



Influenza virus characterization

Summary report, Europe, December 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 31 January 2023 until 31 August 2023 informed the WHO influenza vaccine composition meeting (VCM) in September 2023 when recommendations were made for the southern hemisphere (SH) 2024 influenza season. At the September 2023 VCM it was recommended to change the A(H1N1)pdm09 and A(H3N2) vaccine components for the 2024 SH season. Previously, at the February 2023 VCM, which focused on data from viruses collected after 31 August 2022 until 31 January 2023, it was also recommended to change the A(H1N1)pdm09 vaccine component for the 2023-2024 northern hemisphere (NH) season.

It is recommended vaccines for use in the 2024 SH 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

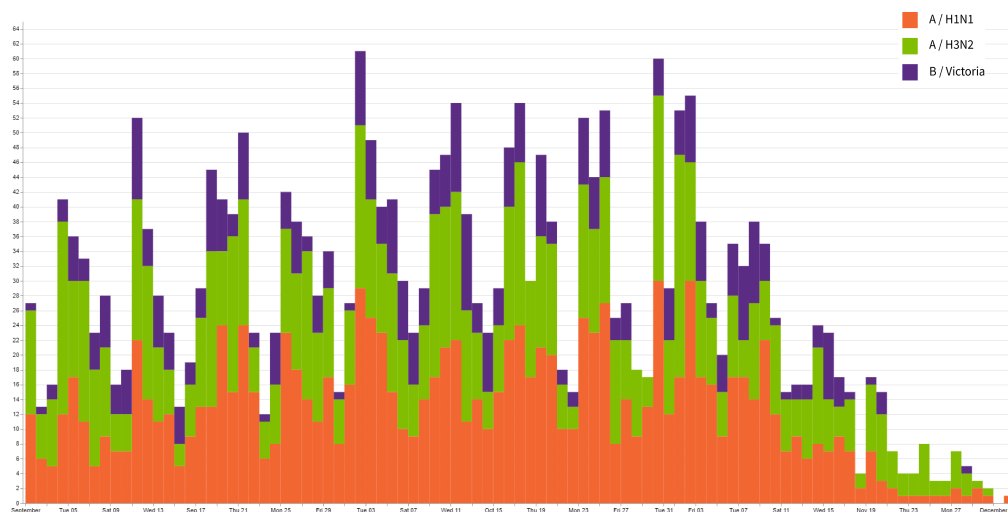
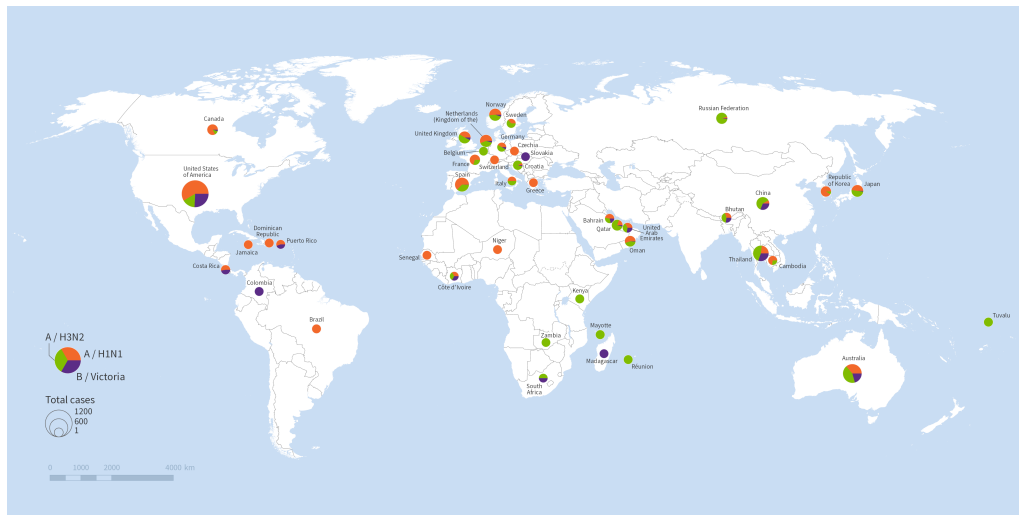
No B/Yamagata-lineage viruses with collection dates after March 2020 have been detected or sequences released in GISAID as of 15 December 2023.

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

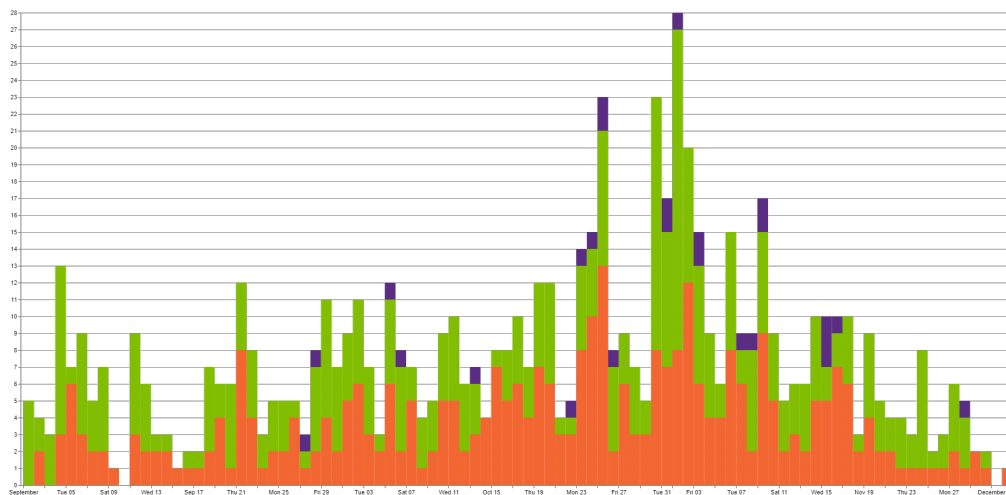
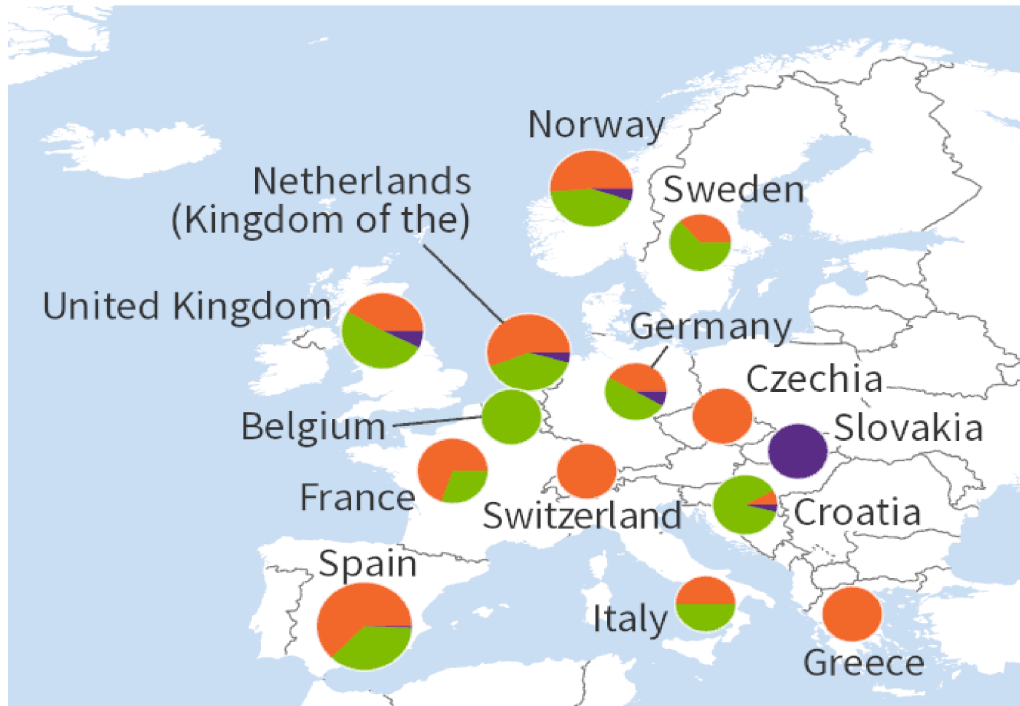
Geographical distribution of influenza viruses with collection dates from 1st September 2023 through to 15th December as deposited in GISAID, coloured by Type/subtype. Geographic markers scaled to detection proportions. Full length HA. Map provided by WHO GIS Centre for Health, DNA/DDI (<https://www.who.int/data/gis>)



Globally, influenza detections have increased since last report in October but still remain under the epidemic threshold of 10%. The relative proportions of A/H1N1, A/H3N2 and B/Victoria varied by geographic region with cocirculation of A/H1N1 and A/H3N2 overall and some detections of B/Victoria, 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 15th December as deposited in GISAID, coloured by Type/subtype. Geographic markers scaled to detection proportions. Full length HA.



In the European region, influenza detections remained low until recent weeks when they started to approach the 10% epidemic threshold.

The majority of countries which reported detections showed co-circulation of A/H1N1 and A/H3N2 as indicated by the different colours in the pie charts.

Summary of influenza detections in the WHO European Region, week 35/2023 to 49/2023

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 to 49) 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)).

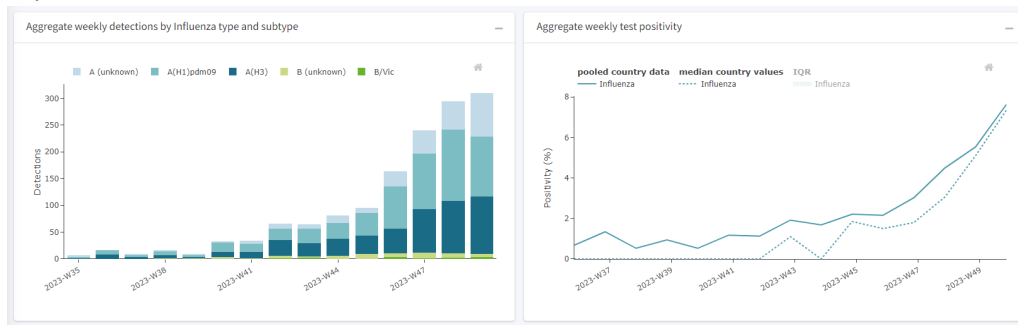
Virus type/subtype/lineage	Cumulative number of detections for weeks 35 to 49/2023				Cumulative number of detections for weeks 35 to 49/2022			
	Sentinel sources	Non-sentinel sources	Totals	%	Sentinel sources	Non-sentinel sources	Totals	%
Influenza A	1362	15158	16520	95	3196	24586	27782	93
A(H1N1)pdm09	607	2600	3207	48	355	4367	4722	45
A(H3N2)	494	3014	3508	52	2283	3584	5867	55
A not subtyped	261	9544	9805	NA	558	16635	17193	NA
Influenza B	66	727	793	5	321	1700	2021	7
Victoria lineage	0	80	80	100	113	113	226	100
Yamagata lineage	0	0	0	NA	0	0	0	NA
Lineage not ascribed	66	647	713	NA	208	1587	1795	NA
Total detections	1428	15885	17313	NA	3517	26286	29803	NA
Total tested	48781	661213	709994	NA	28191	551767	579958	NA

Compared with the same period (weeks 35 to 49) in 2022, for sentinel surveillance the number of tested specimens has nearly doubled, however the number of influenza detections has halved. For non-sentinel surveillance, the number of tested specimens has increased from last season to the current, however detections have decreased by nearly 2 folds. The higher number of detections in 2022 was likely driven by the increase in A(H3N2) detections; in both periods, the proportion of influenza A of unknown subtype was around 60% of the total influenza A detected.

Relative frequencies of type A vs B influenza viruses are similar between both periods, with influenza B detections at 7% in 2022 compared to 5% in the current period. Relative frequencies of influenza A subtypes are similar between both periods with nearly similar frequencies of A(H3N2) viruses (52%) and A(H1N1) (48%) in the current period, compared to a ratio of 55/45% for the same period in 2022.

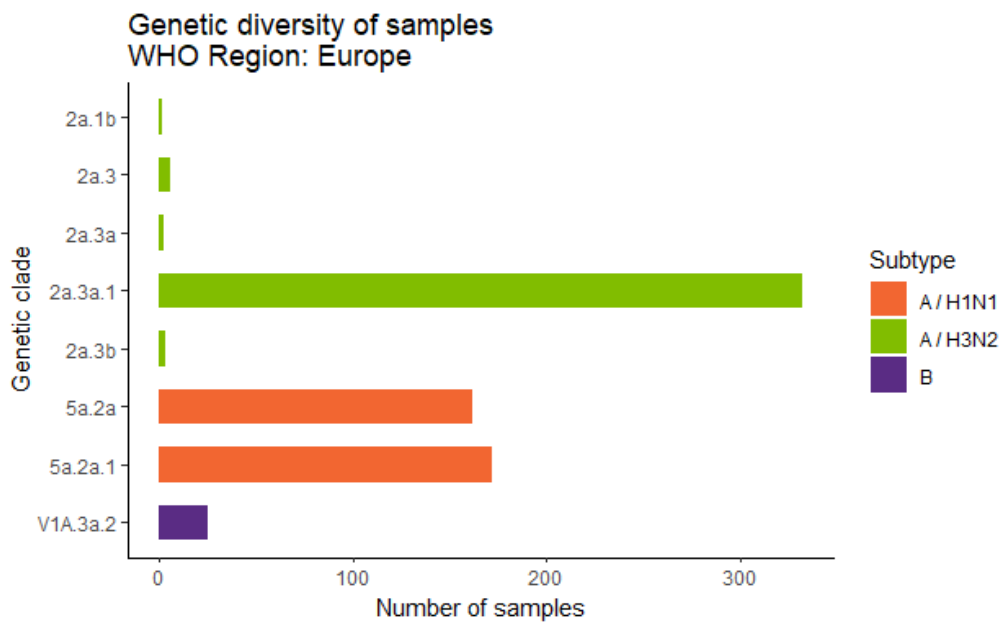
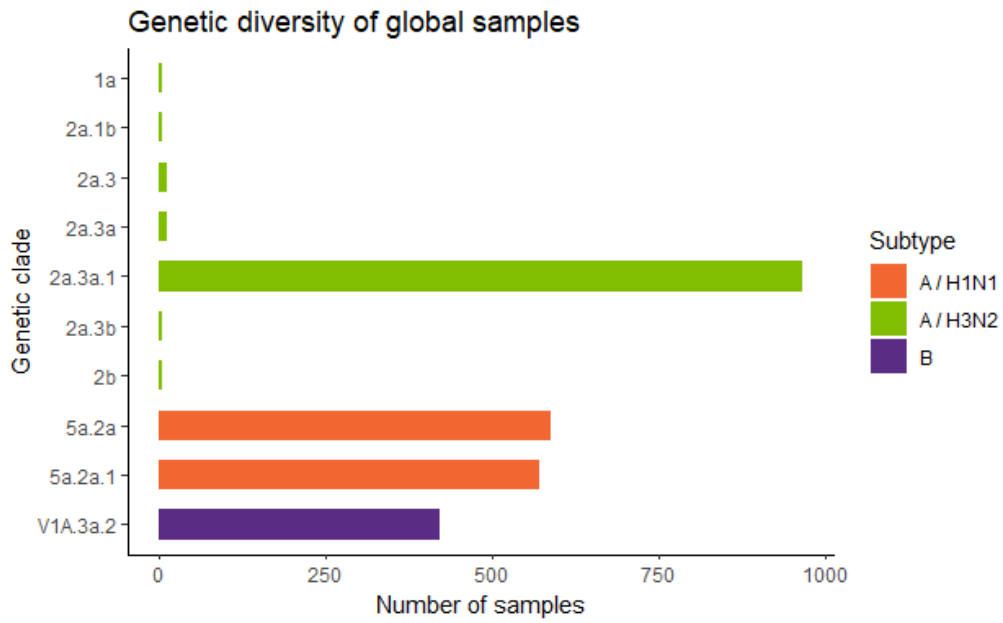
Sentinel surveillance system dynamics, week 35/2023 to 49/2023

Figure adapted from [ERVISS](#)



During the period from week 35 to week 49 of 2023, influenza activity remained at low levels through the reporting period until the last two weeks when it started to approach the epidemic threshold of 10%. Across sentinel surveillance, influenza A/H3N2 and A/H1N1 viruses cocirculated during most of this period with overall frequencies of 48% for A(H1N1) and 52% for A(H3N2).

Genetic diversity by Type/Lineage and group



Influenza A H1N1

Genetic analyses: H1N1

6B.1A.5a.2 (C.1) and 6B.1A.5a.2a.1 (C.1.1. and C.1.1.1) 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 roughly equal proportions.

Within the 5a.2a viruses, characterised by substitutions K54Q, A186T, E224A, R259K and K308R, two clades were observed: one minor clade with D94N and T216A (C.1.7) with root on A/Sydney/5/2021, with viruses detected in Europe, Australia and Oman, and a larger clade defined by substitution I418V (C.1) which was detected in Europe, the US, South-East Asia and some countries in the Middle East and Africa. Other subclades that were reported in previous weeks were not seen during this period, except for one with A48P (C.1.2) with viruses from Thailand.

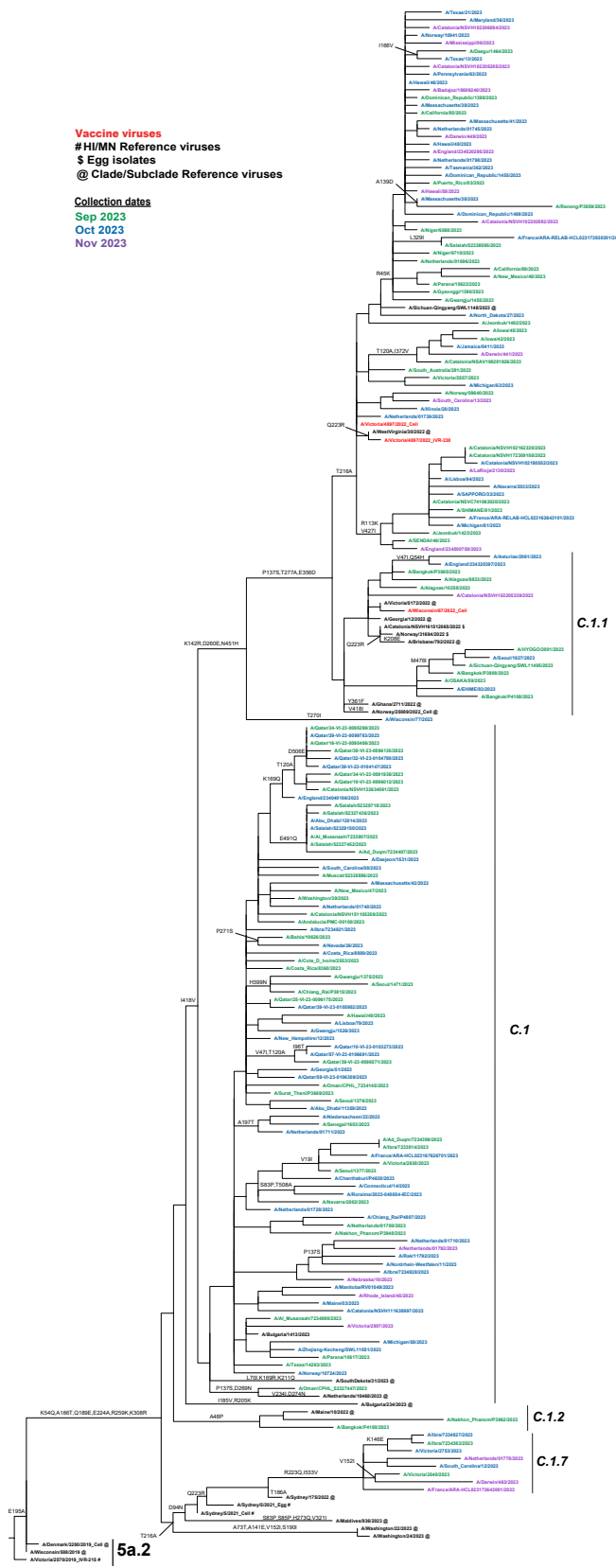
Within the 5a.2a.1 viruses, characterised by substitutions P137S, K142R, D260E, T277A, E356D and N451H, there are two main groups of viruses: a major clade with T216A (C.1.1.1.) represented by A/Victoria/4897/2022 and a minor clade represented by A/Wisconsin/67/2022 (C.1.1). Within the major clade there are 2 distinct subclades: one with R113K and V427I that was detected in Europe, Asia and US and a second subclade with R45K that was seen in the US, Europe and South Korea.

Maximum likelihood phylogenetic trees: H1N1

Maximum likelihood time-resolved 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.

Vaccine viruses
HI/MN Reference viruses
\$ Egg isolates
@ Clade/Subclade Reference viruses

Collection dates
Sep 2023
Oct 2023
Nov 2023



C.1.1.1

5a.2a.1

C.1.1

C.1

5a.2a

C.1.2

C.1.7

5a.2

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

Both cell- and egg-based NH 2023-24 strain A/Victoria/4897/2022 recognises both 5a.2a and 5a.2a.1 test viruses well.

For an overall picture of the past season, see the Annex.

A/H1N1: References

Virus	Genetic group	Virus passage	Ferret ID
IVR-215 (A/Victoria/2570/2019)	6B.1A.5a.2	E4/D7/E3	F37/21
A/Sydney/5/2021	6B.1A.5a.2a	MDCK3/MDCK3	F46/22
A/Sydney/5/2021	6B.1A.5a.2a	E3/E3	F04/22
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

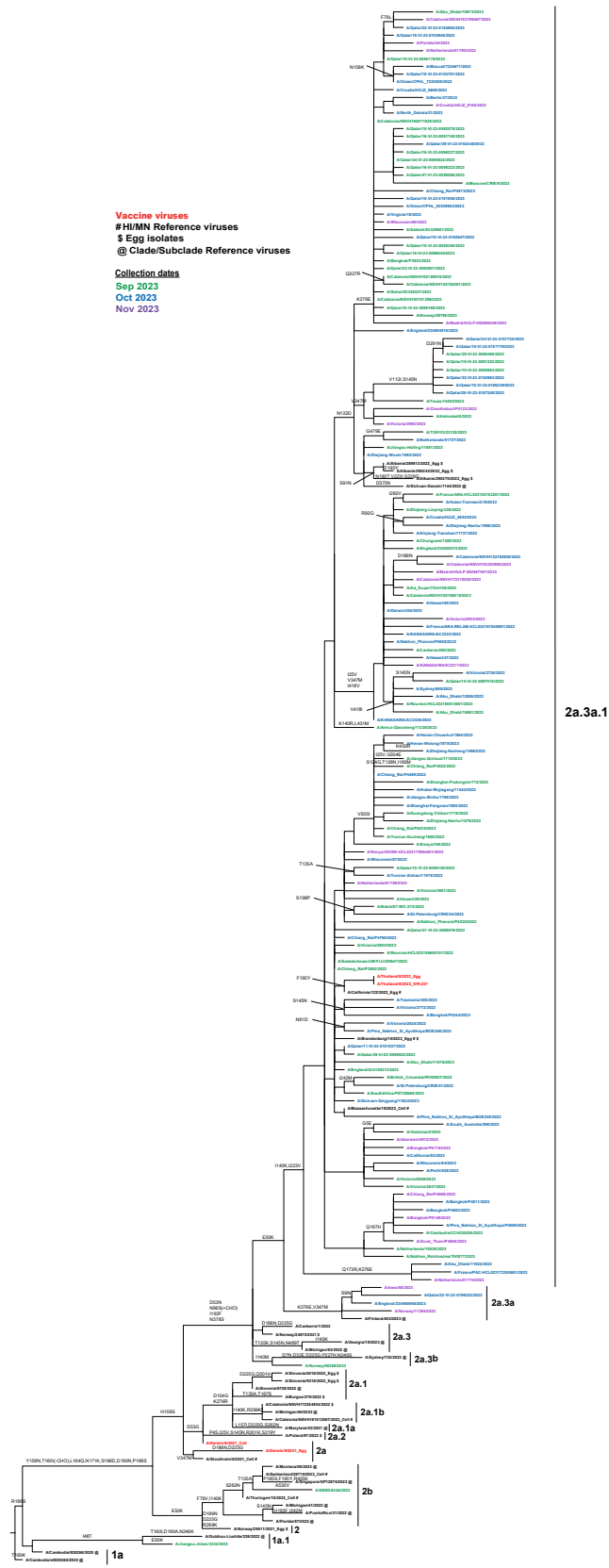
Clade 3C.2a1b.2a.2 (renamed as **2** since February 2023) predominated since 1st February in all geographic regions where H3N2 circulated. Within this clade, cocirculation of multiple genetic clades were observed during most of the southern hemisphere influenza season 2022-2023, with clades **2a.2b**, the **2a.3a.1** and **2a.1b** were the most frequently detected.

During this reporting period, the great majority of H3 viruses detected belong to clade 2a.3a.1, which share substitutions E50K with clade 2a.3a and present additional substitutions I140K and I223V. Within clade 2a.3a.1, viruses with I25V, V347M and I418V were seen in Europe, South-East Asia and Australia, whereas viruses with N122D (potential loss of N-glycosylation) and K276E were detected in Europe, the US, Qatar, Thailand and Oman. Other subclades included: N122D and V347M viruses from US, Australia and Qatar (the latter characterised by V112I and S145N) and a subclade with viruses from China, Europe, US, Australia, Thailand and Qatar with no subclade-specific amino acids.

A few viruses from Europe, US and Qatar with substitutions K276E and V347M cluster within clade 2a.3a.

Maximum likelihood phylogenetic tree: H3N2

Maximum likelihood time-resolved 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 H3N2 viruses circulating in the reporting period

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

For an overall picture of the past season, see the Annex.

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	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 (Am2A1)	F11/22
A/Poland/97/2022	2a.2	S2	F39/22
A/Slovenia/8720/2022	2a.1	SIAT1/MDCK1/SIAT2	F24/22
A/Lille/50053/2022	2a.1	MDCK1/SIAT3	F02/23
A/Catalonia/NSVH161512067/2022	2a.1b	SIAT1/SIAT3	F41/22
A/Albania/289813/2022	2a.3a.1	MDCK1	F21/23
A/Albania/289813/2022	2a.3a.1	E3(Am1A12)	F19/23
A/Brandenburg/15/2022	2a.3a.1	E5(Am1A12)	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 predominated since 1st February 2023 in geographic regions where B/Victoria-lineage viruses were detected.

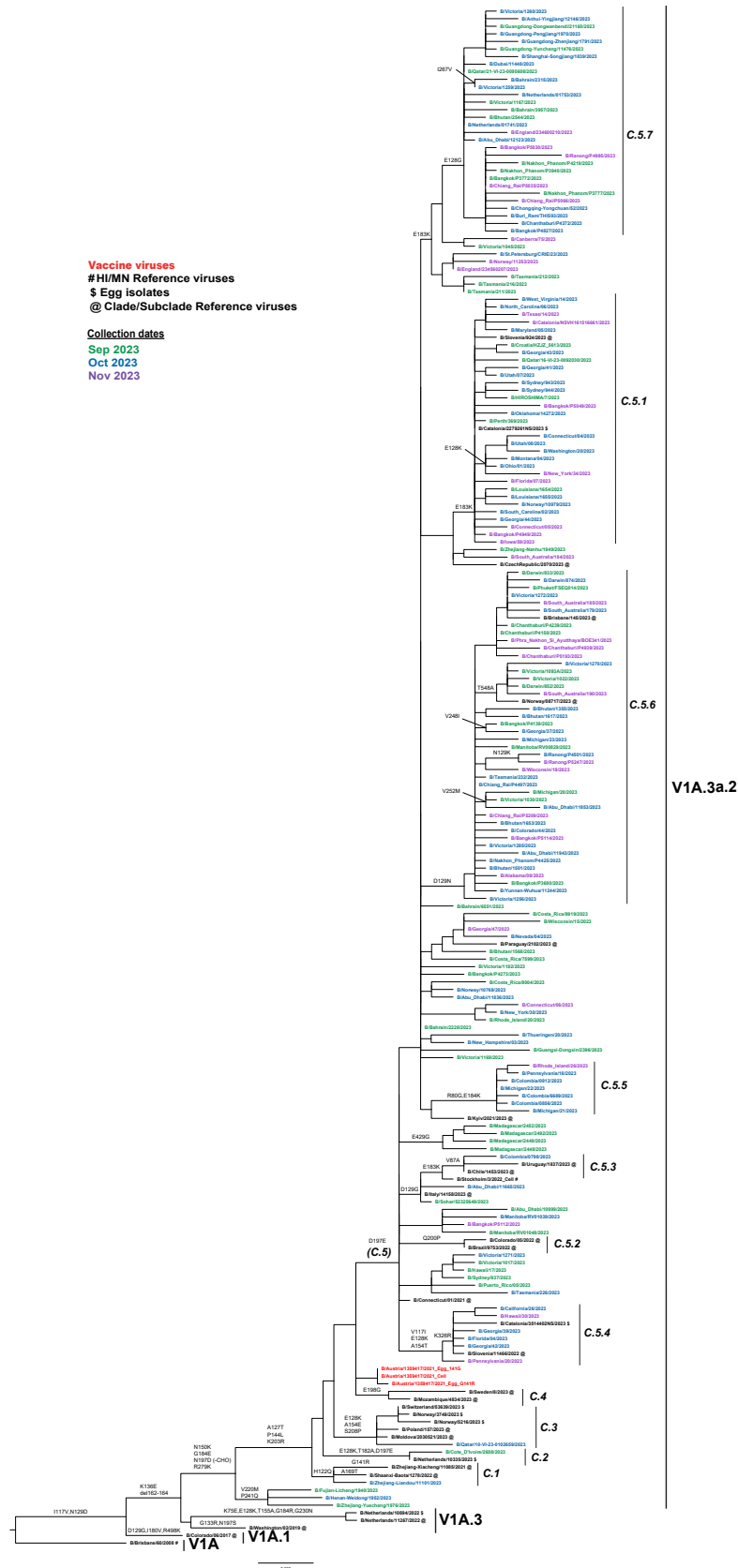
Within V1A.3a.2, the most recent viruses are characterised by additional substitution D197E (C.5). Subclades observed within V1A.3a.2 (C.5) are: C.5.1 with E183K detected in Europe, US and Australia; C.5.4 with V117I, E128K, A154T and K326R detected in Europe and US; C.5.5 with R80G, E184K detected in US and Colombia; C.5.6 with D129N detected in Australia, Thailand and US; C.5.7 with E183K and E128G seen in China, Thailand and Australia.

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 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 past season, see the Annex.

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

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, 131 viruses detected from week 40 to 49/2023 were genetically characterized:

- Of 87 A/H1N1 viruses, all belonged to clade 6B.1A.5a.2 (clade **5a.2**) with 41 (47%) represented by A/Sydney/5/2021 (5a.2a), 26 (30%) by A/Victoria/4897/2022 (5a.2a.1) and 20 (23%) by A/Wisconsin/67/2022 (5a.2a.1), while none were allocated to the 'Subgroup Not Listed' category.
- Of 37 A/H3N2 viruses, all belonged to clade (3C.2a1b.2a.2, renamed as **2**) with 36 (97%) represented by A/Thailand/8/2022 (clade 2a.3a.1) and one virus represented by A/Finland/402/2023 (clade 2a.3a). No viruses were allocated to the 'Subgroup Not Listed' category.
- Of 7 B/Victoria-lineage viruses, all belonged to clade V1A.3a.2, with five (71%) represented by B/Catalonia/2279261NS/2023 (subclade C.5.1) and two viruses represented by B/Connecticut/01/2021 (subclade C.5). 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 to 49 of season 2023-2024.

At the WIC, 8 influenza viruses detected within the WHO EURO Region since 1st September 2023 (weeks 35 to 49/2023) were assessed for susceptibility to antivirals. Of these, 4 A/H1N1 and 4 A/H3N2 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 4 A/H1N1 and 4 A/H3N2 viruses, with all of them showing Normal Inhibition.

Genotypic assessment of 6 H1N1 and 10 H3N2 NA 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.

For 5 H1N1 and 10 H3N2 viruses where PA gene sequencing was successful, no markers associated with reduced inhibition by baloxavir marboxil were identified.

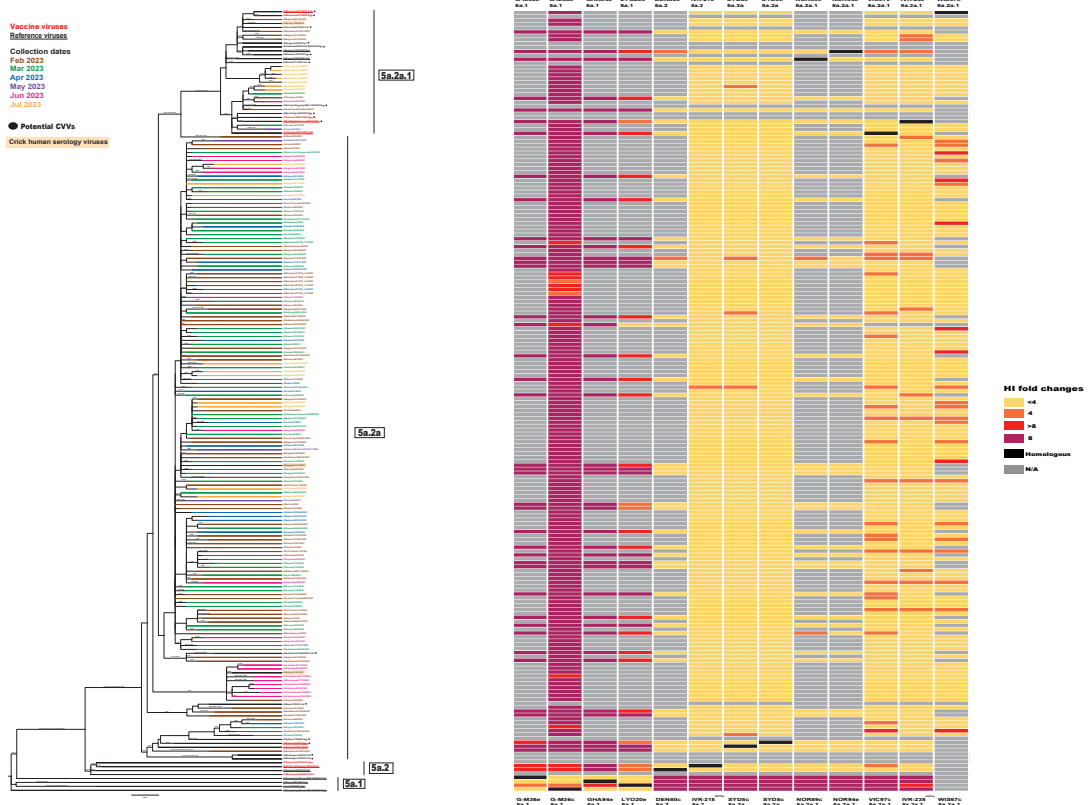
No influenza B viruses detected within the WHO European region were available for antiviral susceptibility characterisation at the WIC within this period.

Annex

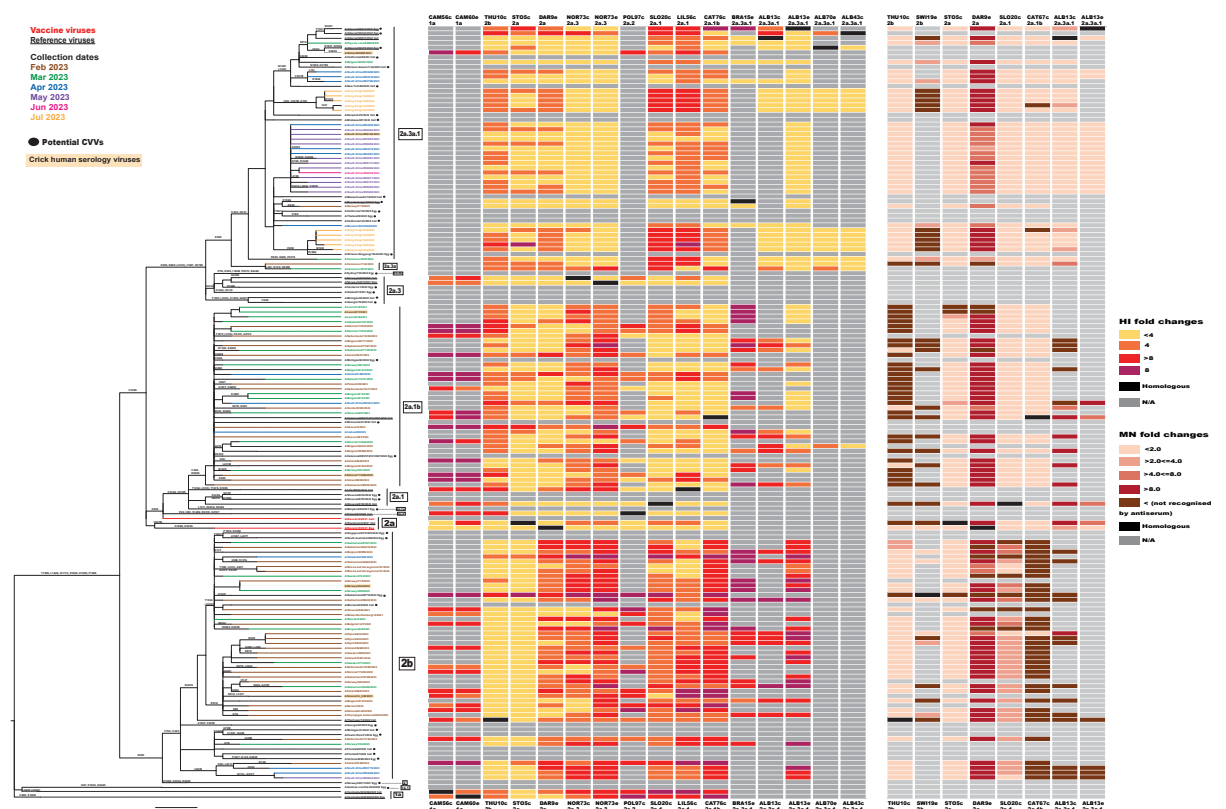
Heatmapped phylogenetic trees represent the combined genetic and antigenic analyses where the correlation between genetic groups, signature amino acids and their antigenic profile (including microneutralisation for A/H3N2) can be observed.

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

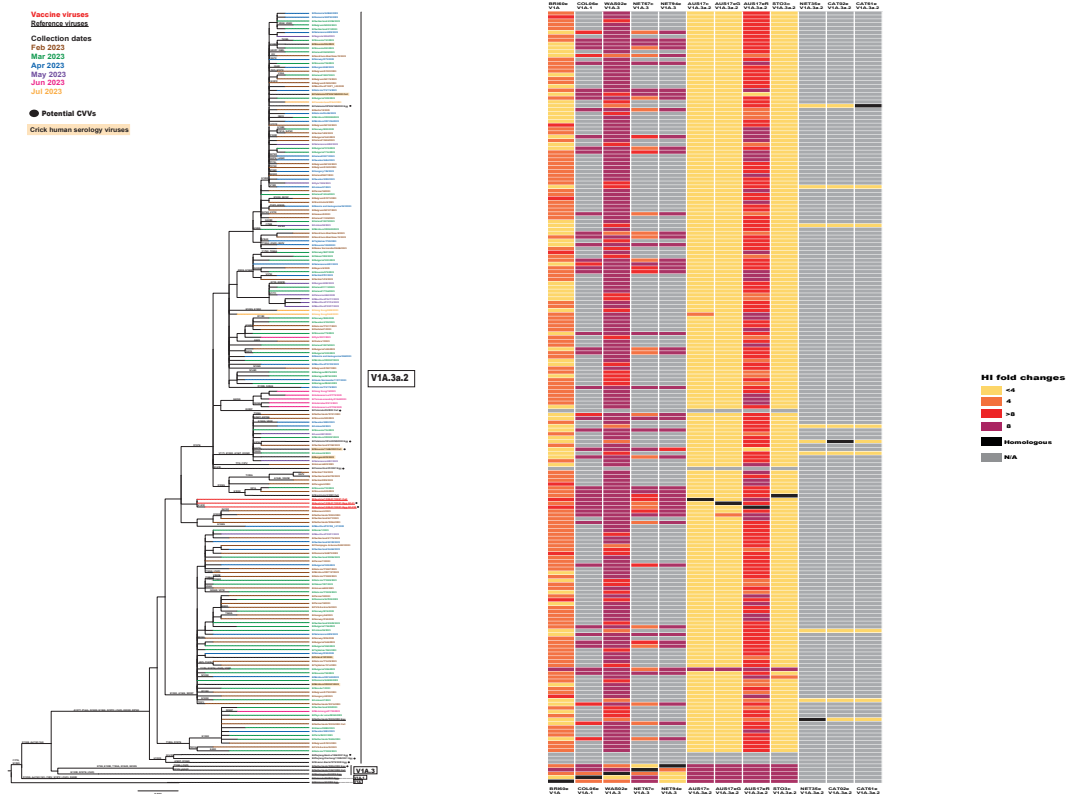
A/H1N1



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/worldwide-influenza-centre/annual-and-interim-reports>



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