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Swiss national SARS-CoV-2 genomic and variants surveillance program: brief intermediate report, focus on C.36.3

1. Rational behind this intermediate report

The WHO currently does not consider the C.36.3 variant, which originated in Egypt, to be a *variant of concern* or *interest* (VOC/I); however as of May 25, 2021, the UK's Public Health England (PHE) has elevated its status from a *variant under monitoring* to a *variant under investigation*. This raises a potential concern that various restrictions may be put on regions with significant C.36.3 clusters.

PHE elevated its status "on the basis of the mutation profile and increased importation from a widening international area".

The increase of 452R detection in the Geneva and in Switzerland are mainly due to 2 different circulating variants: B.1.617.2 (delta) and C.36.3. This report will focus on the circulation of C.36.3 in Switzerland.

C.36.3 Spike mutations: In addition to the L452R mutation found in delta, it contains the 346S mutation which is associated with escape from monoclonal antibodies, but which has a minimal effect on polyclonal sera neutralization. Similarly, it contains multiple N-terminal domain mutations (S12F, W152R), which are also associated with reduced neutralization capacity of some mAbs[1–3]. The accumulation of multiple such mutations could cumulatively lead to effective immune escape[4]. Notably the del69-70 mutation, which is also found in B.1.1.7, is found in C.36.3 sequences, and causes S-gene target failure. Similar to other VOC/Is, it contains a mutation near the furin cleavage site (Q677H).

C.36.3 Nucleocapsid mutations: C.36.3 carries the R203K and G204R mutations, which are also present in B.1.1.7 and P.1, and are linked with increased infectivity[5].

It additionally carries the I82T mutation in the membrane protein, which has been increasing in prevalence and may be relevant[6], as well as multiple Orf1a mutations of unknown significance.

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2. Correspondance between the different variant nomenclatures

WHO name	Pango Lineage	Nexstrain clade
Alpha	B.1.1.7	20I/501Y.V1
Beta	B.1.351	20H/501Y.V2
Gamma	P.1	20J/501Y.V3
Delta	B.1.617.2	21A/S:478K
Epsilon	B.1.427/429	20C/S.452R
Zeta	P.2	20B/S.484K
Eta	B.1.525	20A/S: 484K
Theta	P.3	20B/S:265C
Iota	B.1.526	20C/S: 484K
Kappa	B.1.617.1	21A/S: 154K

3. 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. We aim to have a "harmonized" data set in the future with publicly available FOPH data and sequence data from SPSP. The overall goal of the program is to provide epidemiological trends and to highlight meaningful observations.

This intermediate report is based on the analysis conducted by Richard Neher's team on the C.36.3 circulation in Switzerland from sequences available on GISAID and from Tanja stadler's group.

4. Overview of different circulating variants in Switzerland, with a focus on C.36

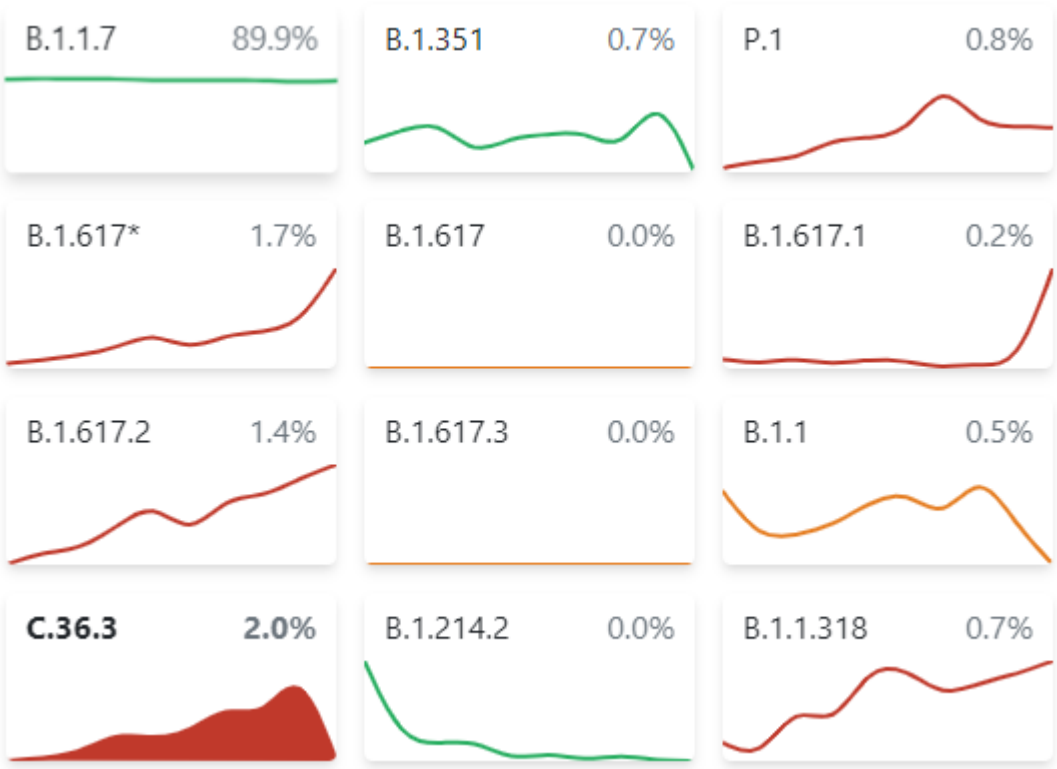


Figure 1: Overview of the circulation of variants in Switzerland during the last 3 months based on available sequences submitted on GISAID. Estimate of the relative frequency of VOCs circulating in Switzerland, based on the 12.5 % of confirmed cases being sequenced in Switzerland. Screenshot from the CoVspectrum website, dynamic navigation for Figures and Tables is available at https://cov-spectrum.ethz.ch/explore/Switzerland/

Neither C.36 nor the C.36.3 sub-variant seem to be taking off in Switzerland up to week 21. Circulation remains minimal, despite a trend towards an increased proportion of total cases. The increased proportion coincides with a decline in the total case numbers, and does not reflect substantial increases in the number of C.36.3 cases (week 16: 14 cases, week 21; 17). Note that due to submission delays, data may be incomplete for the last time points.

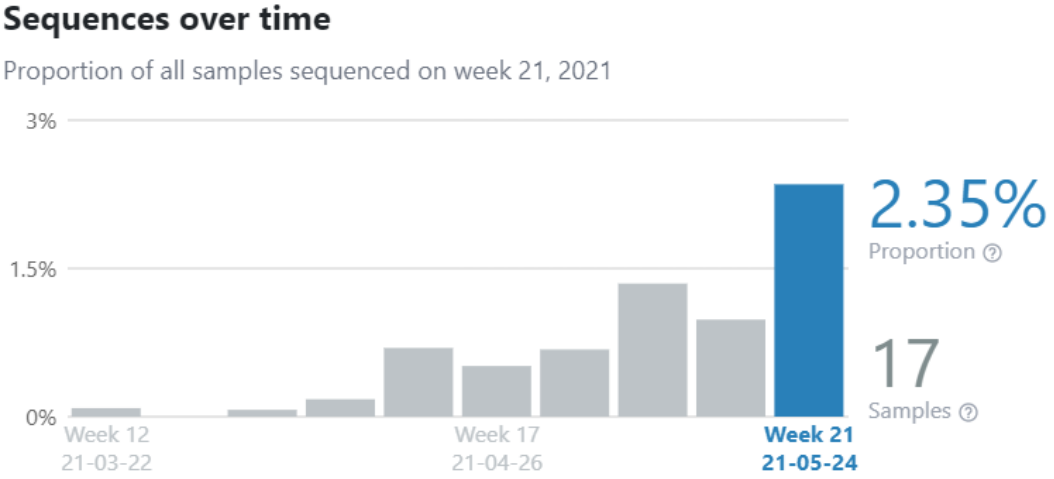


Figure 2: Proportion of C.36 samples sequenced, specifically showing C.36 sequences up to week 21 (24.5.2021). The sequences reported for the most recent week may be much lower than the actual number of sequences because of reporting and GISAID submission delays. As a result the confidence interval for the number of estimated cases is rather high (not shown here but available online at https://cov-spectrum.ethz.ch/explore/Switzerland/.

Division	Number of sequences	Prevalence
Aargau	1	0.03%
Bern	6	0.14%
Geneva	39	0.78%
Schwyz	1	0.12%
Solothurn	1	0.02%
Thurgau	1	0.18%
Ticino	17	1.65%
Zurich	13	0.23%
Unknown	2	0.40%

Table 1: Number and canton of origin of the different sequences of C.36.3 retrieved in Switzerland

Most sequences come from the Geneva area, Zurich and Basel, with prevalence remaining low, as these cantons are the ones from which most of the Swiss sequences originate.

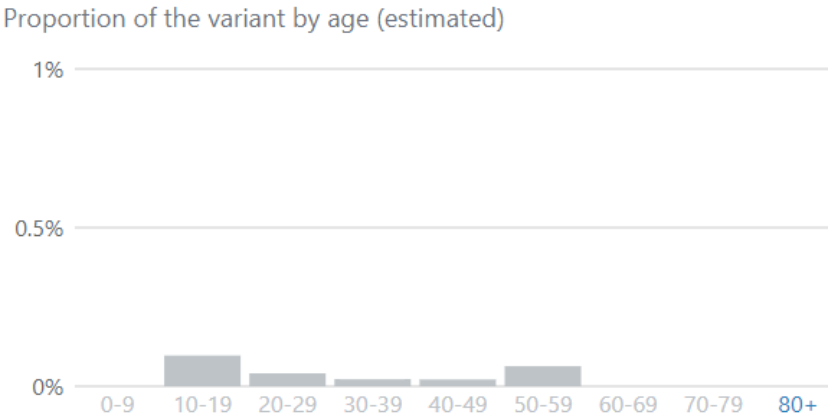
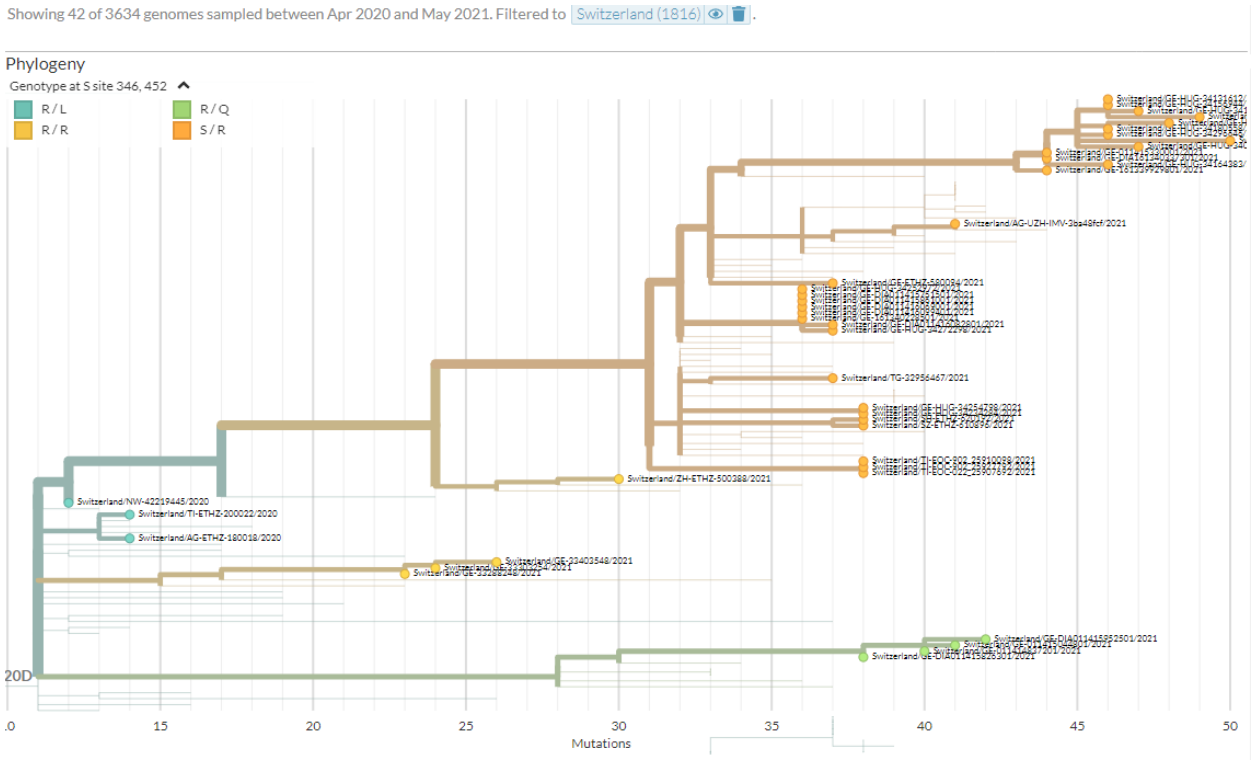


Figure 3: Estimate of the proportion of the C.36.3 variant by age

This variant seems to be distributed equally among adults below 50, retrieved both from children and from adults. Those over 60 (who are the most vaccinated population) seem to be less affected, suggesting that the vaccine remains effective. Absolute case numbers are as follows: 0-9: 0; 10-19: 3; 20-29: 2: 30-39: 1; 40-49: 1; 50-59: 3; >60: 0.

Phylogenetically, there are is a distinct clade circulating in Geneva. The clade in Geneva carries 346S, del 69-70 and 152R, but this Spike mutation profile is not unique and is found elsewhere (including Germany and Norway). Sequences retrieved from Geneva cluster together and are apparently not found anywhere else in the world.

This combination, as explained in the first paragraph, may lead to increased immune escape, although no vaccine breakthroughs have been observed so far.



Screenshot from Nextsrain. Dynamic navigation is available at https://nextstrain.org/groups/swiss/ncov/CH-geneva?c=gt-S_346,452&f_country=Switzerland&label=clade:20D&m=div
Phylogenetic tree constructed from 42 of 3634 genomes, sampled between Apr 2021 and May 2021. The color depicts the genotype at S site in positions 346 and 452, as explained in the legend.

5. Other circulating variants: circulation of variants with 484K in Switzerland

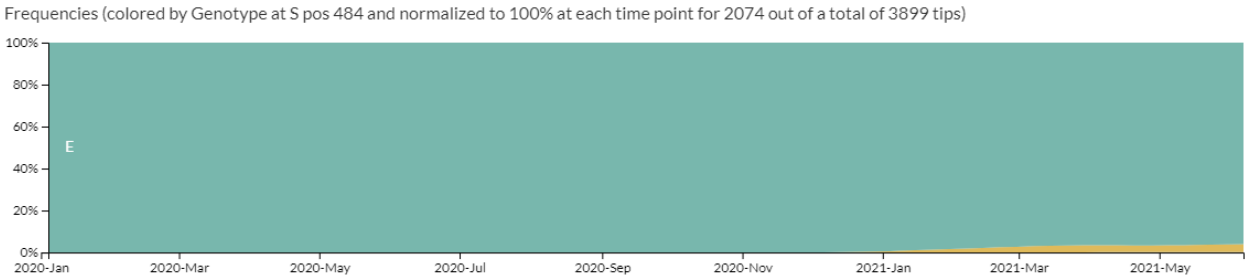


Figure 4: Circulation of variants carrying the 484K mutations in Switzerland Screenshot from Nextrain. Dynamic navigation is available at https://nextstrain.org/groups/swiss/ncov/switzerland/?c=gt-S_484&f_country=Switzerland

The presence of the 484K mutation is stable around 3% of the cases over the time period covering Feb 2021 to May 2021. A slight increase in absolute numbers has been observed during the month of March, but seems to have remained stable during the following months.

4. Conclusion

C.36.3 is circulating in Switzerland with a specific cluster in Geneva. Importantly, contact tracing has been performed for these cases, since screening for the 452R mutation has been done since the beginning of May (4th of May). This contract tracing may have created a positive detection bias for C.36.3.

Of importance, in almost all cases of infection with variants carrying mutations of interest 452R in the Geneva area during the last week (May 31 to June 6), new cases are linked to previously known clusters or to secondary cases linked to a new importation according to the cantonal physician team.

The mutations carried by the 36.3 variant make it a variant that should be followed, and it is a variant under investigation by the UK.

Despite the C.36.3 cluster forming a unique clade in Geneva with a mutation profile that is somewhat concerning, circulation of this variant is rather low over Switzerland. Similarly while we have detected B.1.617.2 cases, the absolute numbers are rather low as well. Note that due to submission delay, an increase in the incidence may be noticed with a 1-2-week delay. An update of the situation of the C.36.3 variant in Switzerland will be included in the next monthly report.

It is too soon and there is not enough data to say that any variant is replacing another in CH.

Diagnostics: S dropout by RT-PCR if del69-70: not expected to impact multiplex screening RT-PCR tests, but may lead to S gene target drop-out.

Numbers of sequences are too low in Switzerland to observe an increase in transmissibility, and no data are available from other countries. Some mutations however are known to produce increased affinity to the cell receptor.

No data are not yet available regarding a particular phenotype. The number of cases is too low in Switzerland to draw any conclusion of the severity/particular phenotype of this variant.

Few in vitro data exist, because it carries, among others, the 452R and del69-70 mutations, there is some potential of this variant to evade previous existing immunity or monoclonal antibodies. No data is available on the efficacy of the current vaccines.

On the treatment side, this variant carries mutations involved in resistance to commercially available monoclonal antibodies such as banlanivimab (452R). No data is available regarding the efficacy of the current available monoclonal antibody cocktail in Switzerland casirivimab/imdevimab.

Acknowledgements:

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

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Appendix :

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