



Influenza virus characterization

Summary report, Europe, March 2024

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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 31 August 2023 until 31 January 2024 informed the WHO influenza vaccine composition meeting (VCM) in February 2024 when recommendations were made for the Northern hemisphere (NH) 2024-2025 influenza season. At the February 2024 VCM it was recommended to change the A(H3N2) vaccine components for the 2024-2025 NH season. Previously, at the September 2023 VCM, which focused on data from viruses collected after 31 January 2023 until 31 August 2023, it was recommended to change the A(H1N1)pdm09 and A(H3N2) vaccine components for the 2024 SH season.

It is recommended that vaccines for use in the 2024-2025 NH influenza season contain the following:

Trivalent: Egg-based Vaccines

- an A/Victoria/4897/2022 (H1N1)pdm09-like virus;
- an A/Thailand/8/2022 (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/Massachusetts/18/2022 (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.

Influenza B/Yamagata-lineage

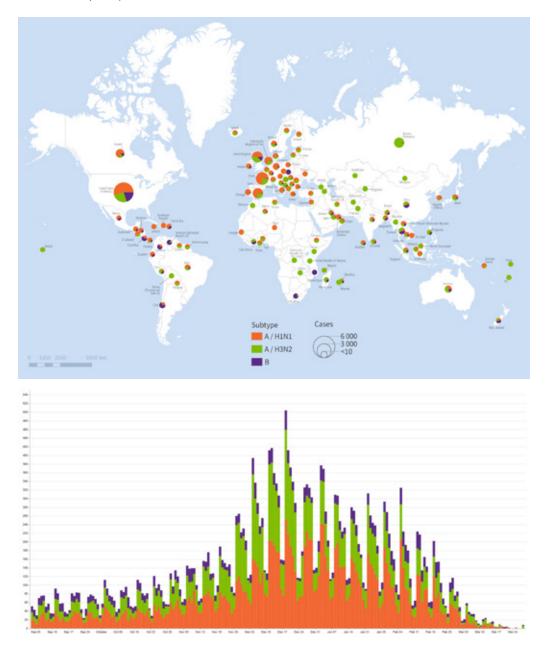
No B/Yamagata-lineage viruses with collection dates after March 2020 have been detected or sequences released in GISAID as of 31st March 2024.

The absence of confirmed detection of naturally occurring B/Yamagata lineage viruses is indicative of very low risk of infection by B/Yamagata lineage viruses. Therefore, it is the opinion of the WHO influenza vaccine composition advisory committee that inclusion of a B/Yamagata lineage antigen in quadrivalent influenza vaccines is no longer warranted, and every effort should be made to exclude this component as soon as possible. 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.

Influenza by type/subtype

Worldwide

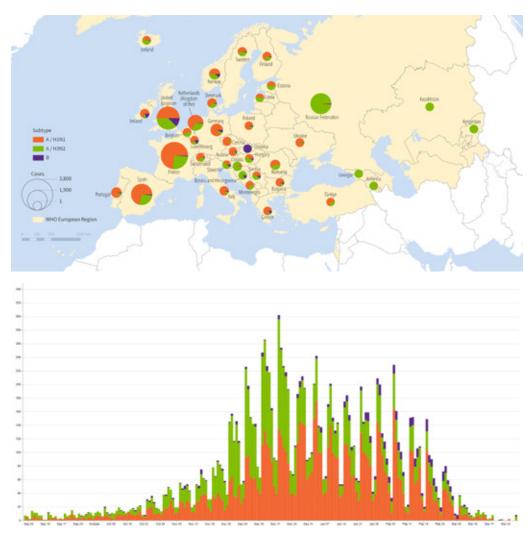
Geographical and time-dependent distribution of influenza viruses with collection dates from 1st September 2023 through to 31st March 2024 as deposited in GISAID (data accessed on 04/04/2024), coloured by Type/subtype. Geographic markers scaled to detection proportions. Full length HA. Map provided by WHO GIS Centre for Health, DNA/DDI. Timeline obtained with Microreact



Globally, influenza detections reached a peak in December 2023 and have decreased since the last report in January 2024. The relative proportions of A/H1N1, A/H3N2 and B/Victoria varied by geographic region with predominance of A/H3N2 in Europe and North and Central America and some predominance of A/H1N1 in Asia, Africa and Australia. Some countries showed some predominance of B/Victoria such as Chile, South Africa and Thailand, 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 September 2023 through to 31st March 2024 as deposited in GISAID (data accessed on 04/04/2024), coloured by Type/subtype. Geographic markers scaled to detection proportions. Full length HA.Map provided by WHO GIS Centre for Health, DNA/DDI.Timeline obtained with Microreact



In the European region, influenza detections have decreased since the last report in January 2024.

The majority of countries which reported detections showed some co-circulation of A/H1N1 and A/H3N2 with some predominance of A/H3N2 viruses and sporadic detections of influenza B/Victoria, as indicated by the different colours in the pie charts.

Summary of influenza detections in the WHO European Region, week 35/2023 to 13/2024

Table 1 shows influenza virus detections in the WHO European Region reported to The European Surveillance System (TESSy) database from 1st September 2023 (weeks 35/2023 to 13/2024) 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 and from ERVISS (European Respiratory Virus Surveillance Summary)).

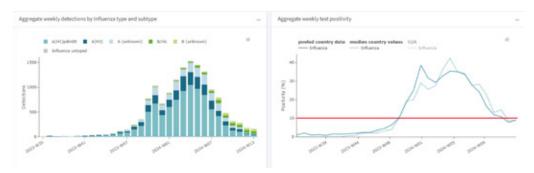
	Cumulative numb	er of detections for wee	ks 35/2023	to 13/2024	13/2024 Cumulative number of detections for weeks 35/2				
Virus type/subtype/lineage	Sentinel sources	Non-sentinel sources	Totals	%	Sentinel sources	Non-sentinel sources	Totals	%	
Influenza A	13158	149214	162372	96	10387	119995	130382	72	
A(H1N1)pdm09	8790	23889	32679	74	3062	19050	22112	61	
A(H3N2)	2327	9247	11574	26	4306	10110	14416	39	
A not subtyped	2041	116078	118119	NA	3019	90835	93854	NA	
Influenza B	975	5212	6187	4	5748	45496	51244	28	
Victoria lineage	521	1033	1554	100	1478	1587	3065	100	
Yamagata lineage	0	0	0	NA	0	0	0	NA	
Lineage not ascribed	454	4179	4633	NA	4270	43909	48179	NA	
Total detections	14133	154426	168559	NA	16135	165491	181626	NA	
Total tested	83489	1441089	1524578	NA	78999	1489930	1568929	NA	

Compared with the same period (weeks 35/2022 to 13/2023), for sentinel surveillance the number of specimens tested is slightly higher, whereas the number of influenza detections has slightly decreased. For non-sentinel surveillance, the number of tested specimens was similar in both seasons, with a minor decrease in the number of detections in the current season. Among sentinel cases, the proportion of influenza A of unknown subtype was around 15% of the total influenza A detected, compared with 30% in last season; for non-sentinel cases, not-subtyped influenza A detections accounted for 70% of the total influenza A detected, with similar proportions for both seasons.

Relative frequencies of type A vs B influenza viruses continue to show predominance of influenza A with a proportion of 96% compared with 72% in 2022-2023. Currently, in Europe there are sporadic detections of influenza B (4%), with most of the global detections circumscribed to a few countries. Relative frequencies of influenza A subtypes have also shifted, with A/H1N1 viruses increasing from 61% to 74% frequency, and a higher proportion of circulating A/H1N1 viruses (74% A/H1N1 vs 26% A/H3N2) compared to last season (61% A/H1N1 vs 39% A/H3N2).

Sentinel surveillance system dynamics, week 35/2023 to 13/2024

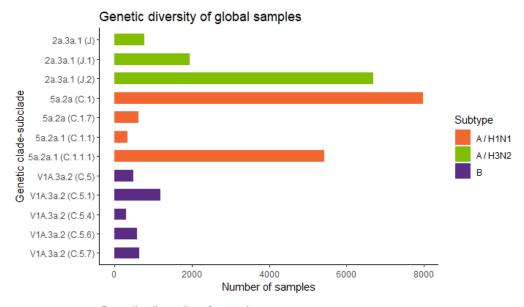
Figure adapted from **ERVISS**

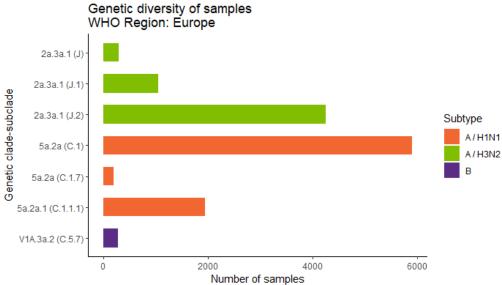


During the period from week 35/2023 to week 13/2024, influenza activity remained at low levels through the reporting period until week 46 when it started to increase, crossing the epidemic threshold of 10% in week 50. This marks a late start of the influenza season when compared with the previous season where the epidemic threshold of 10% had been crossed by week 45.Influenza activity peaked briefly in week 1 and then again in week 5, then started to decrease until it fell below the 10% threshold in week 11.

Across sentinel surveillance, influenza A/H3N2 and A/H1N1 viruses cocirculated with predominance of A/H1N1 during most of this period, with overall frequencies of 67% for A/H1N1 and 18% for A/H3N2. From week 8 onwards the proportion of influenza B increased slightly, to become predominant in week 13, although overall influenza detections are low.

Genetic diversity by Type/Lineage and group





Influenza A/H1N1

Genetic analyses: A/H1N1

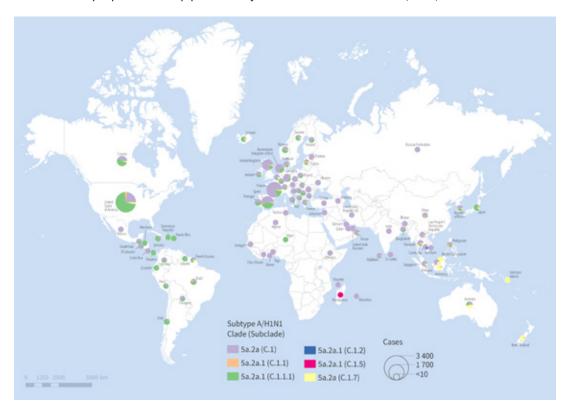
6B.1A.**5a.2a** and 6B.1A.**5a.2a.1** clade viruses both continued to circulate with differing relative proportions depending on region, with a global predominance of 5a.2a viruses.

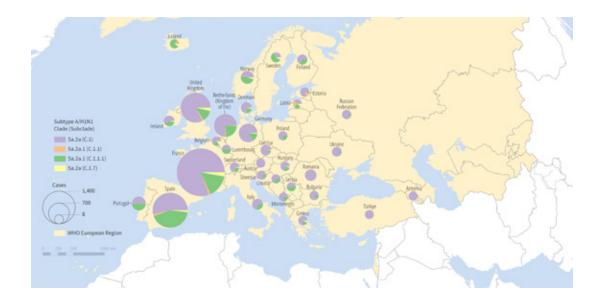
In Europe, both 5a.2a and 5a.2a.1 viruses were detected, with 5a.2a increasing in frequency over time until predominating in 70% of A/H1N1 sequenced viruses.

Within the 5a.2a viruses, characterised by substitutions K54Q, A186T, E224A, R259K and K308R, three subclades were observed: one minor subclade with D94N and T216A (C.1.7, no reference assigned yet), with viruses predominating in Australia, New Zealand and Indonesia, and in minor proportions in Europe and Asia; a larger subclade defined by substitution I418V (A/Sydney/5/2021, subclade C.1) which was predominating in the Middle East, Africa, South-East Asia, Central America and some countries in Europe, and circulated in significant proportions in other countries. This subclade included a cluster characterised by T120A with K169Q or V47I and another with P137S. Other subclades that were reported in previous weeks were not seen during this period or circulation levels were very low.

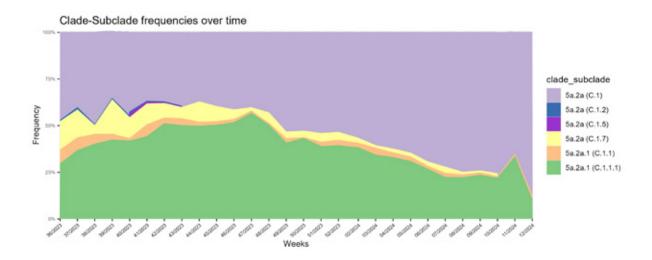
Within the 5a.2a.1 viruses, characterised by substitutions P137S, K142R, D260E, T277A, E356D and N451H, there are two main groups of viruses: a major clade with T216A (C.1.1.1.) represented by A/Victoria/4897/2022, predominating in the Americas, Japan and some countries in Europe, showing additional heterogeneity with a cluster with R45K; and a minor clade represented by A/Wisconsin/67/2022 (C.1.1), circulating in Brazil, US, Eastern Europe and South East Asia.

Global and European geographical distribution of influenza A/H1N1 genetic clades (subclades) viruses, obtained with full HA sequences as deposited in GISAID and classified using Nextclade.Geographic markers scaled to detection proportions. Map provided by WHO GIS Centre for Health, DNA/DDI



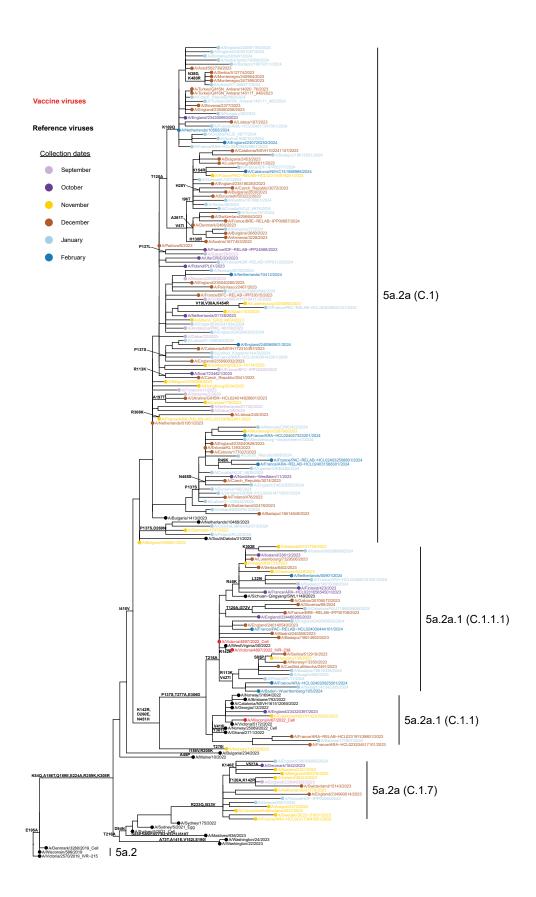


Global time-dependent variation in frequencies of genetic clades-subclades of A/H1N1 viruses collected since 1st September 2023.



Maximum likelihood phylogenetic trees: A/H1N1

Maximum likelihood phylogenetic tree inferred using Iqtree2 from HA sequence data obtained from GISAID from 1st September onwards. Trees were manually curated and, if sequence numbers were > 200, downsampled using Treemer to retain a representative tree topology of 200 sequences with emphasis on viruses from the European region. Annotation of amino acids substitutions was performed with Treetime ancestral reconstruction. References and CVVs are marked as Cell or Egg.



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

HI titres show that the SH2023 vaccine strain (A/Sydney/5/21 cell 5a.2), the cell- and egg-based NH 2023-24 strain (A/Victoria/4897/2022) recognises both 5a.2a and 5a.2a.1 well.

For an overall picture of the genetic and antigenic relationships across viruses collected during the past season, see the Annex.

		<4-fold	difference	4-fold	difference	>4-fold	difference	
Reference Virus	clade	number	percentage	number	percentage	number	percentage	total
IVR-215 (A/Victoria/2570/2019) Egg	5a.2	278	99.6	1	0.4	0	0.0	279
A/Sydney/5/2021 Cell	5a.2a	265	95.0	14	5.0	0	0.0	279
A/Sydney/5/2021 Egg	5a.2a	276	98.9	3	1.1	0	0.0	279
A/Victoria/4897/2022 Cell	5a.2a.1	268	96.1	10	3.6	1	0.4	279
IVR-238 (A/Victoria/4897/2022) Egg	5a.2a.1	261	93.5	16	5.7	2	0.7	279
A/Wisconsin/67/2022 Cell	5a.2a.1	253	90.7	21	7.5	5	1.8	279

A/H1N1: References

Virus	Genetic group	Virus passage	Ferret ID
IVR-215 (A/Victoria/2570/2019)	5a.2	E4/D7/E3	F37/21
A/Sydney/5/2021	5a.2a	MDCK3/MDCK3	F46/22
A/Sydney/5/2021	5a.2a	E3/E3	F04/22
A/Victoria/4897/2022	5a.2a.1	SIAT2/MDCK2	F05/23
IVR-238 (A/Victoria/4897/2022)	5a.2a.1	E3/D6/E1	F07/23
A/Wisconsin/67/2022	5a.2a.1	MDCK2	F17/23

Influenza A/H3N2

Genetic analyses: A/H3N2

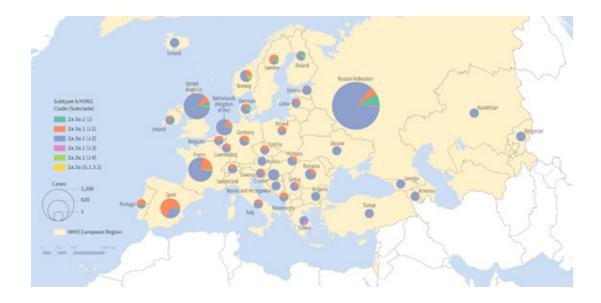
Clade 3C.2a1b.2a.2 (renamed as **2** since February 2023) predominated since 1st February in all geographic regions where A/H3N2 circulated.

During this reporting period, the great majority of H3 viruses detected belong to clade 2a.3a.1, which share substitution E50K with clade 2a.3a and present additional substitutions I140K and I223V (A/Thailand/8/2022, subclade J). Within clade 2a.3a.1, viruses with I25V, V347M and some with I418V (subclade J.1) represented by reference A/Sydney/856/2023 were seen in Europe, South-East Asia and Oceania, whereas viruses with N122D and K276E (subclade J.2) represented by new reference A/Sydney/878/2023 were increasing in frequency over time until becoming the dominant subclade, predominating in Europe, the Americas, the Middle East and Asia. Clade 2a.3a.1 (J) predominated in East Africa and South East Asia, circulating in low proportions in North America, Australia and Europe with no subclade-specific amino acids. Minor subclade J.3 (no reference assigned yet) was seen in the Democratic Republic of the Congo, Greece and China.Minor subclade J.4 (no reference assigned yet) circulated in Middle East, West Africa and Guyana.

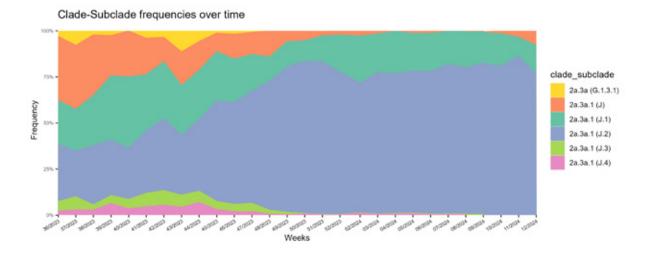
A few viruses predominating in West Africa and El Salvador with substitutions K276E and V347M form a cluster within clade 2a.3a (A/Finland/402/2023).

Global and European geographical distribution of influenza A/H3N2 genetic clades (subclades) viruses, obtained with full HA sequences as deposited in GISAID and classified using Nextclade.Geographic markers scaled to detection proportions. Map provided by WHO GIS Centre for Health, DNA/DDI



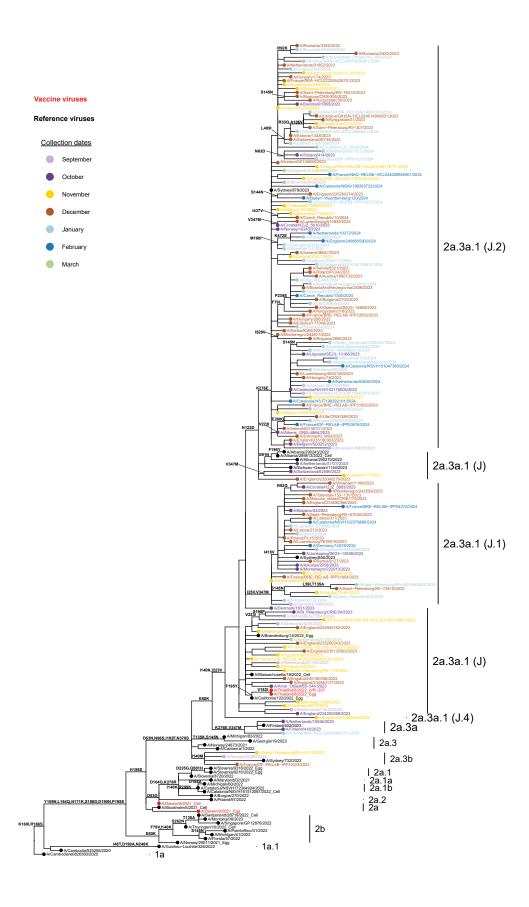


Global time-dependent variation in frequencies of genetic clades-subclades of A/H3N2 viruses collected since 1st September 2023.



Maximum likelihood phylogenetic tree: A/H3N2

Maximum likelihood phylogenetic tree inferred using Iqtree2 from HA sequence data obtained from GISAID from 1st September onwards. Trees were manually curated and, if sequence numbers were > 200, downsampled using Treemer to retain a representative tree topology of 200 sequences with emphasis on viruses from the European region. Annotation of amino acids substitutions was performed with Treetime ancestral reconstruction. References and CVVs are marked as Cell or Egg.



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

We note variable recognition by current 2a.3a.1 reference and vaccine antisera for a number of 2a.3a.1 viruses that have been analysed since September.

For an overall picture of the genetic and antigenic relationships across viruses collected during the past season, see the Annex.

		<4-fold	difference	4-fold	difference	>4-fold	difference	
Reference Virus	clade	number	percentage	number	percentage	number	percentage	tota
A/Thuringen/10/2022 Cell	2b	146	61.6	80	33.8	11	4.6	237
A/Switzerland/28719/2022 Cell	2b	55	23.2	121	51.1	61	25.7	237
A/Stockholm/5/2021 Cell	2a	96	40.5	103	43.5	38	16.0	237
A/Darwin/9/2021 Egg	2a	206	86.9	30	12.7	1	0.4	237
A/Catalonia/NSVH161512067/2022 Cell	2a.1b	57	24.1	129	54.4	51	21.5	237
A/Albania/289813/2022 Cell	2a.3a.1	194	81.9	31	13.1	12	5.1	237
A/Brandenburg/15/2022 Egg	2a.3a.1	2	3.3	13	21.7	45	75.0	60
A/Massachusetts/18/2022 Cell	2a.3a.1	96	40.5	99	41.8	42	17.7	237
A/Thailand/08/2022 Egg	2a.3a.1	174	73.4	59	24.9	4	1.7	237

A/H3N2: HI reagents and references

Virus	Genetic group	Virus passage	Ferret ID
A/Thuringen/10/2022	2b	P1/SIAT2	F36/22
A/Stockholm/5/2021	2a	SIATO/SIAT3	F35/21
A/Darwin/9/2021	2a	E3/E4	F39/21
A/Catalonia/NSVH161512067/2022	2a.1b	SIAT1/SIAT3	F41/22
A/Albania/289813/2022	2a.3a.1	MDCK1	F21/23
A/Brandenburg/15/2022	2a.3a.1	E5(Am1Al2)	F18/23
A/Switzerland/28719/2022	2b	SIAT1	F29/23
A/Massachusetts/18/2022	2a.3a.1	SIAT3/SIAT1	F36/23
A/California/122/2022	2a.3a.1	E1/E1	F33/23
A/Thailand/08/2022	2a.3a.1	E3/E1	F34/23
IVR-237(A/Thailand/08/2022)	2a.3a.1	E3/D7/E1	F35/23

Influenza B

Genetic analyses: B/Victoria

Clade V1A.3a.2 viruses characterised by substitutions A127T, P144L, N150K, G184E, N197D (-CHO), K203R and R279K (B/Austria/1359417/2021, subclade C) predominated since 1st February 2023 in geographic regions where B/Victoria-lineage viruses were detected.

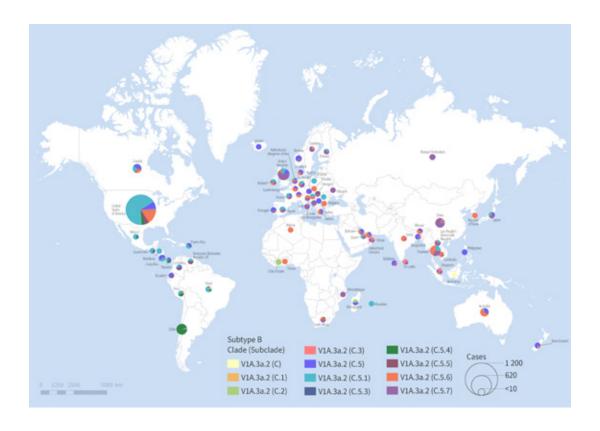
During this reporting period, only a minority of B/Victoria viruses were detected and characterised in Europe. Within V1A.3a.2, the most recent viruses are characterised by additional substitution D197E, represented by B/Connecticut/01/2021 (subclade C.5). Subclades observed within V1A.3a.2 (C.5) are: C.5.1 with E183K represented by B/Catalonia/2279261NS/2023, detected in Central America, Brazil, Peru, the US, Thailand and Europe; C.5.4 (B/Slovenia/924/2023) with V117I, E128K, A154T and K326R detected in the Americas; C.5.5 (B/Paraguay/2102/2023) with R80G, E184K detected in US and Central/South America; C.5.6 (B/Norway/08717/2023) with D129N predominating in Australia, South East Asia, Middle East, Africa and Europe; C.5.7 (no reference assigned yet) with E183K and E128G seen in South East Asia, Europe, Middle East and South Africa.

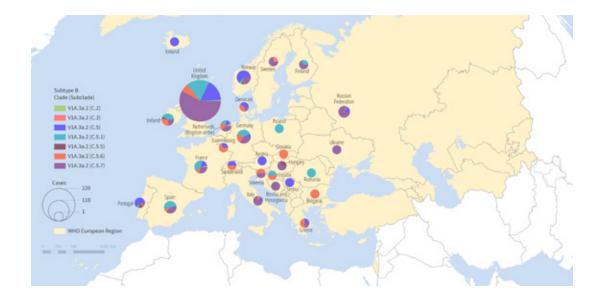
Other C.5 viruses were detected in variable proportions across the globe. Since 1st September 2023 (week 35), subclades C.5.1 and c.5.7 have increased their frequency until becoming the dominant subclades, followed by C.5.6.

No Clade V1A.3 viruses were detected since 1st February 2023.

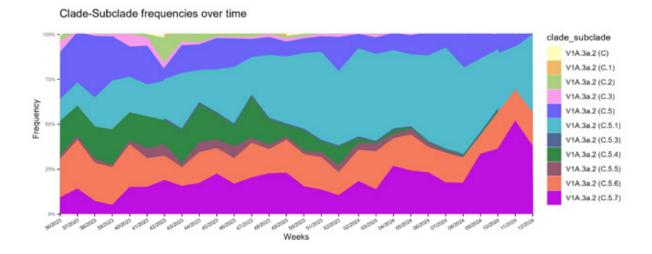
No B/Yamagata lineage viruses have been detected since March 2020.

Global and European geographical distribution and time-dependent frequencies of influenza B/Victoria genetic clades (subclades) viruses, obtained with full HA sequences as deposited in GISAID and classified using Nextclade. Geographic markers scaled to detection proportions. Map provided by WHO GIS Centre for Health, DNA/DDI



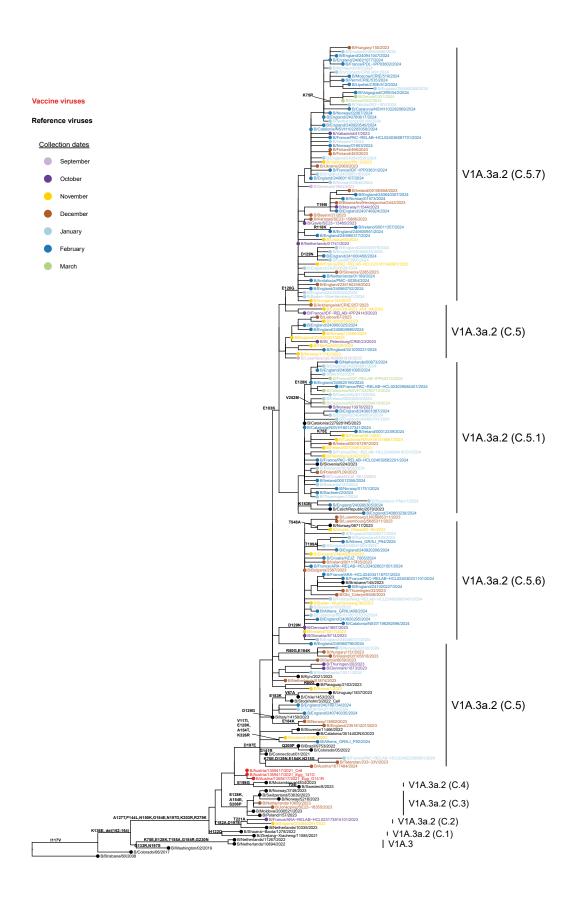


Global time-dependent variation in frequencies of genetic clades-subclades of B/Victoria viruses collected since 1st September 2023.



Maximum likelihood phylogenetic tree: B/Victoria

Maximum likelihood phylogenetic tree inferred using Iqtree2 from HA sequence data obtained from GISAID from 1st September onwards. Trees were manually curated and, if sequence numbers were > 200, downsampled using Treemer to retain a representative tree topology of 200 sequences with emphasis on viruses from the European region. Annotation of amino acids substitutions was performed with Treetime ancestral reconstruction. References and CVVs are marked as Cell or Egg.



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

Very few B/Victoria viruses collected since 1st September have been phenotypically characterized by haemagglutination inhibition (HI). All V1A.3a.2 viruses tested were well-recognised by antisera raised against B/Austria/1359417/2021 and -like viruses.

For an overall picture of the genetic and antigenic relationships across viruses collected during the past season, see the Annex.

		<4-fold	difference	4-fold	difference	>4-fold	difference	
Reference Virus	clade	number	percentage	number	percentage	number	percentage	total
B/Brisbane/60/2008 Egg	V1A	24	40.7	32	54.2	3	5.1	59
B/Austria/1359417/2021 Cell	V1A.3a.2	59	100	0	0	0	0	59
B/Austria/1359417/2021 Egg G141	V1A.3a.2	59	100	0	0	0	0	59
B/Austria/1359417/2021 Egg G141R	V1A.3a.2	0	0	4	6.8	55	93.2	59
B/Stockholm/3/2022 Cell	V1A.3a.2	59	100	0	0	0	0	59

B/Victoria: Reagents and references

Virus	Genetic group	Virus passage	Ferret ID
B/Brisbane/60/2008	V1A	E4/E4	sheep pool
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

Antiviral susceptibility testing

At the WIC, influenza viruses detected within the WHO EURO Region since 1st September 2023 (weeks 35/2023 to 13/2024) were assessed for phenotypic and/or genotypic susceptibility to antivirals. Of these, 292 A/H1N1, 276 A/H3N2 and 83 B/Victoria viruses were phenotypically assessed against oseltamivir and zanamivir. All viruses showed Normal Inhibition (NI) by both NAIs.

Phenotypic testing for susceptibility to baloxavir marboxil was performed for 153 A/H1N1, 147 A/H3N2 viruses and 27 B/Victoria viruses, with all of them showing Normal Inhibition.

Genotypic assessment of 526 A/H1N1, 285 A/H3N2 NA AND 45 B/Victoria gene sequences from influenza viruses detected within the WHO EURO Region since 1st September 2023 and received at the WIC did not find any marker associated with reduced susceptibility to NAI, except for 18 A/H1N1 viruses with S247N substitution and 3 A/H1N1 viruses with a double substitution at positions S247N + I223V. Some of these viruses were tested phenotypically and showed slightly reduced inhibition which was still less than the 10-fold reduction threshold, therefore they were considered as Normally Inhibited.

For 436 A/H1N1, 284 A/H3N2 and 43 B/Victoria viruses where PA gene sequencing was successful, no markers associated with reduced inhibition by baloxavir marboxil were identified.

Summaries of data submitted to TESSy

Genetic characterization

(According to the guidance produced for TESSy reporting at the beginning of the 2023-2024 influenza season)

Overall, 1,424 viruses detected from week 35/2023 to 13/2024 were genetically characterized:

- Of 2933 A/H1N1 viruses, all belonged to clade 6B.1A.5a.2 (clade **5a.2**) with 1957 (67%) represented by A/Sydney/5/2021 (5a.2a), 929 (32%) by A/Victoria/4897/2022 (5a.2a.1) and 40 (1%) by A/Wisconsin/67/2022 (5a.2a.1), while two (<1%) viruses were unclassified and five (<1%) were allocated to the 'Subgroup Not Listed' category.
- Of 1122 A/H3N2 viruses, all belonged to clade (3C.2a1b.2a.2, renamed as **2**) with 1078 (96%) represented by A/Thailand/8/2022 (clade 2a.3a.1), 30 (3%) represented by A/Darwin/9/2021 (clade 2a), 10 (1%) represented by A/Finland/402/2023 (clade 2a.3a) and one virus (<1%) represented by A/Sydney/732/2022 (clade 2a.3b). One (<1%) H3 virus was unclassified and two (<1%) were allocated to the 'Subgroup Not Listed' category.
- Of 39 B/Victoria-lineage viruses, all belonged to clade V1A.3a.2, with 100 (%) represented by B/Catalonia/2279261NS/2023 (subclade C.5.1), 29 (%) represented by B/Connecticut/01/2021 (subclade C.5), 27 (%) represented by B/Austria/1359417/2021 (subclade C) and one virus represented by B/Moldova/2030521/2023 (subclade C.3). No viruses were allocated to the 'Subgroup Not Listed' category.

Susceptibility to antivirals

Between weeks 35 and 39/2023, 8 viruses were assessed for susceptibility to neuraminidase inhibitors and 7 were assessed for susceptibility to baloxavir marboxil. Phenotypically and/or genotypically, no markers associated with reduced susceptibility were identified.

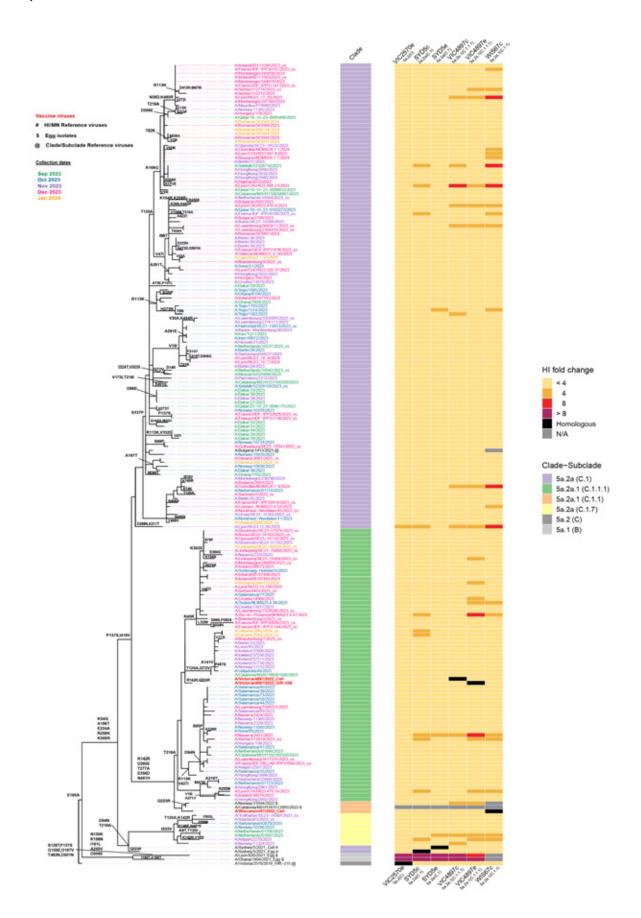
No antiviral susceptibility data was available so far for weeks 40/2023 to 13/2024 of season 2023-2024.

Annex

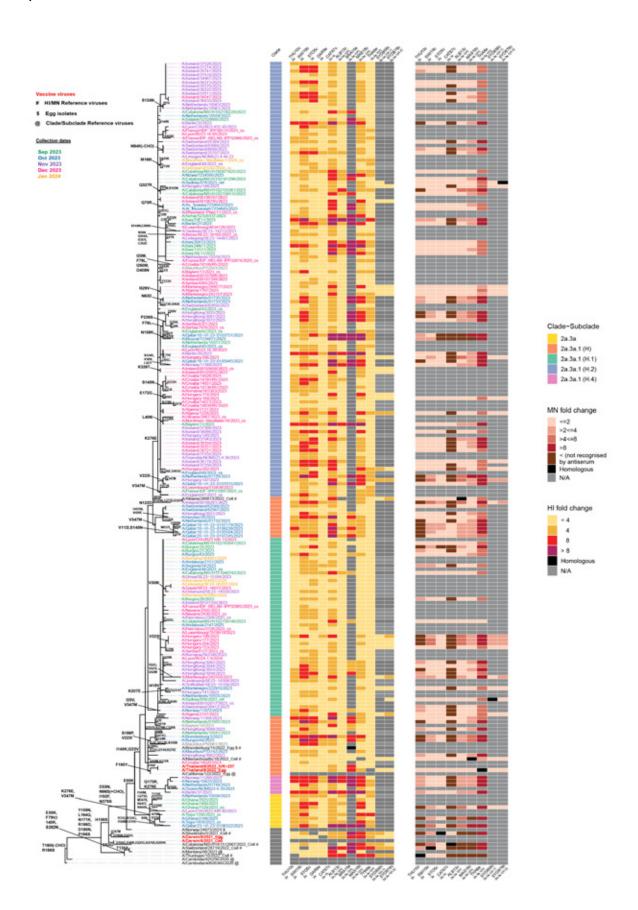
Heatmapped phylogenetic trees represent the combined genetic and antigenic analyses where the correlation between genetic groups, signature amino acids and their antigenic profile (including microneutralisation for A/H3N2) can be observed.

These outputs were generated by the London WHO Collaborating Centre at the WIC for the NH 2024-2025 February VCM with influenza viruses with collection dates between 1st September 2023 and 31st February 2024.

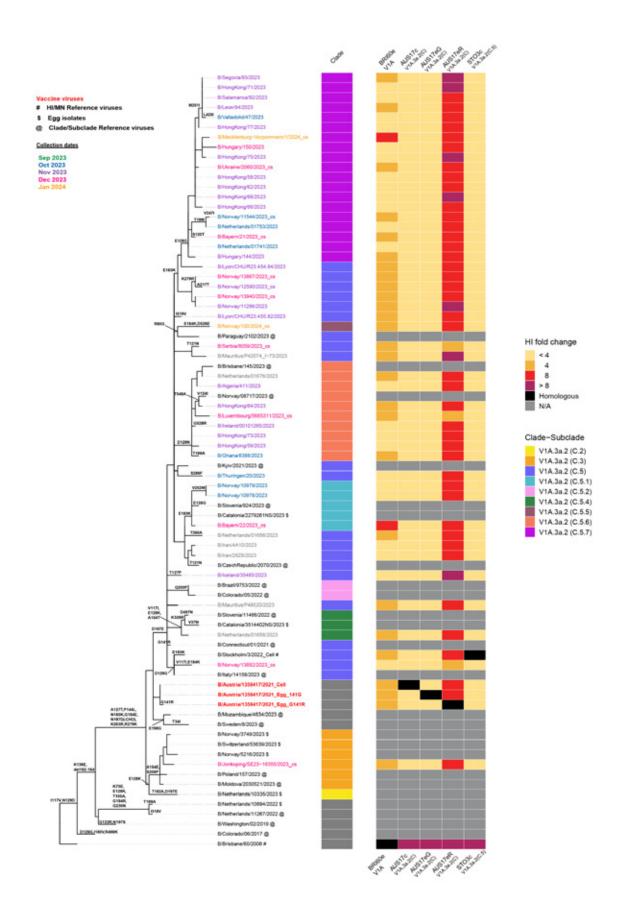
A/H1N1



A/H3N2



B/Victoria



WHO Collaborating Centre reports

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



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