1.7 (Alpha), B.1.617.2 (Delta), and B.1.1529 (Omicron) sequences from Switzerland and successfully submitted to GISAID are shown here).
(Right): Estimated number of sequences of the main VOCs/VOIs and variants under monitoring retrieved during the surveilled period.

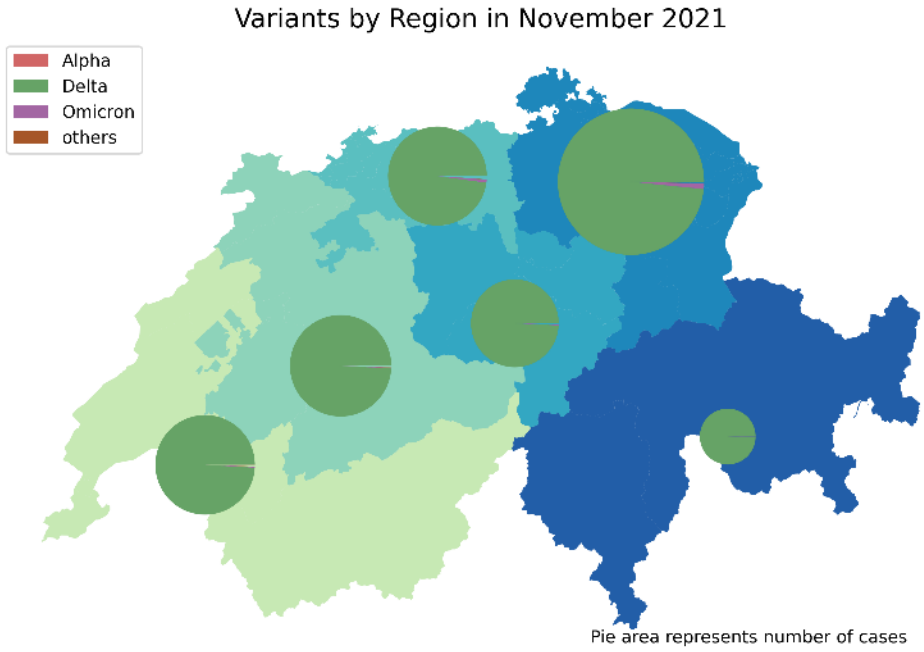


Figure 6: Distribution of variants per region, for November 2021, shown on a map. The size of the pie chart corresponds to the total number of sequences. Note the dominance of Delta or one of its sub-lineages in all regions.

6. 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 results confirmed that Delta remains the only dominant SARS-CoV-2 variant in Switzerland in October 2021. These predictive models suggest that Omicron will soon become the dominant variant in Switzerland. This rapid rise is most readily visible when a log scale is used (figure 7)

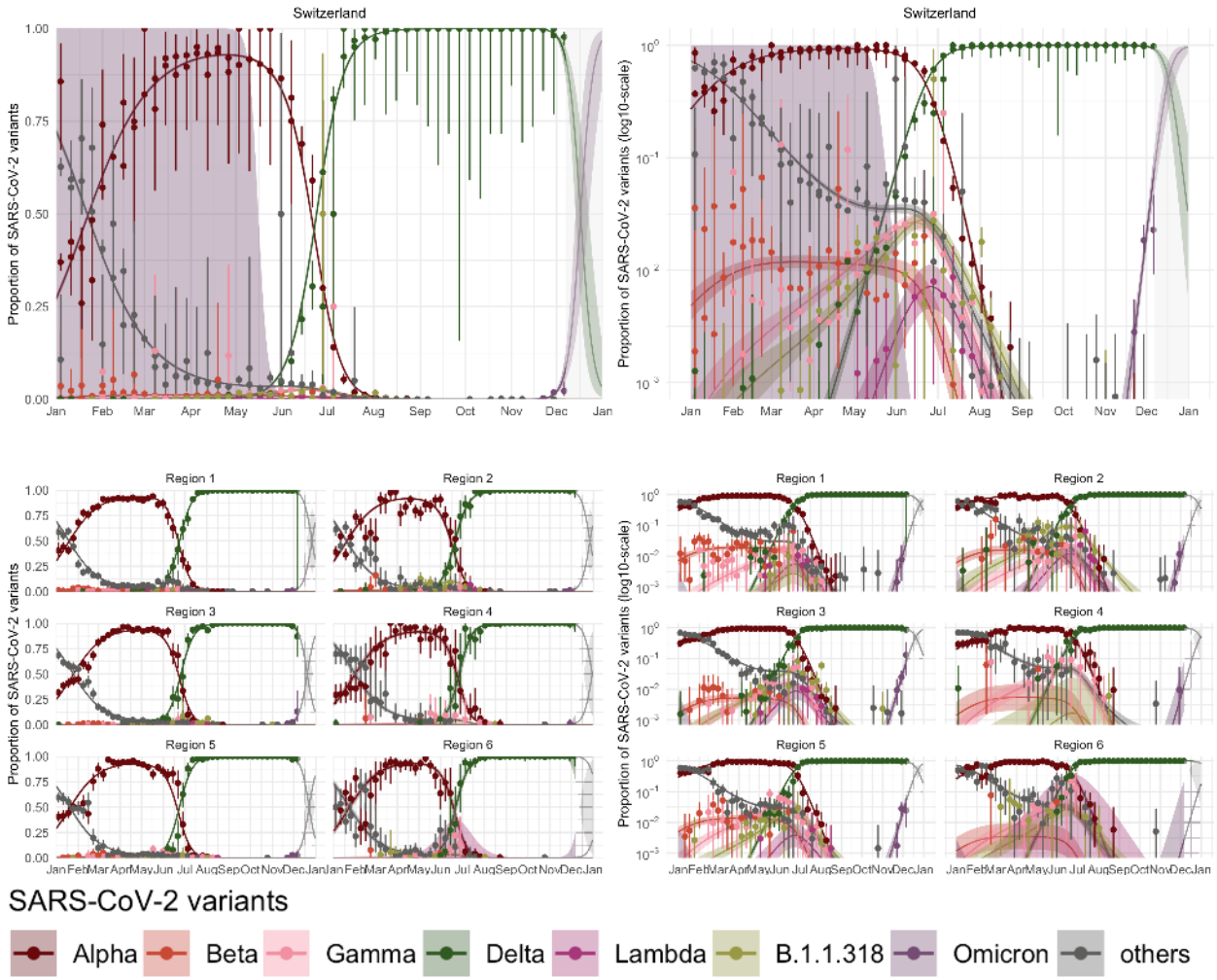


Figure 7: Observed and modeled proportion of SARS-CoV-2 variants over time in Switzerland. In April and May 2021, Gamma and Delta started to replace Alpha, with Delta now outcompeting all other variants. At the end of October, more than 99.9% of the retrieved sequences in Switzerland were due to Delta or one of its sub-lineages. In late November, Omicron arrived in Switzerland and appears poised to rapidly displace Delta. Model fits are based on a multinomial logistic regression with splines.

7. Surveillance of mutations associated with reduced mAb treatment efficacy

A number of mutations have been reported to result in significantly reduced *in vitro* effectiveness of the sotrovimab and casirivimab/imdevimab association monoclonal antibodies used to treat patients in Switzerland. Notably, Omicron is completely resistant to neutralization by casirivimab/imdevimab, and sotrovimab remains the only mAb used in Switzerland that retains effectiveness against Delta and Omicron. The prevalences of mutations reported to escape neutralization by sotrovimab are thus being followed (Table 4).

	337H		337L		337R	337T	
date	Global	Switzerland	Global	Switzerland	Global	Global	Switzerland
01.11.2021	1	0	4	1	0	0	8
08.11.2021	2	0	6	0	0	0	7
15.11.2021	2	0	5	1	0	0	0
22.11.2021	1	0	5	0	0	0	1
29.11.2021	1	0	10	1	0	0	2
06.12.2021	0	0	1	0	0	0	3
13.12.2021	0	0	0	0	0	0	0

	340A		340K		340G		356T
date	Global	Switzerland	Global	Switzerland	Global	Switzerland	Global
01.11.2021	9	0	19	1	1	0	1
08.11.2021	5	0	27	0	2	0	0
15.11.2021	4	0	36	0	1	0	1
22.11.2021	3	0	25	0	4	0	3
29.11.2021	3	0	17	0	5	0	0
06.12.2021	2	0	1	0	1	0	0
13.12.2021	0	0	0	0	0	0	0

Table 4: Global and Swiss counts of sequences bearing escape mutations from therapeutic mAbs used in Switzerland

So far, no known mutations enabling complete escape from sotrovimab have been detected in Switzerland, and they remain rare globally.

8. Wastewater surveillance program

Since August, the B.1.617.2 (Delta) variant has accounted for the vast majority of the sequences identified in all of the six wastewater treatment plants (WWTPs) that are tested on a daily basis. Detection of variants in wastewater can be challenging if the prevalence is low due to low RNA concentrations, as was the case in June and July, and again in October (https://sensors-eawag.ch/sars/overview.html). In this situation, it is especially difficult to distinguish related lineages that share variant-defining mutations. In particular, this is the case, among the sub-clades of B.1.617*, and especially amount the AY.* sub-lineages of B.1.617.2. During the month of November, the dominance of B.1.617.2 (Delta) was obvious in all surveyed WWTPs. However, the RNA levels were higher in the wastewater samples in November.

Signatures of the B.1.1.529 (Omicron) variant have been detected in a sequenced sewage sample of the Basel-Stadt cantonal wastewater surveillance project, dating from November 24. In this project run by the canton of Basel-Stadt, weekly samples are sent to be sequenced, and the next sample (December 1) showed an apparent increase in the strength of the B.1.1.529 signal. Daily samples from dates in between the two signals and before the first have been sent for retrospective sequencing but have not been processed yet. No definitive signature of the Omicron variant have been found up to December 1 in the sequenced samples from any of the 6 wastewater treatment plants covered by the FOPH surveillance program and samples from the canton Zurich.

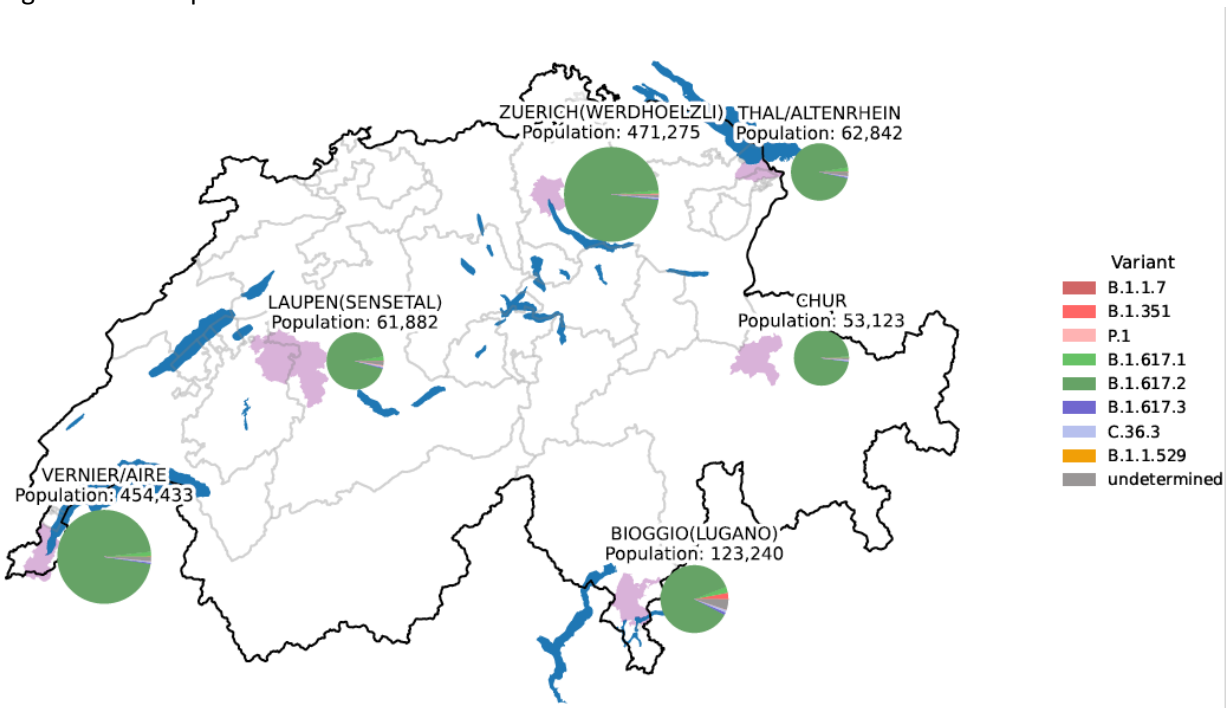


Figure 8: Overview of the average prevalence of variants of SARS- CoV-2 estimated from wastewater samples collected daily during the month of November in WWTPs located in 6 different Swiss locations. Pie chart areas are proportional to population connected to the wastewater treatment plants. Pink shaded areas represent catchment areas (boundaries from 2017). Population connected to Vernier (GE) wastewater treatment plant also includes ~44,000 inhabitants from neighbouring French communities. B.1.617.2 (Delta) is represented in in dark green, B.1.617.1 in light green (Kappa), B.1.617.3 in purple, B.1.1.7 (Alpha) in dark red, B.1.351 (Beta) in light red, P.1 (Gamma) in pink, B.1.1.529 (Omicron) in orange.

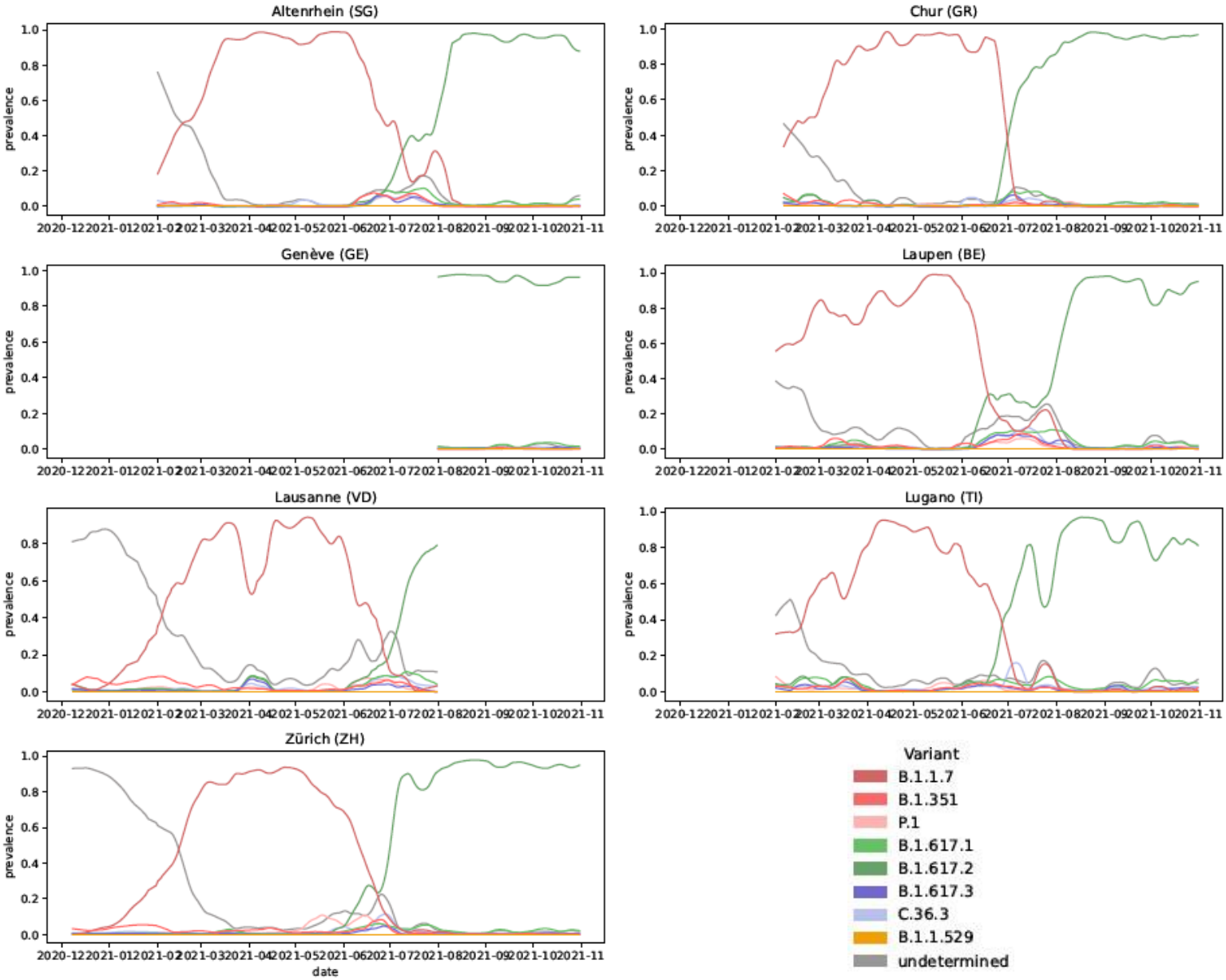


Figure 9: Prevalence of variants of SARS- CoV-2 estimated from wastewater samples collected daily until November 30 (except Lausanne: July 31) in WWTPs located in 7 different Swiss cantons. B.1.617.2 (Delta) is represented in dark green, B.1.617.1 (Kappa), in light green, B.1.617.3 in purple, B.1.1.7 (Alpha) in dark red, B.1.351 (Beta) in light red, P.1 (Gamma) in pink, B.1.1.529 (Omicron) in orange. An online dynamic navigation is available at https://bsse.ethz.ch/cbg/research/computational-virology/sarscov2-variants-wastewater-surveillance.html.

Some of the FOPH surveillance samples are also routinely analyzed using droplet digital PCR (ddPCR) by Dr. Tim Julian's lab at Eawag to quantify the relative prevalence of certain variant-specific mutations. Among the three sites analyzed in this fashion, no signal was detected in the WWTPs Altenrhein and Geneva, but samples from the WWTP Zurich Werdhölzli showed a sustained decrease of the relative prevalence of the S:L452R mutation, a signature of B.1.617.2* (Delta), which indicates a rise of the relative prevalence of Omicron (see Figure 10). Assuming Omicron is the sole responsible for Delta's decrease in relative prevalence (which seems very likely), we estimate from these data a growth rate of Omicron in the population connected to this WWTP of 0.27 per day (95% confidence interval: [0.11 – 0.43]), which amounts to an advantage over Delta of 2.6 (95% confidence interval: [0.70 – 6.73]), i.e., $R_{omicron} = (1 + 2.6)\, R_{delta}$. These findings are based on several model assumptions and on few observations [see https://doi.org/10.1101/2021.08.22.21262024, for details].

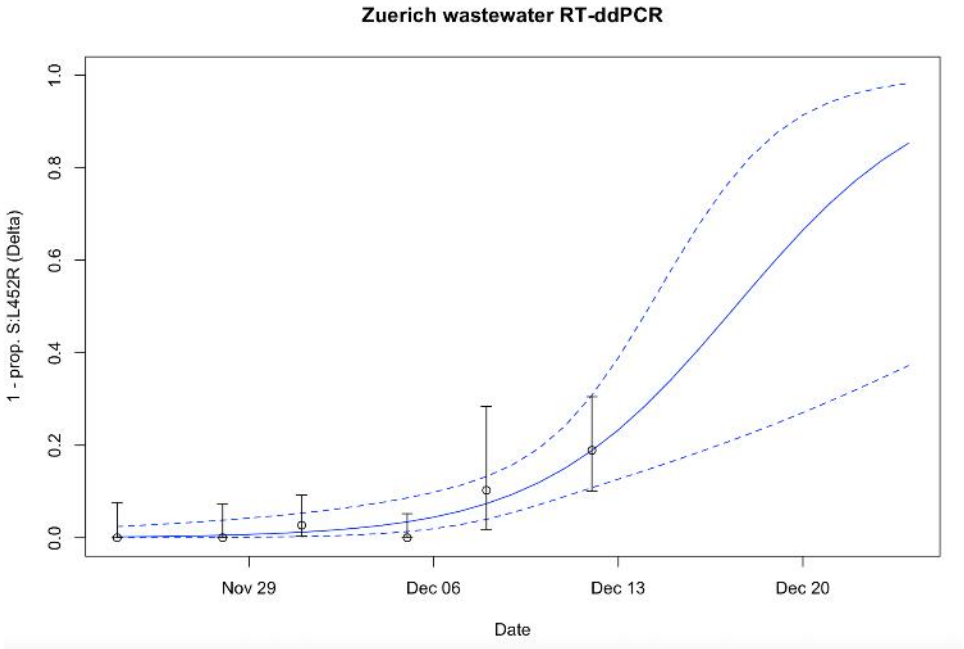


Figure 10: Estimated prevalence of RNA fragments in Zurich Werdhölzli wastewater samples putatively attributable to Omicron on the basis of their lack of S:L452R mutation. Points represent the prevalence estimated in each sample, along with 95% confidence intervals. Solid line represent a logistic growth fit, dashed lines indicate 95% confidence bands.

9. Immunological characterization of the variants

During the months of November and December, sera from convalescent or fully vaccinated subjects were used to monitor the impact on neutralization titers of both additional mutations found in the AY.4.2 Delta sub-lineage and the Omicron Spike proteins.
When comparing neutralization titers obtained with sera from either infected or fully vaccinated subjects, no additional immune escape was found with either the Delta AY.4.2 nor the A222V, Y145H or T95I single mutations, compared to the original Delta B.1.617.2 variant (Figure 11). These results suggest that there should be no change in vaccines effectiveness against the AY.4.2 variant compared to the original Delta lineage.

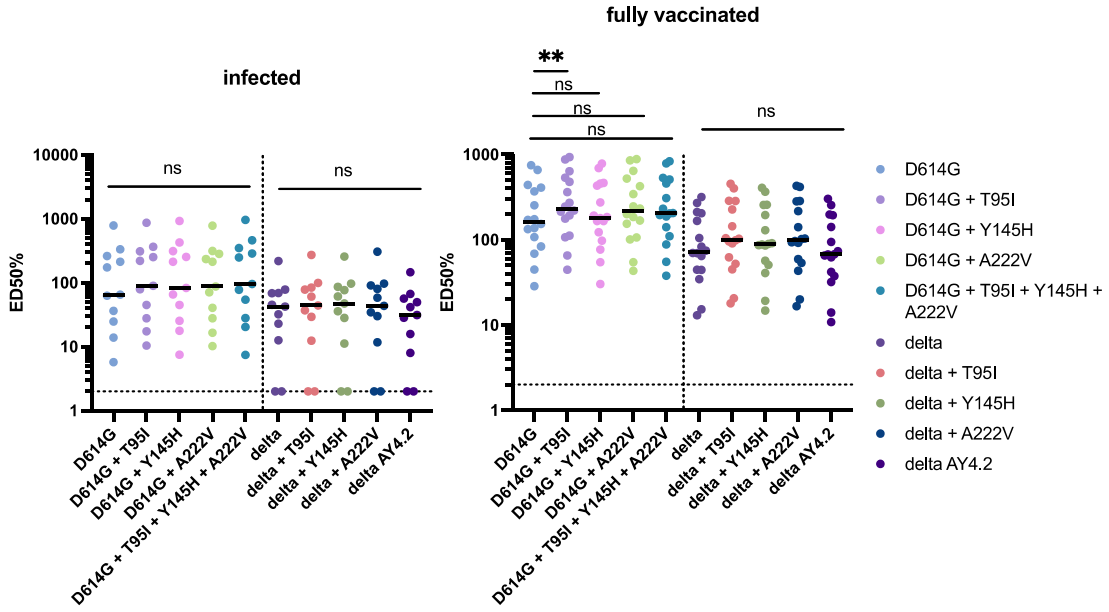
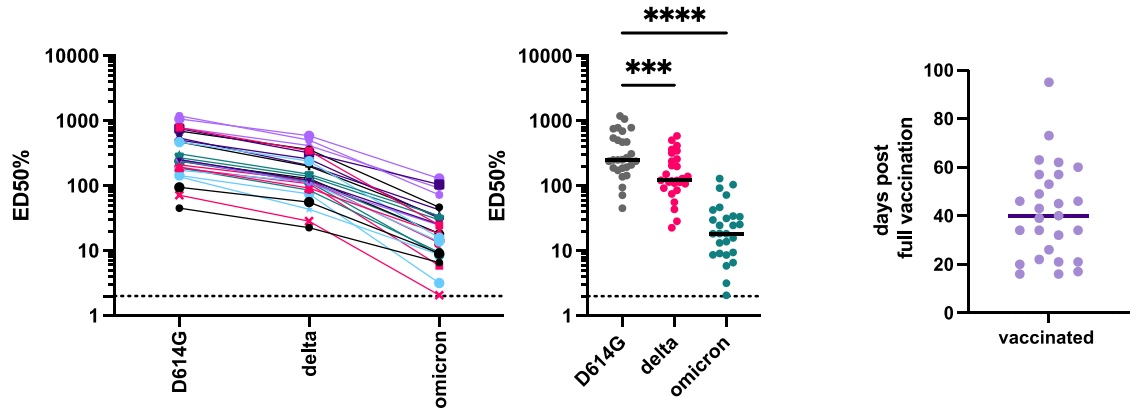


Figure 11: The additional mutations found in AY.4.2 Delta sub-lineage do not result in additional immune escape relative to the original Delta variant.
*The neutralizing activity of sera from convalescent or fully vaccinated subject was assayed in the surrogate spike-ACE2 (S^3-ACE2) neutralization assay, on Spike mutants harboring the T95I, A222V or Y145H mutations found in Delta sub-lineages. These additional mutations were introduced both in the D614G ancestral variant backbone and in the original Delta variant. ED50% indicates the serum dilution needed to achieve 50% of neutralization inhibition, with low ED50% signifying of low neutralization titer. **p< 0.01, ns non-significant. Note the lack of any significant differences in neutralization*

The Omicron lineage is characterized by the presence of more than 30 mutations in the Spike protein, some of which are expected to affect vaccine effectiveness. Similar to recent results from other groups, sera from vaccinees was found to have substantial reductions in neutralizing activity against Omicron. Figure 12 shows that neutralizing activity of sera collected from Pfizer or Moderna vaccine recipients (sampled on average 41.5 days after administering the second dose) displayed 2 and 10 fold reductions in neutralizing activity against Delta and Omicron respectively.



	D614G	delta	omicron
Mean	389.8	187.4	31.19

Figure 12: Reduced neutralization of Omicron by vaccinee sera.
*Sera from 27 fully vaccinated people was assessed for its ability to neutralize D614G, Delta B.1.617.2 and Omicron Spike variants in the S³-ACE2 assay. The mean serum dilution needed to achieve 50% of neutralization inhibition (ED50%) is indicated in the table for each variant. **p< 0.01, ****p< 0.0001. Note the significantly reduced ability to neutralize Omicron's Spike protein.*

The sensitivity of Omicron to Regeneron (imdevimab + casirivimab) and AstraZeneca (tixagevimab plus cilgavimab) monoclonal antibody cocktails was also tested. Both cocktails show a profound reduction in Omicron Spike neutralization in a S³-ACE2 cell free surrogate neutralization assay (Figure 13), confirming results obtained with a live replicative Omicron isolate (not shown).

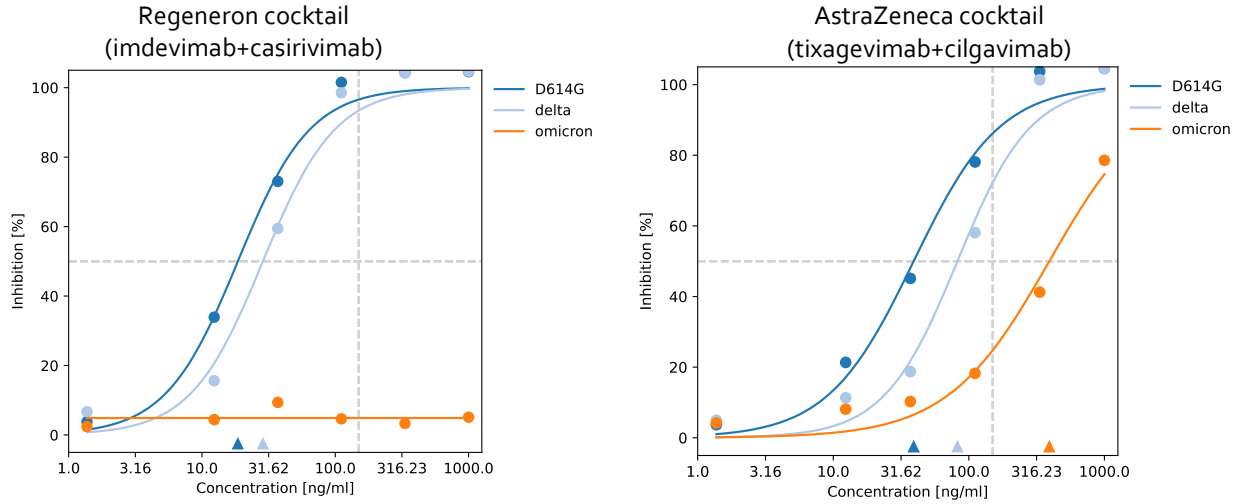


Figure 13: Omicron's sensitivity to Regeneron and AstraZeneca monoclonal antibody cocktails is highly reduced. The neutralizing activity of monoclonal antibody cocktails was tested using the S³-ACE2 assay against the ancestral D614G, the Delta and the Omicron Spikes. Triangles on the X axis indicate the concentration of antibody cocktails necessary to achieve 50% of neutralisation in each case. Note the Regeneron cocktail has a complete loss of activity, and the substantial reduction in the activity of the AstraZeneca cocktail.

Conclusion

In November, over 11,900 sequences were obtained for Switzerland, through this surveillance program, in the midst of a steep increase in case numbers. Each week since this surveillance program started, it has contributed almost all of the Swiss SARS-CoV-2 sequences available on GISAID.

In November, around 8% of the cases reported in Switzerland were sequenced, a significant decrease from the month before, and below the goal of 10%. This reflects a large increase in case numbers, as the total number of sequences doubled despite the drop in proportion. With over 11 thousand sequences generated from all over Switzerland, coverage is deemed to be satisfactory despite falling below the arbitrary 10% threshold. Region 4 and 5 remain the least represented geographical areas.

In November a new variant of concern Omicron (B.1.1.529), with the most spike mutations ever seen was detected, with an apparent origin in southern Africa. Although the first cases in Switzerland were found in travelers coming from South Africa, it is now clear that there is community transmission within Switzerland.

Circulation was nearly exclusively the B.1.617.2 (Delta) variant (and its sub lineages) through most of November, but Omicron sequences were detected in late November and have been observed in increasing numbers in late November and early December. While Omicron remains firmly in the majority of sequences, it is rapidly growing, and it is clearly displacing Delta in other European countries.

Omicron brings with it sharply reduced vaccine efficacy, requiring a third dose to restore reliably detectable neutralizing antibody titer *in vitro*. Casirivimab and imdevimab are ineffective against Omicron, and leave Switzerland with just one remaining antibody, sotrovimab, that is effective against Omicron. Data on the severity of Omicron is currently unreliable or lacking.

No additional diagnostic or treatment issues were noted for any variant other than Omicron in November.

No important geographical breakdown of a particular variant has been noticed. All other variants were only rarely detected, both in clinical samples and in the wastewater surveillance part of the program.

An estimate of the total number of VOCs circulating in Switzerland, corrected by taking in account the fraction of sequencing in Switzerland is available at https://cov-spectrum.ethz.ch/explore/Switzerland.

Acknowledgements:

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

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Appendix:

SARS-CoV-2 epidemiology in Switzerland:

We used publicly available data on COVID-19 as reported by FOPH (https://www.covid19.admin.ch) and sequence data submitted to GISAID to provide a summary of the SARS-CoV-2 epidemiology in Switzerland. Data presented here cover the period from November 1 to December 5.

sup_table_overview_1_Nov_5_Dec.xlsx

Supplementary Table 1: Epidemiological data for Switzerland, its regions and cantons from 1 November 2021 to 5 December 2021: 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	% positives sequenced
44	Nov 1 to Nov 7	78 870	6 627	2 917	8.40%	44.02%
45	Nov 8 to Nov 14	96 877	9 927	2 572	10.25%	25.91%
46	Nov 15 to Nov 21	121 690	14 606	2 991	12.00%	20.48%
47	Nov 22 to Nov 28	148 566	21 408	2 769	14.41%	12.93%
48	Nov 29 to Dec 5	40 962	7 591	701	18.53%	9.23%
	Total	486 965	60 159	11 950	12.35%	19.86%

Supplementary Table 2: Total number of tests performed by the laboratories participating in the surveillance program from November 1 to December 5, 2021.

Week	Date	Basic Surveillance						Augmented Surveillance						Sentinella Laboratories		
		EOC	St-Gallen	Labor Team W *	Risch	SRO	Synlab	USB	IFIK	Diana labs	CHUV	UZH	ICH-VS*	HUG	ETH/ Viollier	All
44	Nov 1 to Nov 7	89	48	186	118	17	0	228	24	44	45	270	86	179	1462	2796
45	Nov 8 to Nov 14	91	48	186	170	51	0	156	63	44	35	291	91	154	1068	2448
46	Nov 15 to Nov 21	81	48	186	205	68	0	200	0	44	78	217	91	225	1432	2875
47	Nov 22 to Nov 28	79	48	186	111	66	0	116	48	94	86	205	83	312	1253	2687
48	Nov 29 to Dec 5	0	0	186	0	0	0	122	45	0	108	257	90	0	0	808
	Total	340	192	930	604	202	0	822	180	226	352	1240	441	870	5215	11614

*Supplementary Table 3: number of sequences submitted to GISAID by each laboratory during the surveilled period (November 1 to December 5, 2021). *including sequencing sent to high-throughput platforms. ND = No data*

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