Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Federal Office of Public Health FOPH
Public Health Directorate Communicable Diseases Division

Schwarzenburgstrasse 157
3003 Bern
Switzerland

Geneva, February 19, 2025

Swiss national RSV, SARS-CoV-2 and Influenza virus genomic surveillance program: December 2024 to January 2025

Geneva Centre for Emerging Viral Diseases

Division of Infectious Diseases

Department of Medicine

Laboratory of virology

Division of Laboratory Medicine

Diagnostic Department

1. Summary:

This report covers the samples collected between 27 November, 2024 and January 16, 2025, corresponding to the second sequencing batch of the integrated RSV, SARS-CoV-2 and influenza virus genomic surveillance program of the 2024/2025 season.

Most of the samples (127/221, 57%) originate from the Sentinella program, complemented by a random selection of samples originating from 6 hospital laboratories (Table 1, Table 2 and Table 3).

A total of 221 samples of respiratory pathogens were sent for sequencing, yielding a total number of 202 sequences: 80 SARS-CoV-2, 89 influenza (among which 66 IA (37 H1N1, 29 H3N2), 23 IB), and 33 RSV (16 RSV-A, 17 RSV-B).

The most common lineages for SARS-CoV-2 were XEC (48%) and KP3.1.1 (28%) (Figure 1). For influenza virus, 26% of the sequences were influenza B and 74% were influenza A: of the influenza A sequences, 56% belonged to the H1N1pdm09 subtype, while 44% belonged to the H3N2 subtype. For RSV, 48.5% of the sequences were RSV-A, and 51.5% were RSV-B.

Only 1 influenza A(H1N1pdm09) specimen, collected within the Sentinella network, carried the amino acid substitution I223T associated with reduced susceptibility to oseltamivir (see Table 5). No other mutations linked resistance to oseltamivir nor baloxavir were observed. No resistance mutation to nirsevimab have been retrieved in circulating RSV samples. Similarly, no high-level nirmaltrelvir/ritonavir resistance mutation has been observed within circulating SARS-CoV-2 strains.

Hurdle: 91% of RSV and 100 % of influenza virus samples sent for sequencing have been successfully published into GISAID. The success rate of SARS-CoV-2 sequencing is lower, with 80/96 (83%) of the sequences accepted by GISAID. This could reflect the use of higher quality control requirements compared to the one used with the previous specific SARS-CoV-2 sequencing assay up to September 2024. A lower threshold for the Ct value for SARS-CoV-2 selection will yet be required for sequencing (Ct value < 28).

Key numbers

Table 1: Origin of the samples and success of the sequencing.

	SARS-CoV-2	Influenza virus	RSV
Sentinella	50	62 (44 A, 18 B)	15
Laboratory network	46	27 (22 A, 5 B)	21
Total	96	89	36
Number of sequences successfully deposited in GISAID	80	89 (66 A (37 H1N1 and 29 H3N2), 23 B)	33 (16 A, 17 B)

Table 2: Sentinella positive specimens (from November 27 to January 16, 2024).

	SARS-CoV-2	Influenza virus	RSV
Total number of positive specimens	66	174 (131 A, 43 B)	34
Meeting sequencing criteria	50	62 (44A, 18B)	15
Included	50	62 (44A, 18B)	15

Sequencing criteria and reasons for non inclusion of samples in the sequencing batch are detailed in the methods section below.

Table 3: Detailed origin of samples by originating lab.

Site	SARS-CoV-2	Influenza virus	RSV
CHUV	10	5	5
HUG*	50	62 (44 A, 18 B)	15
ICH	7	7	6
IFIK	5	5	5
IMV	10	5	5
USB	15	5	0
Total	97	89	36

*All samples provided by the HUG laboratory originate from the Sentinella network.

SARS-CoV-2 lineages

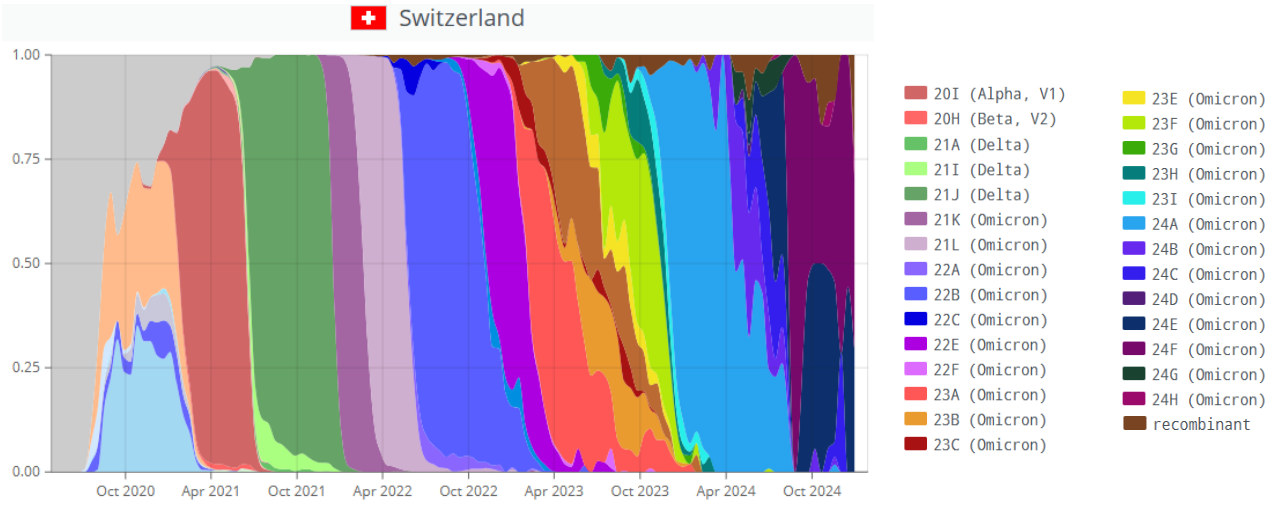

Figure 1: Proportion of Swiss sequences belonging to each pango lineage. Not the co-dominance of XEC (24F) and KP.3.1.1 (24E) in the last sequencing batch. Source: www.covariants.org.

Escape mutation prevalence

Currently, no monoclonal antibodies available in Switzerland are effective at neutralizing most of the SARS-CoV-2 sub-lineages circulating in Switzerland and the rest of the world. The 3CL protease inhibitor, nirmatrelvir/ritonavir Paxlovid®, remains effective against SARS-CoV-2, and we are monitoring the prevalence of mutations that have been shown to reduce its efficacy by 5-fold or more (Table 4).

No resistance mutations were spotted in Switzerland.

Table 4: Prevalence NSP5 mutations of SARS-CoV-2 leading to resistance from nirmatrelvir/ritonavir Paxlovid®.

Mutation	Switzerland	Europe	Mutation	Switzerland	Europe
T25A	0	0	P168Del	0	0
F140L/S	0	0	H172L/N/Q/Y	0	0
G143S	0	0	A173V	0	0
S144A/E/L/P	0	0	R188G	0	0
M165R/T	0	0	Q189K	0	0
E166A/G/K/V	0	0	Q192A/C/D/E/F/G/H/I/K/L/P/R/S/T/V/W/Y	0	0
L167F	0	0	P252L	0	0

Data based on the Stanford University 3CLpro inhibitors mutation list, available at https://covdb.stanford.edu/ (only mutations causing more than a 5 fold reduction in nirsevimab susceptibility are depicted here).

Influenza virus lineages

Among samples retrieved within the Sentinella program since October, most (28/31) H1N1 samples clustered within clade 5a.2a. The remaining ones (n=3) belong to clade 5a.2a.1. All H3N2 samples (n=19) belonged to clade 2a.3a.1. The 20 influenza B specimens clustered within clade V1A.3a.2.

For a graphical representation of the different clades circulating in Switzerland, see the Nextstrain group space for the WHO-Euro region maintained by the World Wide Influenza centre in London and the group of Richard Neher: https://nextstrain.org/groups/WHO-euro-flu.

Escape mutation prevalence

Table 5: Resistance mutations to influenza antivirals mostly used in Switzerland.

A(H1N1)pdm09			A (H3N2)			Influenza B*		
Mutation	Switzerland	Europe	Mutation	Switzerland	Europe	Mutation	Switzerland	Europe
NAI : Oseltamivir			NAI : Oseltamivir			NAI : Oseltamivir		
S110F	0	0	**E119I/V**	0	0	**G104E**	0	
E119A/D/V	0	0	D151E	0	0	E105K	0	
R152K	0	0	**R224K**	0	0	**G108E**	0	
D199E/G/Y	0	0	N245Y	0	0	**E117A/D/G/V**	0	
I223K/L/R/T	1 (T)	3 (1R, 2T)	**Del245-248f**	0	0	**P139S**	0	
S247G/R	0	0	**Del247-250f**	0	0	**G140R**	0	
H275Y	0	18	K249E	0	0	T146K/P	0	
R293K	0	0	E276D	0	0	**R150K**	0	
N295S	0	0	**R292K**	0	0	K152M/N	0	
I427T	0	0	**N294S**	0	0	D197E/N/**Y**	0	
I436N	0	0	N329K/R	0	0	A200T	0	
P458T	0	0	S331R	0	4	**I221L/N/T**	0	
			R371K	0	0	A245T	0	
			Q391K+K249E	0	0	H273Y	0	
			E119V+T148I	0	0	**R292K**	0	
			E119V+I222L/V	0	0	N294S	0	
						R374K	0	
						A395E	0	
						H439P	0	
						Y142H+G145R	0	
						T146P+N169S	0	
PAI: Baloxavir			PAI: Baloxavir			PAI: Baloxavir		
I38S/T	0	0	**I38T**	0	0	I38F/M/T/V	0	
I38F/L/M/V	0	2 (V)	I38F/L/M/N/S/V	0	0			
			L28P	0	0			
E23 G/K/R	0	1 (G)	E23G/K/R	0	0	E23K	0	
K34R	0	0	K34R	0	0			
			A36V	0	0			
A37T	0	0	A37T	0	0			
			E119D	0	0			
E198 K	0	0	E198K	0	0			
E199D/G	0	2 (G)	E199G	0	0			
						E120De	0	
						G199R	0	

Mutations depicted in this table cause reduced inhibition (RI) (for influenza A: 10-to-100-fold increase in IC_{50} values; for influenza B: 5 to 50 fold increase in IC_{50} values), or highly reduced inhibition, in bold (HRI) (for influenza A: >100 fold increase in IC_{50} value; for influenza B: > 50 fold increase in IC_{50} value). NAI: neuraminidase inhibitor (resistance mutation located in the neuraminidase protein). PAI: inhibitor of the cap endonuclease of the acidic protein baloxavir (resistance mutation located in the PA). Data based on last WHO algorithm (v2024). *Result based on sequences originating from Sentinella only.

RSV

RSV-A and RSV-B were retrieved almost in the same proportion in this sequencing batch (RSV-A 48.5%, RSV-B 51.5%).

For a graphical representation of the different strains circulating in Switzerland, see www.nextstrain.org/rsv.

Escape mutation prevalence

Two monoclonal antibodies are available for use as a pre-exposure prophylaxis treatment: palivizumab and nirsevimab.
No mutation associated with a significant decrease in neutralization of the two main anti-RSV existing monoclonal antibodies have been detected in Switzerland.

Table 6 : Resistance mutations to monoclonal antibodies available in Switzerland with an anti-RSV activity.

RSV-A		
Mutation	Switzerland	Europe
Resistance to nirsevimab		
N67T + N208Y	0	0
K68E	0	0
Resistance to palivizumab		
K272 M/T	0	0
S275F	0	0

RSV-B		
Mutation	Switzerland	Europe
Resistance to nirsevimab		
I64T	0	0
I64M + K65R	0	0
K68E/Q	0	0
K68N	0	0
N201S/T	0	0
N208S/D	0	0
K65Q/T	0	0
Resistance to palivizumab		
K272N/Q	0	0
K272R	0	0
KN63R	0	0

Mutations depicted in this table have shown to cause a proven resistance to the mAb (highlighted in bold), or to possibly reduce the neutralization by the mAb. Only resistance causing more than a 5 fold reduced neutralization are presented here. List of mutations originates from the last ANRS – MIE Respiratory viruses group mutation list combined with literature review (https://virusfrenchresistance.org/virus-french-resistance-rsv/, *Fourati*, Lancet, 2024).

Methods:

Samples primarily originate from the **Sentinella** surveillance network, which reflects the circulation of viruses in the community. These are complemented by samples collected from six major tertiary hospital laboratories: **Institut für Medizinische Virologie (IMV)** in Zurich, **Centre Hospitalier Universitaire Vaudois (CHUV)** in Lausanne, **Hôpitaux Universitaires de Genève (HUG)** in Geneva, **Universitätsspital Basel (USB)**, **Institut Central des Hôpitaux (ICH)** in Sion, and **Institut für Infektionskrankheiten (IFIK)** in Bern. Samples are obtained from both outpatient departments and hospital wards to reach a predefined target of approximately **200 samples per batch**.
Only samples that meet the **sequencing criteria*** are sent for sequencing.

Note that all Sentinella specimen are processed at the Geneva University Hospitals, Laboratory of Virology.

Sequencing criteria

- Influenza virus A/B and RSV A/B: Ct values < 25; SARS-CoV-2: Ct value < 32
- AND (if documented) absence of co-infection with another respiratory virus

Reasons for Sentinella specimen meeting sequencing criteria not to be sent to sequencing: missing tube, not enough volume, other reason

Samples are processed with the Illumina Respiratory Virus Oligo Panel (Illumina) according to manufacturer's instructions. Analyses are performed by the 2030 Health Genome Center and transferred to the Swiss Pathogen Surveillance platform (SPSP) before submission in GISAID, as recommended by WHO.

Analysis of resistance mutation is performed by the team of Richard Neher, based on specific mutations list for each virus determined either by WHO documentation, literature review, or other available algorithms. For Influenza, this analysis covers all data in GISAID, for RSV and SARS-CoV-2 these data are restricted to data in NCBI.

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

This report was prepared by Pauline Vetter, Marc Friedli, Samuel Cordey, Richard Neher and Aitana Neves. Additional acknowledgments are due to: the Health 2030 Genome Center and the Swiss Pathogen Surveillance platform (SPSP). We thank Tania Spedaliero and Ana Rita Goncalves, from the NRCI for the sharing of the number of the positive Sentinella specimens.