Influenza virus characterization

Summary report, Europe, August 2023

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Summary of the latest WHO Influenza Vaccine Composition meetings

Genetic and antigenic characterization data generated at the Worldwide Influenza Centre for viruses with collection dates after 31st August 2022 until 7th February 2023 informed the WHO influenza vaccine composition meeting (VCM) in February 2023 when recommendations were made for the northern hemisphere 2023-2024 influenza season. At the February 2023 VCM it was recommended to change the A(H1N1)pdm09 vaccine component for the 2023-2024 northern hemisphere season. Previously, at the September 2022 VCM, which focused on data from viruses collected after 31 January 2022 until 31 August 2022, it was also recommended to change the A(H1N1)pdm09 vaccine component for the 2023 southern hemisphere season.

It is recommended vaccines for use in the 2023-24 northern hemisphere influenza season contain the following:

Trivalent: Egg-based Vaccines

- an A/Victoria/4897/2022 (H1N1)pdm09-like virus;
- an A/Darwin/9/2021 (H3N2)-like virus; and
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

Trivalent: Cell- or recombinant-based Vaccines

- an A/Wisconsin/67/2022 (H1N1)pdm09-like virus;
- an A/Darwin/6/2021 (H3N2)-like virus; and
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

Quadrivalent: egg- or cell culture- or recombinant-based vaccines Above 3 components; and a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

For cell culture-produced vaccines: A/Wisconsin/67/2022 (H1N1)pdm09-like virus

Influenza B/Yamagata-lineage

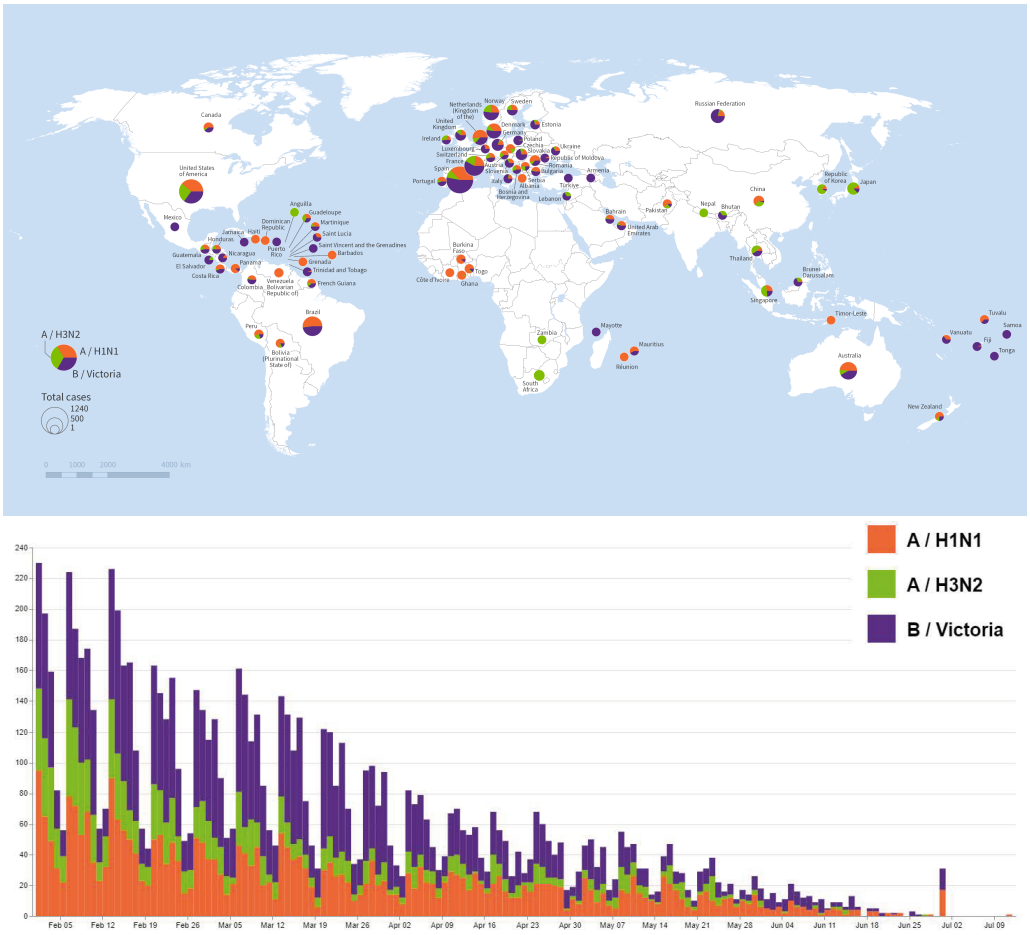
It is assumed that no B/Yamagata-lineage viruses have been detected after March 2020 as no sequences for such viruses with collection dates after this had been released in GISAID as of 31 August 2023.

A continued effort by all NICs of GISRS is required to identify B/Yamagata-lineage viruses for detailed characterization to determine if there are any in circulation that are not LAIV-related.

Influenza by type/subtype

Worldwide

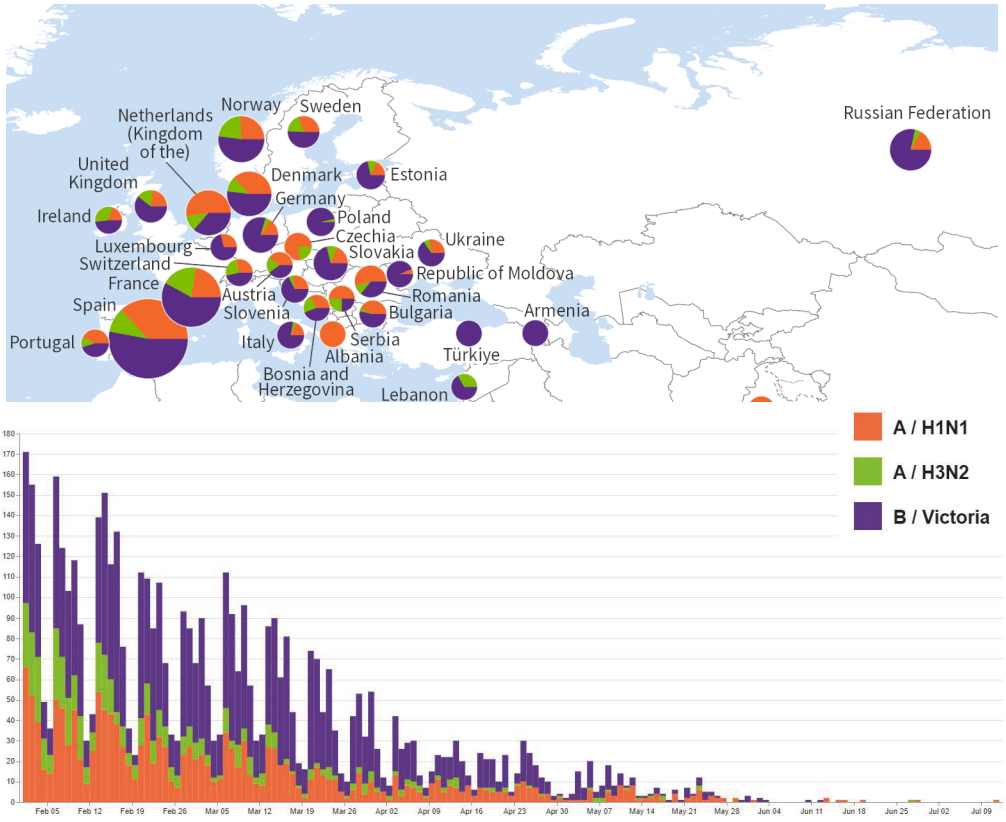
Geographical distribution of influenza viruses with collection dates from 1st February 2023 through to 31st August as deposited in GISAID, coloured by Type/subtype. Geographic markers scaled to detection proportions. Full length HA. Map provided by WHO GIS Centre for Health (https://www.who.int/data/gis)



Globally, influenza detections declined through the reporting period. However the relative proportions of A/H1N1, A/H3N2 and B/Victoria varied by geographic region as indicated by the different colours in the pie charts by country.

European region

Geographical distribution in the European region of influenza viruses with collection dates from 1st February 2023 through to 31st August as deposited in GISAID, coloured by Type/subtype. Geographic markers scaled to detection proportions. Full length HA.



In the European region, influenza detections declined through the reporting period. However the relative proportions of A/H1N1, A/H3N2 and B/Victoria varied by country as indicated by the different colours in the pie charts with the shift in predominance being from H3 to H1 to B/Victoria as the season ended.

Summary of influenza detections in the WHO European Region, week 40/2022 to 30/2023

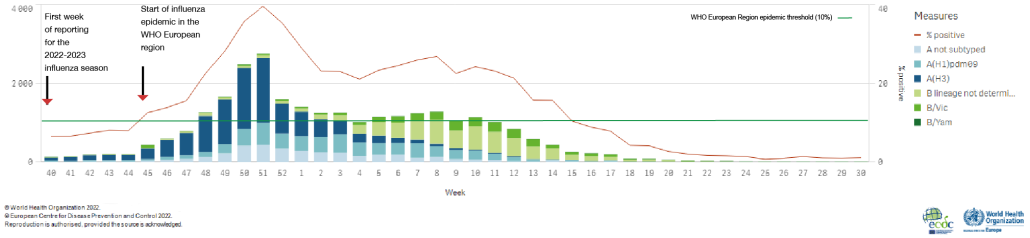
Table 1 shows influenza virus detections in the WHO European Region reported to The European Surveillance System (TESSy) database from the start of reporting for the 2022-2023 season (week 40/2022 to 30/2023) compared with the same period in the previous season. For type-percentage calculations, the denominator is total detections; for subtype and lineage, it is the total influenza A subtyped and total influenza B lineage determined, respectively. As not all countries have a true non-sentinel testing denominator, no percentage calculations for total tested are shown (Data taken from Flu News Europe reports).

	Cumulative number of detections for weeks 40/2022-30/2023				Cumulative number of detections for weeks 40/2021-30/2022			
Virus type/subtype/lineage	Sentinel sources	Non-sentinel sources	Totals	%	Sentinel sources	Non-sentinel sources	Totals	%
Influenza A	19610	197254	216864	74.2	7706	135465	143171	98.1
A(H1N1)pdm09	5798	31864	37662	51.3	402	2627	3029	7.9
A(H3N2)	10100	25611	35711	48.7	6158	29038	35196	92.1
A not subtyped	3712	139779	143491	NA	1146	103800	104946	NA
Influenza B	8681	66868	75549	25.8	115	2627	2742	1.88
Victoria lineage	2662	5564	8226	100	24	108	132	100
Yamagata lineage	0	0	0	NA	0	2	2	NA
Lineage not ascribed	6019	61304	67323	NA	91	2517	2608	NA
Total detections (total tested)	28 291 (142 778)	264 122 (2 467 784)	292 413 (2 610 562)	NA	7 821 (73 863)	138 092 (2 944 362)	145 913 (3 018 225)	NA

Compared with the 2021-2022 influenza season, for sentinel surveillance the number of tested specimens has doubled, with a 4-fold increase in influenza detections. For non-sentinel surveillance, there has been a 16% decrease in the number of tested specimens, however detections have increased by 1.7-fold. Overall the increase in testing and detections could be attributed to full relaxation of Covid19 restrictions with a “back to normal” respiratory disease surveillance attitude worldwide. Relative frequencies of type A vs B influenza viruses have changed, with influenza B detections increasing from 1.9% in 2021-2022 to nearly 26% in the current season.

Sentinel surveillance system dynamics, week 40/2022 to 30/2023

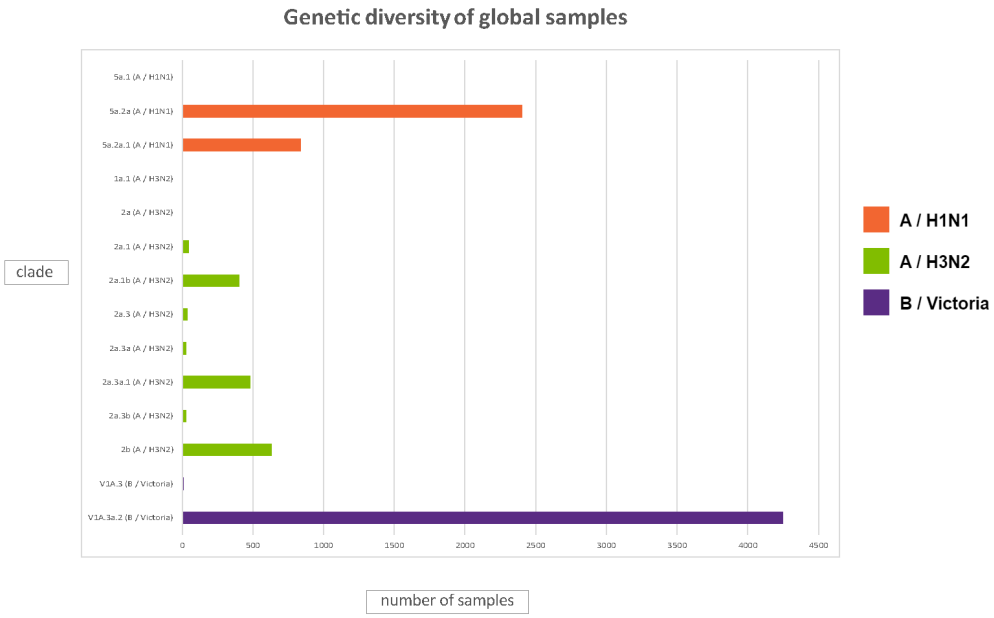
Figure adapted from FluNewsEurope weeks 25-30/2023 report (https://flunewseurope.org/Archives)

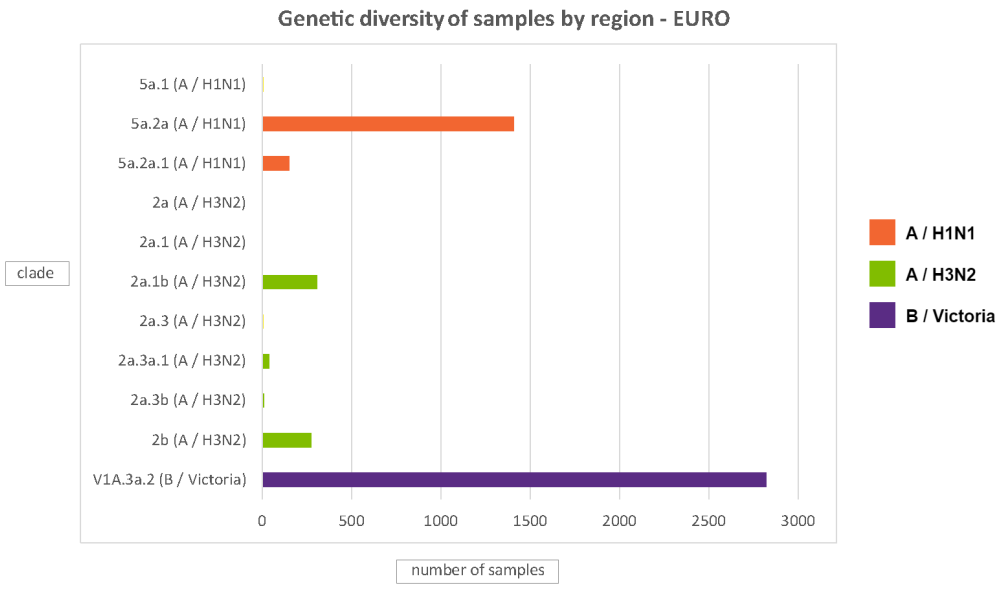


Influenza activity crossed the epidemic threshold of 10% in week 45/2022. It reached a peak of 39% positivity at week 51/2022 and then decreased to 21% until week 4/2023. After fluctuating around 25% positivity from week 6 to 11/2023, it fell below 10% in week 16/2023.

Across sentinel surveillance, influenza A/H3 viruses predominated during most of the season until week 4/2023, when A/H1 and influenza B detection frequencies started to rise with influenza B predominating for the remaining of the season.

Genetic diversity by Type/Lineage and group





Influenza A H1N1

Genetic analyses: H1N1

Globally 6B.1A.**5a.2a** and 6B.1A.**5a.2a.1** clade viruses both continued to circulate with differing relative proportions depending on region.

In Europe, both 5a.2a and 5a.2a.1 viruses were detected, with 5a.2a viruses being the larger proportion.

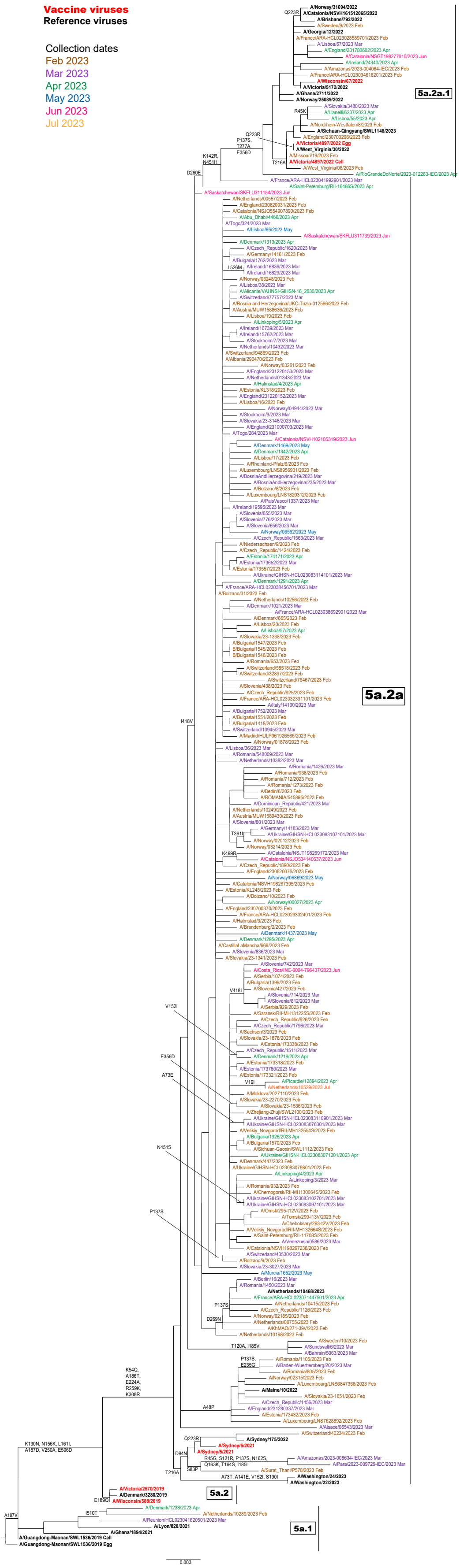
Within the 5a.2a viruses, the A/Sydney/5/2021-like viruses were detected but in the minority. We note two subgroups; one detected primarily in Northern Brazil (R45G, S121R, P137S, A141T, I185L, plus Q163K, N162S, T164S) and the other represented by the potential CVVs A/Washington/2/20222 or A/Washington/24/2022 (A73T, A141E, V152I, S190I).

The larger 5a.2a group has split into three groups defined by the following references, with some additional amino acid substitutions: A/Maine/10/2022 -like (A48P) A/Netherlands/10468/2022-like (I418V, D269N, P137S) and the remaining group, without a potential CVV or reference, defined by I418V.

Within the 5a.2a.1 viruses, there are two main groups of viruses (P137S, T277A, E356D) - either A/Wisconsin/67/2022-like or A/Victoria/4897/2022-like. Again, more recent viruses from Brazil have additional amino acid substitutions e.g. at positions T164S, I161L, Q163K with a second group additionally acquiring K156N, N162S.

Maximum likelihood phylogenetic trees: H1N1

Maximum likelihood time-resolved phylogenetic tree inferred using Iqtree2 from HA sequence data obtained from GISAID from 1st February onwards, manually curated and then downsampled using Treemer to retain a representative tree topology of 250 sequences from the European region. References and CVVs are marked as Cell or Egg.


Vaccine viruses
Reference viruses
Collection dates
Feb 2023
Mar 2023
Apr 2023
May 2023
Jun 2023
Jul 2023
5a.2a.1
5a.2a
5a.2
5a.1
0.003

Summary of the antigenic properties of H1N1 viruses circulating in the reporting period

Since February, the H1N1 viruses that have been phenotypically characterized have been well-recognized by ferret antisera raised against representative 6B.1A.5a.2a.1 and 6B.1A.5a.2 viruses.

A/H1N1: References

Virus	Genetic group	Virus passage	Ferret ID
A/Guangdong-Maonan/SWL1536/2019	6B.1A.5a.1	C2/MDCK1	F09/20
A/Guangdong-Maonan/SWL1536/2019	6B.1A.5a.1	E3/E2	F12/20
A/Ghana/1894/2021	6B.1A.5a.1	E2/E1	F02/22
A/Lyon/820/2021	6B.1A.5a.1	E1/E2	F06/22
A/Denmark/3280/2019	6B.1A.5a.2	MDCK4/MDCK5	F28/20
A/Norway/25089/2022	6B.1A.5a.2	MDCK2	F38/22
A/Sydney/5/2021	6B.1A.5a.2a	MDCK3/MDCK1	F40/22
A/Sydney/5/2021	6B.1A.5a.2a	E3/E2	F04/22
IVR-215 (A/Victoria/2570/2019)	6B.1A.5a.2	E4/D7/E2	F37/21
A/Norway/25089/2022	6B.1A.5a.2a.1	MDCK3	F38/22
A/Norway/31694/2022	6B.1A.5a.2a.1	E3/E1 10-3.	F48/22
A/Victoria/4897/2022	6B.1A.5a.2a.1	SIAT2/MDCK2	F05/23
IVR-238 (A/Victoria/4897/2022)	6B.1A.5a.2a.1	E3/D6/E1 10-6	F07/23
A/Wisconsin/67/2022	6B.1A.5a.2a.1	MDCK2	F17/23

Influenza A H3N2

Genetic analyses: H3N2

Clade 3C.2a1b.2a.2 predominated since 1st February in all geographic regions where H3N2 circulated.
We observed continued co-circulation of multiple genetic clades - however the 2a.**2b**, the 2a.**3a.1** and 2a.**1b** were the most frequently detected.
Potential CVVs were located throughout the phylogeny representing nearly all of the genetic subgroups in these clades.

Maximum likelihood phylogenetic tree: H3N2

Maximum likelihood time-resolved phylogenetic tree inferred using Iqtree2 from HA sequence data obtained from GISAID from 1st February onwards, manually curated and then downsampled using Treemer to retain a representative tree topology of 250 sequences from the European region. References and CVVs are marked as Cell or Egg.

Vaccine viruses

Reference viruses

Collection dates

Feb 2023

Mar 2023

Apr 2023

May 2023

Jun 2023

Jul 2023

Summary of the antigenic properties of H3N2 viruses circulating in the reporting period

Since February, the H3N2 viruses that have been phenotypically characterized have been well-recognized by ferret antisera raised against representative viruses within their genetic group. Some heterogeneity in recognition and reduction in cross-reactivity has been observed among the different co-circulating genetic groups.

A/H3N2: HI reagents and references

Virus	Genetic group	Virus passage	Ferret ID
A/Cambodia/925256/2020	1a	SIAT5	F03/21
A/Cambodia/e0826360/2020	1a	E5/E2	F10/21
A/Thuringen/10/2022	2b	P1/SIAT2	F36/22
A/Stockholm/5/2021	2a	SIAT0/SIAT3	F35/21
A/Darwin/9/2021	2a	E3/E4	F39/21
A/Norway/24873/2021	2a.3	SIAT2	F10/22
A/Norway/24873/2021	2a.3	E3 (Am2Al1)	F11/22
A/Poland/97/2022	2a.2	S2	F39/22
A/Slovenia/8720/2022	3C.2a1b.2a.2	SIAT1/MDCK1/SIAT2	F24/22
A/Lille/50053/2022	2a.1	MDCK1/SIAT3	F02/23
A/Catalonia/NSVH161512067/2022	3C.2a1b.2a.2	SIAT1/SIAT3	F41/22
A/Albania/289813/2022	2a.3a.1	E3(Am1AI2)	F19/23

A/H3N2: MN reagents and references

Virus	Genetic group	Virus passage	Ferret ID
A/Thuringen/10/2022	2b	P1/S3 10-3	F36/22
A/Stockholm/5/2021	2a	S0/S4 10-3	F15/22
A/Darwin/9/2021	2a	E3/E4	F05/22
A/Slovenia/8720/2022	2a.1	S1/MDCK1/S1 10-3	F24/22
A/Catalonia/NSVH161512067/2022	2a.1b	S1/S3	F41/22
A/Albania/289813/2022	2a.3a.1	MDCK1	F21/23
A/Albania/289813/2022	2a.3a.1	E4	F19/23

Influenza B

Genetic analyses: B/Victoria

Clade V1A.3a.2 viruses predominated since 1st February 2023 in geographic regions where B/Victoria-lineage viruses were detected.
No Clade V1A.3 viruses were detected since 1st February 2023.
No B/Yamagata lineage viruses have been detected since March 2020.

Maximum likelihood phylogenetic tree: B/Victoria

Maximum likelihood time-resolved phylogenetic tree inferred using Iqtree2 from HA sequence data obtained from GISAID from 1st February onwards, manually curated and then downsampled using Treemer to retain a representative tree topology of 250 sequences from the European region. References and CVVs are marked as Cell or Egg.

Vaccine viruses
Reference viruses

Collection dates
Feb 2023
Mar 2023
Apr 2023
May 2023
Jun 2023

Summary of the antigenic properties of B/Victoria lineage viruses circulating in the reporting period

Since February, the B/Victoria lineage viruses that have been phenotypically characterized have been well-recognized by ferret antisera raised against representative V1A.3a.2 viruses.

B/Victoria: Reagents and references

Virus	Genetic group	Virus passage	Ferret ID
B/Brisbane/60/2008	V1A	E4/E4	sheep pool
B/Washington/02/2019	V1A.3	E3/E3	F20/20
B/Stockholm/3/2022	V1A.3a.2	SIAT1/MDCK3	F28/22
B/Austria/1359417/2021	V1A.3a.2	SIAT1/MDCK4	NIB F01/21
B/Austria/1359417/2021 G141	V1A.3a.2	E3/E5	F15/21
B/Austria/1359417/2021 G141R	V1A.3a.2	E3/E5	F44/21

Summaries of data submitted to TESSy

Genetic characterization

(According to the guidance produced for TESSy reporting at the beginning of the 2022-2023 influenza season)

Overall, 7 259 viruses detected over the course of the 2022-2023 season (weeks 40/2022-30/2023) were genetically characterized:

• Of 2 740 A/H1N1 viruses, all but five belonged to clade 6B.1A.5a.2 with 721 represented by A/Norway/25089/2022 (5a.2a.1), 918 by A/Sydney/5/2021 (5a.2a) and 44 by A/Victoria/2570/2019 (5a.2), while 1 052 were allocated to the 'Subgroup Not Listed' category. Five were clade 6B.1A.5a.1 viruses represented by A/Guangdong-Maonan/SWL1536/2019.

• Of 2 932 A/H3N2 viruses, 2 803 belonged to the 'Bangladesh-like' clade (3C.2a1b.2a.2) with 1 704 represented by A/Bangladesh/4005/2020 (2), 213 represented by A/Darwin/9/2021 (2a) and 886 represented by A/Slovenia/8720/2022 (2a.1). Three viruses carried HA genes belonging to clade 3C.2a1b.1a represented by A/Denmark/3264/2019. A total of 126 viruses were allocated to the 'Subgroup Not Listed' category.

• Of 1 587 B/Victoria-lineage viruses, 1 266 were clade V1A.3a.2 represented by B/Austria/1359417/2021. The remaining 321 viruses were allocated to the 'Subgroup Not Listed' category.

Susceptibility to antivirals

Up to week 30/2023, 2 690 viruses were assessed for susceptibility to neuraminidase (NA) inhibitors (NAIs): 1 030 A/H3N2, 832 A/H1N1 and 352 B viruses were assessed genotypically, and 261 A/H3N2, 166 A/H1N1 and 48 B viruses were assessed phenotypically. Genotypically, two A/H1N1 viruses were found to carry the NA H275Y marker, indicative of highly reduced inhibition (HRI) by NAIs oseltamivir and peramivir, and phenotypically no viruses with reduced inhibition (RI) were identified. Susceptibility to the PA inhibitor baloxavir marboxil (BXM) was assessed genotypically for 2 067 viruses: 1 150 A/H3N2, 561 A/H1N1 and 356 B viruses. No markers of reduced susceptibility to BXM were detected.

Between weeks 21 and 30/2023, three viruses were assessed for susceptibility to neuraminidase inhibitors and to baloxavir marboxil. Phenotypically and/or genotypically, no markers associated with reduced susceptibility were identified.

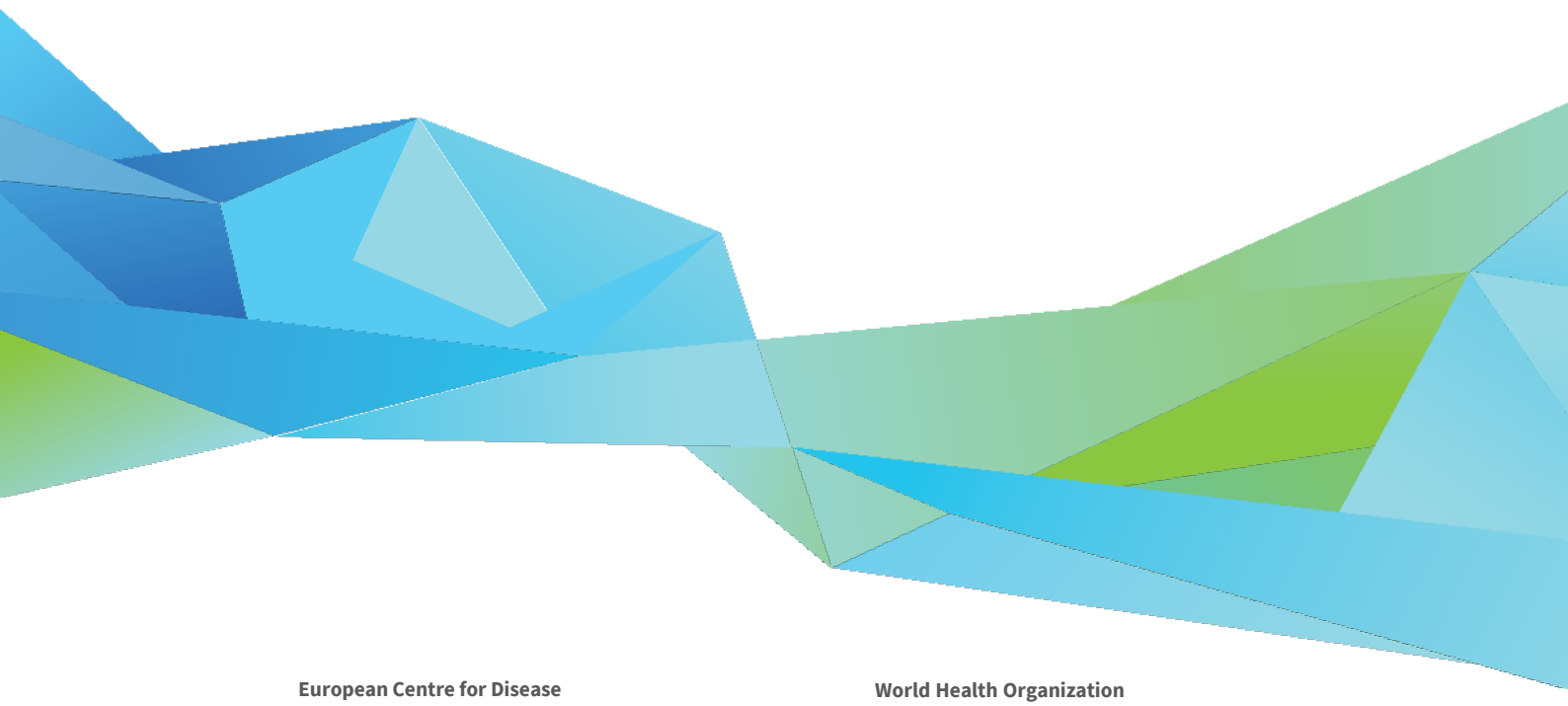
At the WIC, 1 124 influenza viruses detected within the WHO EURO Region during the 2022-2023 season were assessed phenotypically against oseltamivir and zanamivir: 360 A/H1N1, 527 A/H3N2 and 237 B/Victoria-lineage. All viruses showed Normal Inhibition (NI) by both NAIs, except for three A/H1N1 viruses: A/Salamanca/637/2022, A/Israel/R10810/2022 and A/Netherlands/10294/2023 showed HRI by oseltamivir and carried the NA H275Y amino acid substitution.

Genotypic assessment of 958 H1N1-, 1181 H3N2- and 699 B/Victoria-associated NA gene sequences deposited in GISAID for viruses with collection dates between week 40/2022 and 35/2023 did not find any marker associated with reduced susceptibility to NAIs.

For 2 105 viruses where PA gene sequencing was successful, no markers associated with reduced inhibition by BXM were identified.

WHO Collaborating Centre reports

A description of results generated by the London WHO Collaborating Centre at the WIC and used at the February 2023 WHO VCM, and previous ones, can be found at https://www.crick.ac.uk/partnerships/worldwide-influenza-centre/annual-and-interim-reports



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