



Influenza virus characterization

Summary report, Europe, July 2022

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Summary

This is the eighth report for the 2021-2022 influenza season. The June 2022 characterization report¹, gave a breakdown of influenza detections across the World Health Organization (WHO) European Region reported to TESSy up to week 25/2022. As of week 30/2022, 145 913 detections had been reported (a rise of nearly 13 000 since week 20/2022) resulting from extended late season influenza activity. Of these 145 913 detections, 98% were type A viruses, with A(H3N2) still dominating (84%) over A(H1N1)pdm09 (16%), but by a lower margin than in the June report (92%:8%), and 2% type B of which only 134 were ascribed to a lineage, with all but two being B/Victoria. This represents a large increase (144 903, 144-fold) in detections compared to the 2020-2021 season, on the back of a great increase (1 926 053, 176%) in the number of samples tested. However, while there have been clear indications of an influenza epidemic in 2021-2022 with the epidemic threshold of 10% positivity within sentinel specimens having been crossed for 17 weeks as of week 25/2022 (unlike in 2020-2021), numbers of detections are reduced compared to earlier seasons (e.g., 12% reduced compared to 2019-2020). The increased testing but reduced number of influenza detections is undoubtedly related to the emergence of SARS-CoV-2 and measures introduced to combat it.

Thirteen shipments from countries within the WHO European Region were received at the London WHO Collaborating Centre, the Francis Crick Worldwide Influenza Centre (WIC) since the June report. This report focuses on viruses with collection dates within 2022 for which HA gene sequences were submitted to, and released in, the EpiFlu™ database of the Global Initiative on Sharing All Influenza Data (GISAID) after June 2022 for influenza type A viruses and March for influenza B/Victoria-lineage viruses, together with sequences generated and antigenic data determined at the WIC.

Globally relatively few A(H1N1)pdm09 viruses have been detected in the course of the 2021-2022 season. 6B.1A.5a.1 and 6B.1A.5a.2 genetic subgroups have been detected which are clearly antigenically different, as shown by viruses from 11 WHO Region countries (6B.1A.5a.1) and Croatia/Italy/the Netherlands (6B.1A.5a.2) characterized here. 6B.1A.5a.1 viruses have been most numerous in Europe but 6B.1A.5a.2 viruses are currently dominant in some southern hemisphere countries, notably Australia, and greater numbers have recently been detected in Europe. An emergent 6B.1A.5a.1 genetic group showing antigenic drift, defined by HA1 P137S and G155E amino acid substitutions, has been detected. At the February 2022 WHO influenza vaccine composition meeting (VCM) the recommendation was to retain A/Victoria/2570/2019-like viruses (6B.1A.5a.2) as the vaccine component for the northern hemisphere 2022-2023 influenza season.

In Europe and across the world A(H3N2) viruses have been dominant with the vast majority of recently detected viruses falling in the 'Bangladesh-like' (3C.2a1b.2a.2) subgroup, except in China where significant numbers of 3C.2a1b.2a.1 viruses have been detected. While small clusters of viruses showing antigenic drift have emerged among the 'Bangladesh-like' viruses, the great majority of these viruses retained good recognition by post-infection ferret antisera raised against egg-propagated A/Darwin/9/2021 (3C.2a1b.2a.2) which was recommended for egg-based vaccines to be used in the 2022 southern hemisphere season. Antisera raised against a range of cell culture- and egg-propagated 3C.2a1b.2a.2 viruses generally gave good recognition of 3C.2a1b.2a.2 test viruses.

At the February 2022 WHO VCM the recommendation was to change the A(H3N2) vaccine components for the northern hemisphere 2022-2023 influenza season to match those used in the 2022 southern hemisphere season.

In Europe and across the world few B/Victoria-lineage viruses have been detected during the 2021-2022 influenza season. All fall within subclade V1A.3 represented by B/Washington/02/2019, the vaccine virus recommended for inclusion in influenza vaccines for the 2021-2022 northern hemisphere season. A large majority of HA sequences from recently detected viruses, in geographically dispersed countries, have fallen in the V1A.3a group defined by a series of HA1 amino acid substitutions including N150K, with most falling in the V1A.3a.2 subgroup with defining HA1 A127T, P144L and K203R amino acid substitutions. At least three virus genetic clusters have emerged among B/Washington/02/2019-like (V1A.3) viruses, one of which was recently detected in the Netherlands and characterized by HA1 G184R amino acid substitution – here we show that such viruses are not well recognised by the entire panel of post-infection ferret antisera and a hyperimmune sheep antiserum raised against B/Brisbane/60/2008. Post-infection ferret antisera raised against B/Washington/02/2019-like viruses do not recognise V1A.3a.2 viruses well, and B/Austria/1359417/2021-like (V1A.3a.2) viruses were recommended for use in the southern hemisphere 2022 and the northern hemisphere 2022-2023 influenza seasons.

¹ Influenza virus characterization: summary report, Europe, June 2022. World Health Organization Regional Office for Europe and European Centre for Disease Prevention and Control; Copenhagen and Stockholm; 2022 (<https://apps.who.int/iris/handle/10665/363629>, accessed 19 October 2022).

No cases of infection with circulating B/Yamagata-lineage viruses have been confirmed since March of 2020. All HA gene sequences from the 77 viruses detected in 2020, inclusive of 16 from the WHO European Region, belonged to genetic clade Y3 and had three HA1 amino acid substitutions (L172Q, D229N and M251V) compared to B/Phuket/3073/2013-like viruses which are still recommended for use in quadrivalent influenza vaccines. **There is need to share all B/Yamagata-lineage viruses detected recently for detailed characterization to determine if there are any in circulation that are not related to Live Attenuated Influenza Vaccines.**

Table 1 shows a summary of influenza virus detections in the WHO European Region reported to The European Surveillance System (TESSy) database during the 2021-2022 season (weeks 40/2021-30/2022), compared to the same period in the 2020-2021 season. There has been a great increase in the number of samples from patients fulfilling Influenza-Like Illness (ILI) and/or Acute Respiratory Infection (ARI) criteria being tested (1 926 053, 176%), even when compared with a more ‘normal’ season, 2019-2020 (2 076 674, 220%: results not shown), which led into the COVID-19 pandemic. With this increased testing there has been a rise in the number of influenza-positive samples (144 903, 144-fold), though there was a reduction compared to the same period in 2019-2020 (18 974, 12%: results not shown). These data probably relate to a number of factors: (i) significant numbers of samples taken from patients fulfilling ILI and/or ARI criteria being infected with other agents, possibly SARS-CoV-2, the virus responsible for the COVID-19 pandemic; (ii) residual effects of measures introduced to help curtail the spread of SARS-CoV-2, and; (iii) with large swathes of the human population now carrying a significant level of immunity to SARS-CoV-2 following either infection and/or vaccination, influenza has been able to re-establish itself after nearly two years of low-level circulation.

With these caveats, and being mindful of the low number of detections during of the 2020-2021 season, the ratio of type A to type B detections has increased compared to the 2020-2021 season (1.2:1 to 52:1), with a greater dominance of A(H3N2) over A(H1N1)pdm09 viruses. While the number of influenza B virus detections has increased from 468 to 2 742 (586%), only small numbers were ascribed to a lineage in both time periods (Table 1) though, based on sequences available in GISAID, B/Yamagata lineage viruses with collection dates after March 2020 have not been characterized genetically. Currently, it appears that measures introduced relating to the COVID-19 pandemic are still having an effect but there has been clear indication of an influenza season in the Region during 2021-2022 with the rate of influenza positivity in sentinel samples having been at or above 10%, the epidemic threshold set for the Region, for 17 weeks during a bi-phasic season (weeks 49/2021 to 1/2022 and weeks 8-19/2022) with A(H3N2) viruses dominating (Figure 1).

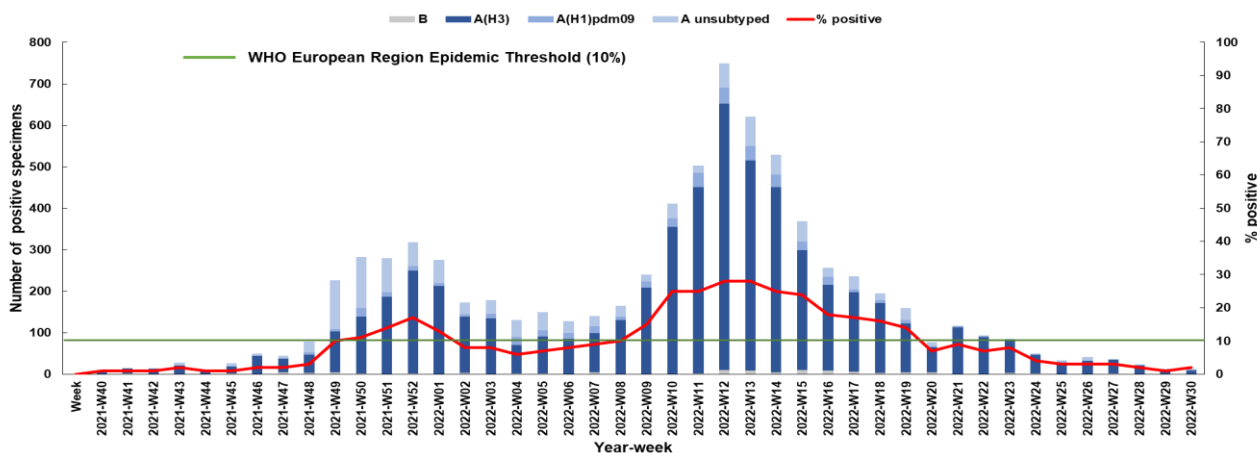
Table 1. Influenza virus detections in the WHO European Region from the start of reporting for the 2021-2022 season (weeks 40/2021-30/2022)^a

Virus type/subtype/lineage	Cumulative number of detections for weeks 40/2021-30/2022			Totals ^a		Cumulative number of detections for weeks 40/2020-32/2021			Totals ^a	
	Sentinel sources	Non-sentinel sources	Totals	%	Ratios	Sentinel sources	Non-sentinel sources	Totals	%	Ratios
Influenza A	7706	135465	143171	98.1	52:1	29	513	542	53.7	1.2:1
A(H1N1)pdm09	4022	2627	6649	15.9		13	69	82	56.9	
A(H3N2)	6158	29038	35196	84.1	5.3:1	8	54	62	43.1	0.8:1
A not subtyped	1146	103800	104946			8	390	398		
Influenza B	115	2627	2742	1.9		18	450	468	46.3	
Victoria lineage	24	108	132	98.5	66:1	2	11	13	81.3	4.3:1
Yamagata lineage	0	2	2	1.5		0	3	3	9.7	
Lineage not ascribed	91	2517	2608			16	436	452		
Total detections (total tested)	7 821 (73 863)	138 092 (>2 944 362)	145 913 (>3 018 225)			47 (48 181)	963 (>1 043 991)	1 010 (>1 092 172)		

^a Numbers taken from Flu News Europe to week 30/2022, week 32/2021 and week 30/2020 reports for the three influenza seasons

^a Percentages are shown for total detections (types A & B [in bold type], and for viruses ascribed to influenza A subtype and influenza B lineage). Ratios are given for type A:B [in bold type], A(H3N2):A(H1N1)pdm09 and Victoria:Yamagata lineages.

Figure 1. Influenza positivity in sentinel-source specimens by week (2021-2022) – WHO/Europe^a



^a Figure adapted from FluNewsEurope week 26-30/2022 (<https://flunewseurope.org/Archives>)

Genetic and antigenic characterization data generated at the WIC for viruses with collection dates after 31 August 2020 until 31 January 2021, up to a report deadline of 15 February 2021, contributed to the WIC virus characterization report that was presented at the WHO influenza vaccine composition meeting (VCM) in February 2021 when recommendations were made for the northern hemisphere 2021-2022 season [1]. Data generated on viruses with collection dates after 31 January 2021 until 31 August 2021 informed the September 2021 VCM when recommendations were made for the 2022 southern hemisphere season [2]. Data presented in the February report for viruses with collection dates after 31 August 2021 until 31 January 2022 contributed to the most recent VCM (21-24 February) where recommendations were made for the 2022-2023 northern hemisphere influenza seasons [3].

For the 2022-2023 northern hemisphere season it was recommended to change the A(H3N2) and B/Victoria-lineage components of influenza vaccines to match those used in 2022 southern hemisphere vaccination campaigns.

Due to the relatively low number of influenza-positive specimens detected until recently, and thereby available for sharing with WIC, this and recent influenza characterization reports (<https://www.ecdc.europa.eu/en/seasonal-influenza/surveillance-and-disease-data/influenza-virus-characterisation>) have been based mainly on phylogenetic analyses of complete HA gene sequences submitted to GISAID's EpiFlu™ database, inclusive of sequences generated at the WIC. Here A(H1N1)pdm09, A(H3N2) and B/Victoria-lineage HA gene phylogenies for viruses with collection dates after 31 December 2021, for representative non-WIC generated sequences available in GISAID, generated for the June report are presented (Figures 2a, 3a and 4a). Additional phylogenies (Figures 2b, 3b and 4b) are presented for HA sequences derived from viruses with collection and HA sequence submission dates from the days indicated in Table 2, with a sequence download date of 15 August 2022. The numbers of HA sequences, downloaded from GISAID, numbers remaining after de-duplication and the numbers used in the new representative phylogenies generated for this July report are shown.

Table 2. Summary of the numbers of HA gene sequences available and used in generating the new phylogenies presented in this report

Virus subtype/lineage	Global HA sequences available for viruses collected in the 2021-2022 season as of 2022-08-15				
	Virus collection date (from)	Sequence submission date (from)	Number Downloaded	Number de-duplicated and aligned	Number used in phylogenies*
A(H1N1)pdm09	2022-05-01	2022-07-01	240	232	232
A(H3N2)	2022-05-01	2022-07-01	1232	1076	250
B/Victoria	2022-04-01	2022-04-01	226	188	188
B/Yamagata	2022-01-01	2022-01-01	0	0	0

* Inclusive of sequences generated recently at the WIC, but not including sequences from reference and vaccine viruses

Eighty-four shipments of specimens (virus isolates and/or clinical specimens) were received at the WIC from WHO Global Influenza Surveillance and Response System (GISRS) recognised National Influenza Centres (NICs) in a total of 39 WHO European Region Member States (Table 3). Of the 2 270 samples received 2 149 (95%) were type A viruses and 121 (5%) were type B viruses. Thirteen of the shipments were received in July 2022 and contained samples from the second phase of the epidemic (Figure 1) many of which are still in the virus characterization process (Table 3). NICs were requested to send clinical specimens with real-time RTPCR Ct values of ≤ 30 and/or virus isolates, all those available for A(H1N1)pdm09 and influenza type B (as relatively few have been detected), and a representative selection of A(H3N2) samples.

A total of 530 viruses from the WHO European Region, 78 A(H1N1)pdm09, 399 A(H3N2) and 53 B/Victoria-lineage, have been characterized antigenically since the June report (Tables 4, 5 and 6 respectively).

2021-2022 and 2022-2023, and southern hemisphere 2022 (egg-based A/Victoria/5270/2019-like and cell-based A/Wisconsin/588/2019-like) influenza seasons are shown in red [1, 3, 2]. The seven subclades are defined by the following HA amino acid substitutions:

1. Subclade **6B.1A.1** viruses, represented by the 2019-2020 vaccine virus **A/Brisbane/02/2018**, carry an HA gene mutation encoding **HA1 S183P** amino acid substitution.
2. Subclade **6B.1A.2** viruses, represented by **A/Denmark/2728/2019**, carry HA gene mutations encoding **HA1 S183P** and **L233I** with **HA2 V193A** amino acid substitutions – a group within this subclade has emerged with additional **HA1** amino acid substitutions of **N129D**, **K130N**, **P137S**, **N156K** and **K211R** (e.g. **A/Hong Kong/110/2019**).
3. Subclade **6B.1A.3** viruses, represented by **A/Norway/3737/2018**, carry HA gene mutations encoding **HA1 T120A** and **S183P** amino acid substitutions.
4. Subclade **6B.1A.4** represented by **A/Hungary/20/2018** carries HA gene mutations encoding **HA1 N129D**, **A144E** and **S183P** amino acid substitutions.
5. Subclade **6B.1A.5** viruses carry HA gene mutations encoding **HA1 S183P** and **N260D** amino acid substitutions and split into two groups designated **6B.1A.5a** represented by **A/Norway/3433/2018** with additional **HA1** amino acid substitutions of **N129D** and **T185A**, and **6B.1A.5b** represented by **A/Switzerland/3330/2017** with additional amino acid substitutions of **HA1 E235D** and **HA2 V193A**. Two subgroups within the **6B.1A.5a** group have been defined based on **HA1** amino acid substitutions of **D187V/A** and **Q189E** (**6B.1A.5a.1**) or **K130N**, **N156K**, **L161I** and **V250A** (**6B.1A.5a.2**).
6. Subclade **6B.1A.6** viruses, represented by **A/Ireland/84630/2018**, carry HA gene mutations encoding **HA1 T120A** and **S183P** amino acid substitutions, like subclade **6B.1A.3** viruses, but fall within a separate phylogenetic branch which is closer to subclade **6B.1A.5** viruses.
7. Subclade **6B.1A.7** viruses, represented by **A/Slovenia/1489/2019**, carry HA gene mutations encoding **HA1 K302T** and **HA2 I77M**, **N169S** and **E179D** amino acid substitutions sometimes with additional **HA1** substitutions of **E68D**, **S121N** and **L161I** (e.g. **A/Moscow/193/2019**). Note: a group within this subclade has emerged with **P183S** (reversion), **T185I**, **I240V** and **I286L** substitutions in **HA1** (e.g. **A/Estonia/120012/2019**).

The phylogeny prepared for the June report was based on HA sequences derived from viruses with collection dates after 31 December 2021 that had been submitted to GISAID after 29 May 2022. Viruses of subgroup **6B.1A.5a.1** continued to dominate in the WHO European Region with a few detections reported by Canada and the USA (Figure 2a). For viruses with the most recent collection dates, subgroup **6B.1A.5a.2** continued to dominate in Australia and a significant number were also detected in England, together with a single sequence reported from a detection in Canada.

The phylogeny prepared for this report focuses on HA sequences derived from viruses with collection dates after 30 April 2022 for which HA sequences were submitted to GISAID after June 2022 (Table 2). Of the 19 sequences derived from viruses detected in the WHO European Region, 17 fall in subgroup **6B.1A.5a.1** and two in subgroup **6B.1A.5a.2** (Figure 2b). Sequences derived from small numbers of **6B.1A.5a.1** viruses recently detected in Australia, South Africa and the USA were also reported. As indicated in both phylogenies recently detected viruses in subgroup **6B.1A.5a.2** all have **HA1 K54Q**, **A186T**, **Q189E**, **E224A**, **R259K** and **K308R** substitutions compared to the vaccine virus, A/Victoria/2570/2019 (Figures 2a and 2b) and virus clusters have emerged defined by amino acid substitutions: (i) **HA1 A48P** in Australia; (ii) **HA1 K142R**, **D260E** and **HA2 N124H**, often with **HA1 P137S**, **T277A** and **HA2 E29D** and **I91V** in South Africa with one each from Croatia and Spain; (iii) **HA1 I265T** in Australia, and: (iv) **HA1 T216A** often with **D94N** that shows greater geographic distribution (Abu Dhabi, Australia, Qatar, Somalia and the USA).

The panel of post-infection ferret antisera used in HI assays, five raised against subgroup **6B.1A.5a.1** viruses and three against **6B.1A.5a.2** viruses, gives clear discrimination of test viruses in the two subgroups (Tables 4-1 and 4-2). Of the 73 **6B.1A.5a.1** test viruses, detected across 11 countries, 72 (98.6%), 72 (98.6%), 69 (94.5%), 70 (95.9%) and 66 (90.4%) were recognised well (within fourfold of the homologous titres) by antisera raised against A/Ireland/87733/2019, cell culture- and egg-propagated A/Guangdong-Maonan/SWL1536/2019 (vaccine viruses for the 2020-2021 northern hemisphere season), A/Ghana/1894/2021 and A/Lyon/820/2021, respectively. Two less well recognised viruses, A/Baleares/837/2022 and A/Parma/06/2022, have **HA1 P137S** and **G155E** amino acid substitutions. Poor recognition of viruses in this cluster has been mentioned in previous reports.

Of the five **6B.1A.5a.2** viruses, detected in Croatia (n = 2, cluster (ii) above with four HA1 and three HA2 substitutions), Italy (n = 1, cluster (iv) with **HA1 T216A** substitution) and the Netherlands (n = 2, cluster (iv) with **HA1 T216A** and **D94N** substitutions), all were recognised well by antisera raised against three different **6B.1A.5a.2** reference viruses. This includes the vaccine virus (IVR-215: A/Victoria/2570/2019) for the 2021-2022 northern hemisphere season and indicates that a variety of genetically clustered viruses, defined by specific HA1 amino acid substitutions, cannot be discriminated antigenically by the post-infection ferret antisera used in HI assays.

At the most recent WHO VCM, held in Geneva 21-24 February 2022, A/Victoria/2570/2019-like viruses were recommended for use in the northern hemisphere 2022-2023 influenza season [3]. This decision was largely based on antisera induced by **6B.1A.5a.1** subgroup viruses in ferrets and humans yielding poor recognition of **6B.1A.5a.2** subgroup viruses and most of the human population unlikely to have been exposed to **6B.1A.5a.2** subgroup viruses given their low-level circulation during the COVID-19 pandemic.

Figure 2a. Phylogenetic comparison of influenza A(H1N1)pdm09 HA genes (GISAID/WIC, June 2022)

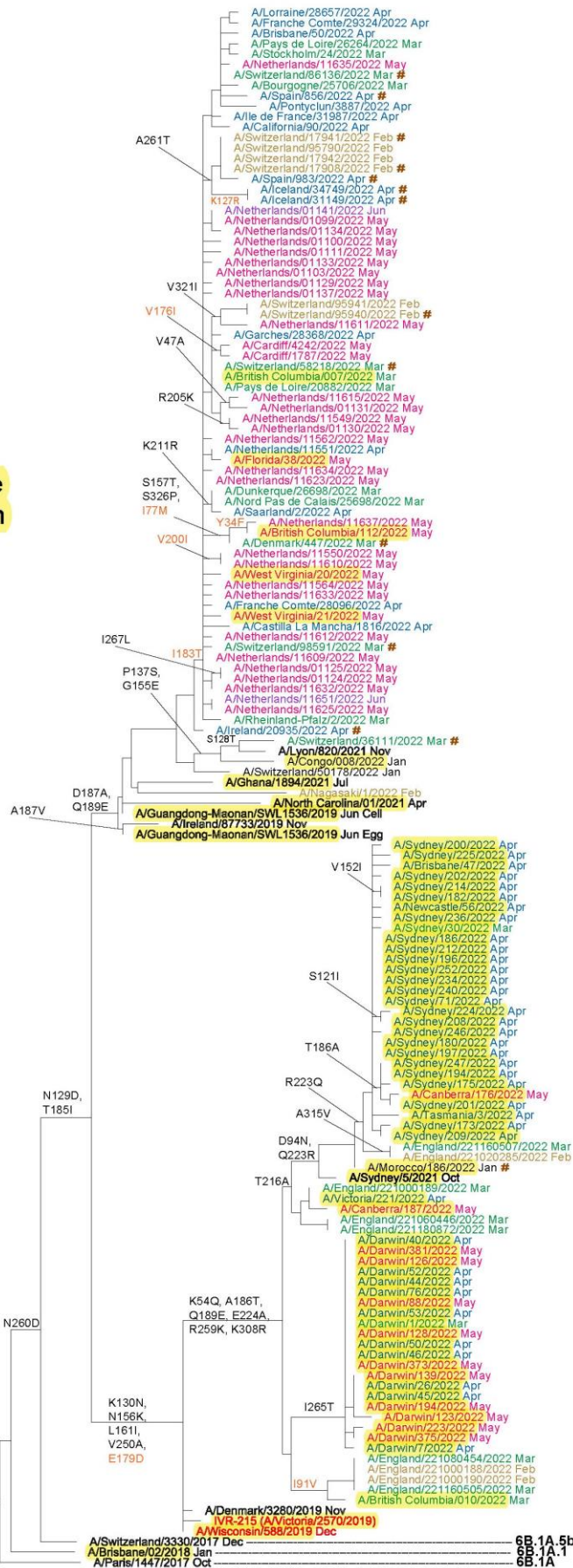
Vaccine viruses
Reference viruses

Collection date
Feb 2022
Mar 2022
Apr 2022
May 2022
Jun 2022

HA2 numbering

recent WIC sequences

Countries outside of the WHO European Region



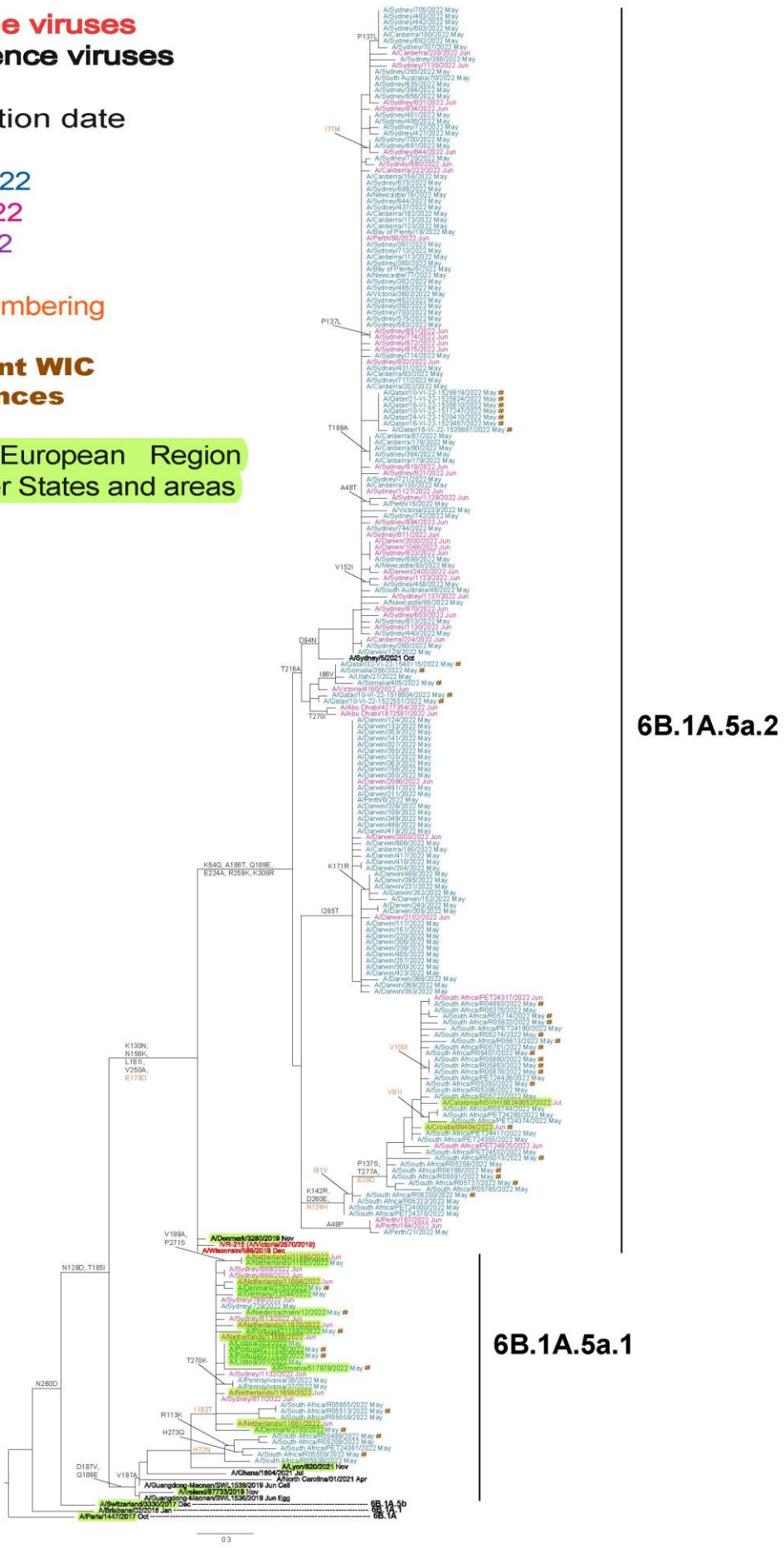
6B.1A.5a1

6B.1A.5a2

0.09

Figure 2b. Phylogenetic comparison of influenza A(H1N1)pdm09 HA genes (GISAID/WIC, July 2022)

Vaccine viruses
Reference viruses
 Collection date
 May 2022
 Jun 2022
 Jul 2022
 HA2 numbering
recent WIC sequences
 WHO European Region Member States and areas



6B.1A.5a.2

6B.1A.5a.1

Table 4-2. Antigenic analysis of influenza A(H1N1)pdm09 viruses by HI

Viruses	Other Information	Passage history	Collection date	Passage history	Haemagglutination inhibition titre									
					Alire 87733/19 Egg St Jude's F1820 ¹ 6B.1A.5a.1	AG-M SWL1536/19 MDCK F09/20 ¹ 6B.1A.5a.1	AG-M SWL1536/19 Egg F12/20 ¹ 6B.1A.5a.1	AGhana 1894/21 Egg F02/22 ¹ 6B.1A.5a.1	ALydon 820/21 Egg F06/22 ¹ 6B.1A.5a.1	A/Denmark 3280/19 MDCK F28/20 ¹ 6B.1A.5a.2	IVR-215 AVictoria/2570/19 Egg F37/21 ¹ 6B.1A.5a.2	A/Sydney 5/21 Egg F04/22 ¹ 6B.1A.5a.2		
REFERENCE VIRUSES														
A/Ireland/87733/2019			2019-11-03	E4	640	1280	1280	640	320	40	80	40	40	
A/Guangdong-Maonan/SWL1536/2019			2019-06-17	C2/MDCK1	640	1280	1280	1280	320	40	80	40	40	
A/Guangdong-Maonan/SWL1536/2019			2019-06-17	E3/E2	320	1280	1280	640	160	40	80	40	40	
A/Ghana/1894/2021			2021-07-21	E2/E1	640	1280	640	1280	160	40	80	40	40	
A/Lyon/620/2021			2021-11-16	E1/E2	80	320	320	160	640	40	40	40	40	
A/Denmark/3280/2019			2019-11-10	MDCK4/MDCK5	<	<	40	<	40	1280	1280	1280	1280	
IVR-215 (A/Victoria/2570/2019)			2018-11-22	E4/D7/E2	40	80	80	80	160	1280	1280	1280	2560	
A/Sydney/5/2021			2021-10-16	E3/E1	40	40	80	40	160	1280	2560	1280	2560	
TEST VIRUSES														
A/Murcia/10207/2021			2021-12-05	MDCK1	320	640	1280	640	160	40	80	40	40	
A/Canarias/558/2022			2022-01-01	MDCK1	640	1280	2560	1280	320	40	80	40	40	
A/Belgium/S0141/2022			2022-01-06	MDCK1	640	2560	640	320	160	<	40	40	<	
A/Galicia/1460/2022			2022-01-09	MDCK1	320	1280	1280	640	320	40	40	40	40	
A/Galicia/1459/2022			2022-01-09	MDCK1	640	1280	2560	1280	320	40	80	40	40	
A/Belgium/S0120/2022			2022-01-17	MDCK1	640	2560	1280	640	320	40	40	40	40	
A/Belgium/S0197/2022			2022-01-30	MDCK1	320	2560	2560	640	160	40	40	40	40	
A/Belgium/S0360/2022			2022-02-10	MDCK1	320	1280	1280	640	160	40	40	40	40	
A/Belgium/S0372/2022			2022-02-16	MDCK1	320	1280	1280	640	160	40	40	40	40	
A/Belgium/S0449/2022			2022-02-24	MDCK1	320	1280	1280	640	160	40	40	40	40	
A/Belgium/S0447/2022			2022-02-24	MDCK1	160	640	640	160	80	<	40	40	<	
A/Belgium/S0472/2022			2022-02-25	MDCK1	320	1280	640	320	160	40	40	40	40	
A/Belgium/S0810/2022			2022-03-03	MDCK1	320	1280	1280	640	160	40	40	40	40	
A/Belgium/S0429/2022			2022-03-03	MDCK1	160	320	640	160	160	<	40	40	40	
A/Belgium/S0782/2022			2022-03-04	MDCK1	640	2560	2560	1280	320	40	80	40	40	
A/Belgium/S0631/2022			2022-03-07	MDCK1	640	2560	2560	1280	320	40	80	40	40	
A/Belgium/S0906/2022			2022-03-18	MDCK1/MDCK1	320	2560	1280	640	160	40	40	40	40	
A/Belgium/S0859/2022			2022-03-18	MDCK1	640	2560	2560	1280	320	40	80	40	40	
A/Belgium/S0824/2022			2022-03-20	MDCK1	320	2560	2560	1280	320	40	80	40	40	
A/Belgium/S0825/2022			2022-03-21	MDCK1/MDCK1	640	2560	1280	1280	160	40	40	40	40	
A/Belgium/S0856/2022			2022-03-22	MDCK1/MDCK1	320	1280	640	640	160	40	80	40	40	
A/Baleares/1472/2022			2022-03-23	MDCK1	320	1280	640	640	160	40	40	40	40	
A/Belgium/S0793/2022			2022-03-27	MDCK1/MDCK1	640	2560	1280	1280	320	40	80	40	40	
A/Belgium/S0175/2022			2022-03-28	MDCK1/MDCK1	640	2560	1280	1280	320	40	80	40	40	
A/Belgium/S0767/2022			2022-03-30	MDCK1/MDCK1	160	1280	640	320	160	40	80	40	40	
A/Belgium/S0769/2022			2022-03-31	MDCK1/MDCK1	80	320	320	160	80	<	40	40	<	
A/Belgium/S1111/2022			2022-04-05	MDCK1/MDCK1	640	1280	2560	1280	320	40	80	40	40	
A/Belgium/S1001/2022			2022-04-10	MDCK1/MDCK1	320	640	640	640	160	40	80	40	40	
A/Belgium/S1041/2022			2022-04-12	MDCK1/MDCK1	320	640	640	640	160	40	80	40	40	
A/Belgium/S1003/2022			2022-04-13	MDCK1/MDCK1	320	640	640	640	160	40	80	40	40	
A/Spain/856/2022			2022-04-15	MDCK2	1280	1280	1280	1280	320	40	40	40	40	
A/Belgium/S0418/2022			2022-06-30	MDCK1	160	1280	640	320	160	40	40	40	<	
A/Croatia/86404/2022			2022-07-01	MDCK1	<	<	<	<	<	640	1280	1280	640	
A/Croatia/86715/2022			2022-07-01	MDCK1	<	40	40	<	<	1280	1280	1280	1280	

* Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used)

1 <= <40; 2 <= <80; ND = Not Done

Vaccine
SH 2021
NH 2021-22
SH 2022
NH 2022-23

Vaccine
NH 2020-21

Influenza A(H3N2) virus analyses

A(H3N2) viruses with HA sequences in clade **3C.2a** have been dominant since the 2014-15 influenza season with group **3C.2a1b** viruses predominating over the course of the 2019-2020 season in most WHO-defined regions of the world but for the European Region where there was equivalence of clade **3C.3a** viruses. The HA gene sequences of viruses in both clades **3C.2a** and **3C.3a** continue to diverge. Notably, clade **3C.3a.1** viruses had evolved to carry **HA1** amino acid substitutions of **L3I**, **S91N**, **N144K** (loss of a N-linked glycosylation motif at residues 144-146), **F193S** and **K326R**, and **D160N** in **HA2**, compared with cell culture-propagated A/Stockholm/6/2014. Greater variation has been observed among clade **3C.2a** viruses, resulting in the designation of new subclades/groups/subgroups. Amino acid substitutions that define these subclades/groups/subgroups are:

- Subclade **3C.2a1**: Those in clade **3C.2a** plus **N171K** in **HA1** and **I77V** and **G155E** in **HA2**, most also carry **N121K** in **HA1**, e.g. **A/Singapore/INFIMH-16-0019/2016** (a former vaccine virus).
- Group **3C.2a1a**: Those in subclade **3C.2a1** plus **T135K** in **HA1**, resulting in the loss of a potential glycosylation site, and **G150E** in **HA2**, e.g. **A/Greece/4/2017**.
- Group **3C.2a1b**: Those in subclade **3C.2a1** plus **E62G**, **R142G** and **H311Q** in **HA1**, often with additional amino acid substitutions – notably **HA1 T135K** (resulting in the loss of a potential glycosylation site) commonly with **T128A** (resulting in the loss of a potential glycosylation site), the **3C.2a1b.1** subgroup (e.g. **A/La Rioja/2202/2018**) or **HA1 T131K** and **HA2 V200I**, the **3C.2a1b.2** subgroup (e.g. **A/South Australia/34/2019**). Distinct clusters of viruses within both these subgroups have emerged defined by specific **HA1** and/or **HA2** amino acid substitutions: **3C.2a1b.1a** with additional amino acid substitutions of **HA1 A138S**, **F193S** and **S198P**, many also with **G186D** and **D190N** (e.g. **A/Denmark/3284/2019**); **3C.2a1b.1b** with additional amino acid substitutions of **HA1 S137F**, **A138S** and **F193S** (e.g. **A/Hong Kong/2671/2019**); **3C.2a1b.2a** with additional amino acid substitutions of **HA1 K83E** and **Y94N** with **HA2 I193M** (e.g. **A/Slovenia/1637/2020**); **3C.2a1b.2b** with **HA2 V18M** substitution, often with additional **HA1** substitutions (e.g. **A/Bretagne/1323/2020**).
- Clade **3C.3a**: represented by a former vaccine virus, **A/Switzerland/9715293/2013**, with recently circulating clade **3C.3a.1** viruses carrying additional substitutions of **S91N**, **N144K** (resulting in the loss of a potential glycosylation site), and **F193S** in **HA1** and **D160N** in **HA2**, e.g. **A/England/538/2018** and **A/Kansas/14/2017**, the A(H3N2) vaccine virus for the 2019-2020 northern hemisphere influenza season.

The significant geographic spread of viruses in the antigenically distinct **3C.2a1b.1b** cluster, influenced the selection of an A/Hong Kong/2671/2019-like or an A/Hong Kong/45/2019-like virus as the A(H3N2) component of vaccines for the 2020-2021 northern hemisphere and 2021 southern hemisphere influenza seasons.

The first phylogeny is based on a representative set of HA sequences derived from viruses with collection dates after 28 February 2022 made available in GISAID and generated at the WIC from 01 May 2022 (Figure 3a). Small numbers of ‘Cambodia-like’ **3C.2a1b.2a.1** (from China) and **3C.2a1b.1a** (from Sweden) viruses were reported on. The vast majority of recently collected viruses were ‘Bangladesh-like’ (**3C.2a1b.2a.2** with **HA1** substitutions of **Y159N**, **T160I** (loss of a glycosylation site), **L164Q**, **G186D**, **D190N** and **Y195F**). The latter viruses were split into five subgroups defined by specific **HA1** amino acid substitutions: (i) **S205F** and **A212T**; (ii) **E50K**; (iii) **D53N** and **P289S**; (iv) **D53N**, commonly with **N96S** (gain a glycosylation site) and **I192F**; (v) **D53G** often with **I25V**, **R201K** and **S219Y** or **D104G** and **K276R**. Subgroups (iii), (iv) and (v) also share **HA1 H156S** amino acid substitution.

The second phylogeny is based on a representative set of HA sequences derived from viruses with collection dates after 30 April 2022 made available in GISAID and generated at the WIC from 01 July 2022 and shows a very similar profile to the first phylogeny (Table 2 and Figure 3b). Subgroups (iv; **HA1** substitutions of **D53N**, **N96S** and **I192F**) and (v; **HA1** substitutions of **D53G**, **D104G** and **K276R**) dominate in both phylogenies. Sequences derived from samples collected in the WHO European Region are dispersed throughout the trees with the ‘Bangladesh-like’ (**3C.2a1b.2a.2**) viruses falling into multiple virus clusters defined by specific amino acid substitutions (Figures 3a and 3b).

The locations of HA sequences for egg- and cell culture-propagated cultivars of A/Cambodia/e0826360/2020 (**3C.2a1b.2a.1**) recommended for use in northern hemisphere 2021-2022 vaccines [1], are indicated in red on the phylogenies, as are egg- and cell-culture based ‘Bangladesh-like’ vaccines to be used in the 2022 southern hemisphere and northern hemisphere seasons, A/Darwin/9/2021 and A/Darwin/6/2021 (**3C.2a1b.2a.2**) respectively [2, 3] (Figures 3a and 3b).

As described in many previous reports², influenza A(H3N2) viruses had been difficult to characterize antigenically by HI assay due to variable agglutination of red blood cells (RBCs) from guinea pigs, turkeys, and humans, often with the loss of ability to agglutinate any of these RBCs. As was highlighted first in the November 2014 report³, this was a significant problem for most viruses that fell in genetic clade **3C.2a**, although there was some alleviation of this during 2019-2020 with continuation into the 2020-2021 influenza season. This issue is now much alleviated for 'Bangladesh-like' **3C.2a1b.2a.2** viruses which agglutinate guinea pig RBCs well, allowing HI assays to be performed with a single A(H3N2) virus from the Netherlands failing to yield a sufficient HA titre with guinea pig RBCs to allow HI analysis (Table 3).

While the number of detections of seasonal influenza viruses was low from April 2020 to July 2021, compared to previous years, the WHO Collaborating Centres for Influenza have shown viruses in these emerged virus clusters to be antigenically distinguishable from one another and other A(H3N2) virus subgroups.

Results for 399 A(H3N2) viruses fully characterized antigenically since the June report are shown in Tables 5-1 to 5-9. Table 5-1 is repeated from the June report but with genetic group information added. All data, based on fold change compared to homologous titres, is summarised in Table 5-10. Of the test viruses, three fell in the **3C.2a1b.1a** cluster and the remaining 396 were 'Bangladesh-like' **3C.2a1b.2a.2** viruses. The three **3C.2a1b.1a** viruses, detected in Sweden (n = 2) and the Netherlands (n = 1), were generally recognised well, within fourfold of the respective homologous titres, by antisera raised against six of nine reference viruses inclusive of that raised against the northern hemisphere 2021-2022 vaccine virus; while the antiserum raised against the 2022-2023 vaccine virus had a high homologous titre (1280) it still recognised the **3C.2a1b.1a** viruses at titres of at least 80 (Tables 5-1 and 5-3).

The 'Bangladesh-like' **3C.2a1b.2a.2** test viruses were recognised well only by post-infection ferret antisera raised against viruses with **3C.2a1b.2a.2** HAs. Antisera raised against cell culture-propagated A/Bangladesh/4005/2020, A/Stockholm/5/2021 and A/England/214191723/2021 all recognised greater than 97% of the test viruses at titres within fourfold of the respective homologous titres. Although only small numbers of test viruses were analysed for antisera raised against egg-propagated A/Slovenia/8720/2022, A/Slovenia/9216/2022, A/Slovenia/9318/2022 and A/Wyoming/01/2021 they were generally recognised well. The antiserum raised against egg-propagated A/Darwin/9/2021, the northern hemisphere 2022-2023 vaccine virus, recognised 302 (76%) of the test viruses at titres within fourfold of the homologous titres. However, this lower percentage for antiserum raised against egg-propagated A/Darwin/9/2021 is largely related to high homologous titres (2560) in two of the assays (Tables 5-8 and 5-9) and all the **3C.2a1b.2a.2** test viruses reacted with a titre of at least 160, well above the threshold of 40 that has been determined as the cut-off for a protective effect.

Results of HI assays with panels of post-infection ferret antisera raised against A(H3N2) vaccine and reference viruses for viruses detected in EU/EEA countries can be seen in previous influenza characterization reports on [ECDC's website](#). Overall, these data show strong clade/subclade-specific recognition of test viruses by post-infection ferret antisera raised against cell culture-propagated reference viruses, with limited cross-clade/subclade recognition and further reductions in recognition of cell culture-propagated recently circulating viruses by antisera raised against A(H3N2) egg-propagated vaccine viruses.

² For example, the September 2013 report: Influenza virus characterisation, summary Europe, September 2013. Stockholm: European Centre for Disease Prevention and Control; 2013 (<https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/influenza-virus-characterisation-sep-2013.pdf>, accessed 19 October 2022).

³ Influenza virus characterisation, summary Europe, November 2014. Stockholm: European Centre for Disease Prevention and Control; 2014 (<https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/ERLI-Net%20report%20November%202014.pdf>, accessed 19 October 2022).

Figure 3a. Phylogenetic comparison of influenza A(H3N2) HA genes (GISAID/WIC, June 2022)

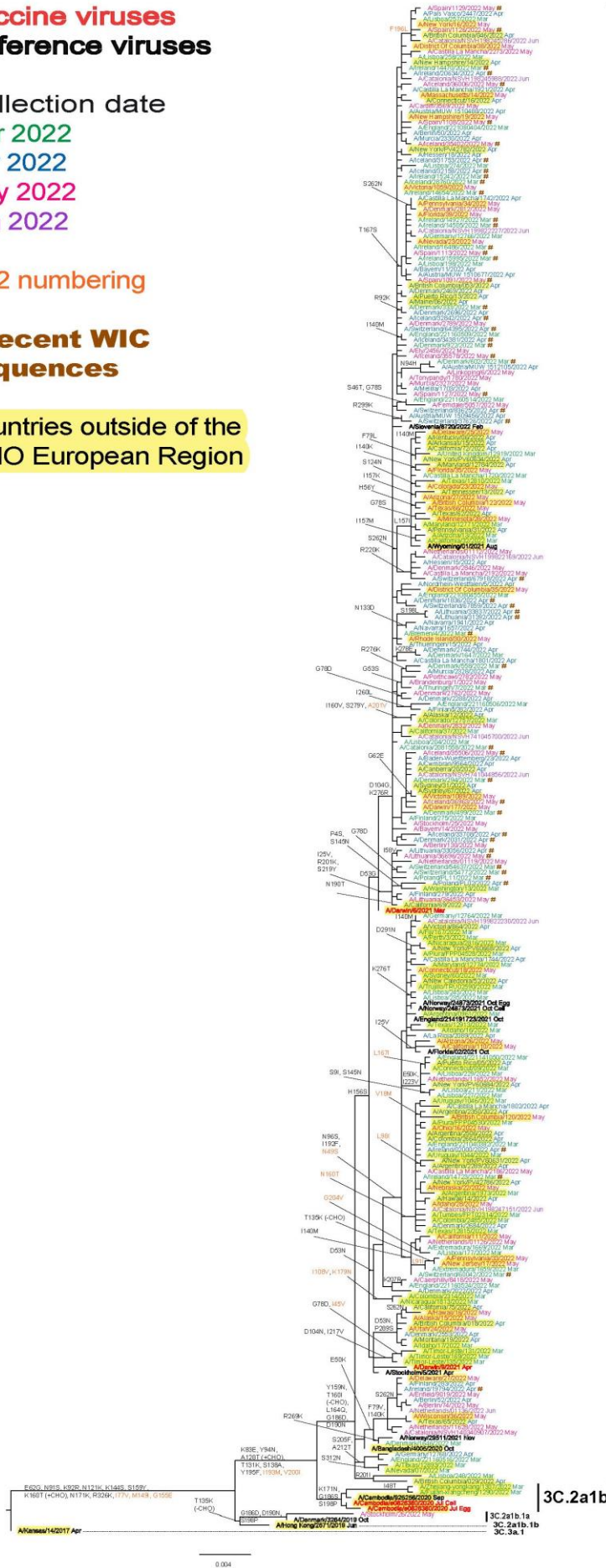
Vaccine viruses
Reference viruses

Collection date
Mar 2022
Apr 2022
May 2022
Jun 2022

HA2 numbering

recent WIC sequences

Countries outside of the WHO European Region



3C.2a1b.2a.2

3C.2a1b.2a.1

3C.2a1b.1b

3C.3a.1

Figure 3b. Phylogenetic comparison of influenza A(H3N2) HA genes (GISAID/WIC, July 2022)

Vaccine viruses
Reference viruses

Collection date

May 2022

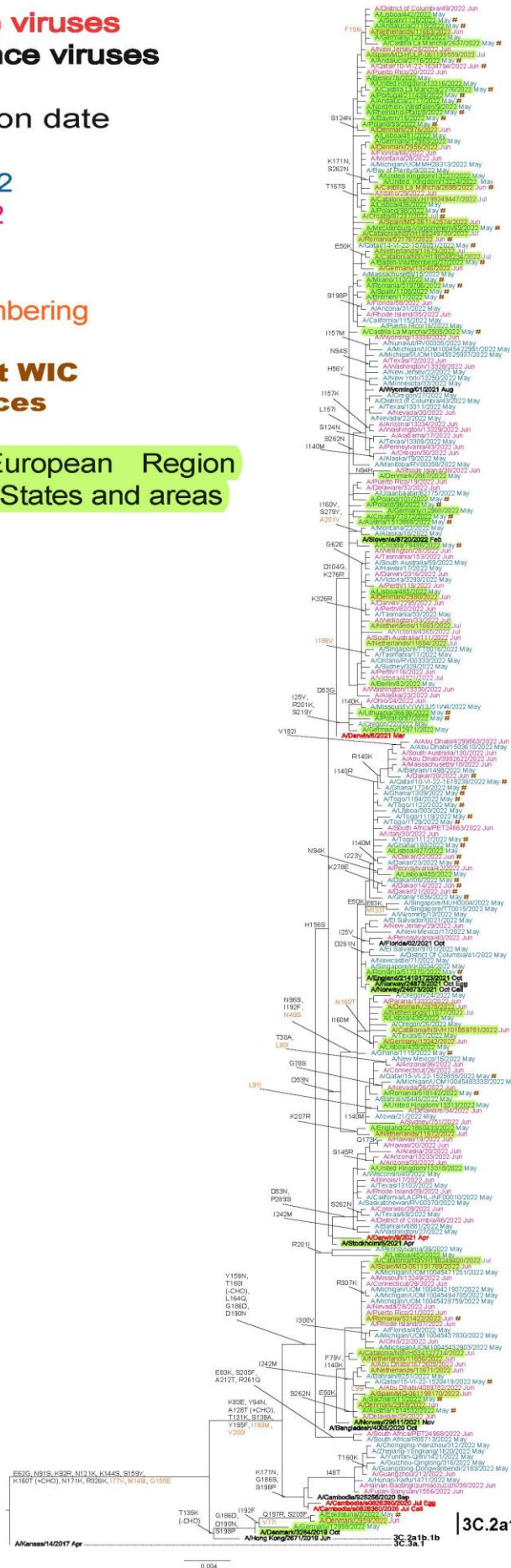
Jun 2022

Jul 2022

HA2 numbering

recent WIC sequences

WHO European Region
Member States and areas



3C.2a1b.2a.2

3C.2a1b.2a.1

3C.2a1b.1a

Table 5-3. Antigenic analysis of influenza A(H3N2) viruses by HI

Viruses	Other information	Passage history	Collection date	Passage history	Haemagglutination inhibition titre									
					A/Denmark 3264/19 SIAT F19/20 ¹ 3C.2a1b.1a	A/HK 2671/19 Cell SI Judes F21/20 ¹ 3C.2a1b.1b	A/Camb 925258/20 SIAT F03/21 ¹ 3C.2a1b.2a.1	A/Bang 4005/20 SIAT F07/21 ¹ 3C.2a1b.2a.2	A/Stock 5/21 SIAT F35/21 ¹ 3C.2a1b.2a.2	A/Eng 214191723/21 SIAT F07/22 ¹ 3C.2a1b.2a.2	A/Darwin 9/21 Egg F38/21 ¹ 3C.2a1b.2a.2	A/Kansas 14/17 SIAT F17/19 ¹ 3C.3a.1		
REFERENCE VIRUSES														
A/Denmark/K3264/2019		SIAT3/SIAT4	2019-10-25	SIAT3/SIAT4	320	320	640	320	320	320	80	320	160	
A/Hong Kong/2671/2019		MDCK1/SIAT4	2019-06-17	MDCK1/SIAT4	160	320	640	160	160	40	40	320	160	
A/Cambodia/925258/2020		SIAT5	2020-09-25	SIAT5	160	640	320	320	160	40	320	320	160	
A/Cambodia/e0826360/2020		ESI/E2	2020-07-16	ESI/E2	80	160	1280	320	160	320	320	160	80	
A/Bangladesh/4005/2020		SIAT3	2020-10-04	SIAT3	160	320	320	640	640	640	640	640	320	
A/Stockholm/5/2021		S0/S3	2021-04-16	S0/S3	80	80	80	320	640	320	320	640	40	
A/England/214191723/2021		MDCK1/SIAT3	2021-10-12	MDCK1/SIAT3	40	80	80	160	320	640	640	640	40	
A/Darwin/9/2021		ESI/E4	2021-04-17	ESI/E4	160	80	640	320	640	640	640	1280	80	
A/Kansas/14/2017		SIAT3/SIAT2	2017-12-14	SIAT3/SIAT2	40	80	80	80	160	160	80	80	640	
TEST VIRUSES														
A/Netherlands/0009/2021		Hck1/SIAT1	2021-11-30	Hck1/SIAT1	<	<	40	80	160	320	320	320	<	
A/Netherlands/0103/2021		Hck1/SIAT1	2021-12-13	Hck1/SIAT1	40	<	40	80	160	320	320	320	<	
A/Netherlands/0001/2022		Hck1/SIAT1	2022-01-02	Hck1/SIAT1	160	40	160	160	640	320	320	640	160	
A/Netherlands/0009/2022		Hck1/SIAT1	2022-01-05	Hck1/SIAT1	80	<	80	320	320	160	160	320	80	
A/Netherlands/00110/2021		Hck1/SIAT1	2021-12-22	Hck1/SIAT1	320	160	320	180	160	<	80	80	80	
A/Norway/12347/2022		SIAT3	2022-02-25	SIAT3	80	<	40	320	320	320	320	640	80	
A/Moldova/18402/2022		SIAT1	2022-02-28	SIAT1	40	<	40	80	320	640	320	640	40	
A/Moldova/20035/2022		SIAT1	2022-03-07	SIAT1	80	<	40	320	320	160	160	320	80	
A/Moldova/20046/2022		SIAT1	2022-03-10	SIAT1	40	<	40	80	160	640	640	640	40	
A/Moldova/20813/2022		SIAT1	2022-03-15	SIAT1	160	<	80	320	320	160	320	320	80	
A/Moldova/20838/2022		SIAT1	2022-03-17	SIAT1	40	<	40	80	160	640	640	640	80	
A/Moldova/20837/2022		SIAT1	2022-03-17	SIAT1	40	<	40	80	160	320	320	320	<	
A/Netherlands/10502/2022		MDCk-MIX2/SIAT1	2022-03-24	MDCk-MIX2/SIAT1	80	<	40	80	320	320	320	320	80	
A/Moldova/6662/2022		SIAT1	2022-04-04	SIAT1	160	<	80	320	320	640	640	640	80	
A/Moldova/649/2022		SIAT1	2022-04-05	SIAT1	160	<	80	320	320	640	640	640	80	
A/Netherlands/10884/2022		MDCk-MIX2/SIAT1	2022-04-05	MDCk-MIX2/SIAT1	160	<	80	320	320	320	320	320	160	
A/Netherlands/10866/2022		MDCk-MIX2/SIAT1	2022-04-07	MDCk-MIX2/SIAT1	<	<	<	<	160	80	160	160	<	
A/Moldova/7267/2022		SIAT1	2022-04-11	SIAT1	160	<	80	320	320	640	640	640	80	
A/Moldova/773/2022		SIAT1	2022-04-13	SIAT1	160	<	80	320	320	640	640	640	80	
A/Netherlands/1119/2022		MDCk-MIX2/SIAT1	2022-04-13	MDCk-MIX2/SIAT1	160	<	80	160	320	320	320	640	160	
ALithuania/33816/2022		SIAT1	2022-04-14	SIAT1	40	<	40	80	160	320	320	640	<	
ALithuania/33828/2022		SIAT1	2022-04-14	SIAT1	80	<	40	80	160	320	320	640	<	
A/Netherlands/11201/2022		MDCk-MIX2/SIAT1	2022-04-15	MDCk-MIX2/SIAT1	160	<	80	320	320	320	320	640	160	
A/Moldova/7877/2022		SIAT1	2022-04-19	SIAT1	40	<	40	80	160	640	640	640	<	
A/Netherlands/00832/2022		Hck1/SIAT1	2022-04-19	Hck1/SIAT1	80	<	40	80	160	160	160	160	80	
A/Moldova/7896/2022		SIAT1	2022-04-21	SIAT1	40	<	40	80	160	640	640	640	<	
ALithuania/36119/2022		SIAT1	2022-04-28	SIAT1	160	<	80	320	640	640	640	640	80	
ALithuania/36453/2022		SIAT1	2022-05-02	SIAT1	40	<	40	80	160	320	320	640	<	
ALithuania/36666/2022		SIAT1	2022-05-05	SIAT1	160	<	80	320	320	640	640	640	80	

¹Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used)
1 <= <40, ND = Not Done

Table 5-4. Antigenic analysis of influenza A(H3N2) viruses by HI

Viruses	Other information	Passage history	Collection date	Haemagglutination inhibition titre																
				ADenmark	AHK	A/Camb	A/Camb	A/Bang	A/Stock	A/Eng	A/Darwin	A/Kansas								
REFERENCE VIRUSES																				
ADenmark/326/4/2019		SIAT3/SIAT4	2019-10-25	320	160	640	320	320	160	160	40	320	160	160						
AHong Kong/2671/2019		MDCK1/SIAT4	2019-06-17	320	160	640	320	320	160	160	40	320	160	160						
ACambodia/925256/2020		SIAT5	2020-09-25	160	160	640	320	320	160	160	40	320	160	160						
ACambodia/60926360/2020		ES/E2	2020-07-16	160	<	80	320	1280	160	160	160	160	160	80						
ABangladesh/4005/2020		SIAT3	2020-10-04	160	40	160	320	320	640	640	640	640	640	160						
AStockholm/5/2021		S0/S3	2021-04-16	80	<	80	320	320	640	640	640	640	640	80						
AEngland/2114191/23/2021		MDCK1/SIAT3	2021-10-12	40	<	80	160	160	320	320	640	640	640	40						
ADarwin/9/2021		E3/E4	2021-04-17	160	<	80	640	640	1280	640	640	1280	160	160						
AKansas/14/2017		SIAT3/SIAT2	2017-12-14	40	<	80	80	80	80	80	80	80	640	640						
TEST VIRUSES																				
AJorenburg/5/2022		SIAT1/SIAT1	2022-01-14	160	<	80	320	320	320	320	160	320	320	80						
ABitobjan/1/2/2022		SIAT3/SIAT1	2022-01-20	160	<	80	640	640	640	640	640	1280	160	160						
AfVG-Trieste/05/2022		SIAT2/SIAT1	2022-01-25	80	<	40	80	160	320	320	320	640	40	40						
AParma/2/2022		SIAT4/SIAT1	2022-02-02	40	<	40	160	320	640	640	320	640	40	40						
AfVG-Trieste/1/3/2022		SIAT2/SIAT1	2022-02-15	40	<	40	80	160	320	320	320	640	40	40						
AfVG-Trieste/1/6/2022		SIAT2/SIAT1	2022-02-17	80	<	40	80	160	640	640	320	640	40	40						
AParma/5/1/2022		SIAT3/SIAT1	2022-03-08	160	<	80	640	640	320	320	320	320	160	160						
AMilano/37/2022		SIAT3/SIAT1	2022-03-14	160	<	80	320	320	640	640	640	640	80	80						
AMilano/30/2022		SIAT4/SIAT1	2022-03-14	80	<	40	80	320	640	640	640	1280	80	80						
ABolzano/16/2022		SIAT2/SIAT1	2022-03-14	80	<	40	160	320	320	320	320	320	160	160						
ASassar/1/2/2022		SIAT1/SIAT1	2022-03-16	80	<	40	80	320	640	640	640	640	40	40						
AMilano/3/2/2022		SIAT3/SIAT1	2022-03-16	40	<	40	160	160	320	320	320	640	40	40						
ASassar/4/4/2022		SIAT1/SIAT1	2022-03-29	80	<	40	80	80	320	320	320	640	40	40						
ASassar/7/2022		SIAT1/SIAT1	2022-04-01	40	<	40	80	160	640	640	640	640	40	40						
ASassar/9/2022		SIAT1/SIAT1	2022-04-08	80	<	40	80	160	640	640	640	640	40	40						
APerugia/2/3/2022		SIAT3/SIAT1	2022-04-12	40	<	40	80	80	320	320	320	640	40	40						
ABolzano/21/2/2022		SIAT2/SIAT1	2022-04-13	80	<	40	160	320	320	320	320	640	40	40						
AfVG-Trieste/3/66/2022		SIAT3/SIAT1	2022-04-14	40	<	40	80	160	160	160	160	640	40	40						
AfVG-Trieste/3/81/2022		SIAT3/SIAT1	2022-04-22	40	<	40	80	80	320	320	320	640	40	40						
ABolzano/24/2022		SIAT2/SIAT1	2022-04-29	80	<	40	160	160	640	640	640	640	80	80						
AMilano/11/2/2022		SIAT3/SIAT1	2022-05-03	80	<	40	160	320	320	320	320	640	40	40						
										Vaccine NH 2021-22							Vaccine SH 2022 NH 2022-23			

*Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used)
1 <= <40, ND = Not Done

Table 5-7. Antigenic analysis of influenza A(H3N2) viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre								
				Post-infection ferret antisera								
				A/Denmark	A/HK	A/Camb	A/Camb	A/Bang	A/Stock	A/Eng	A/Darwin	A/Kansas
				3264/19	2671/19	925256/20	e0826360/20	4005/20	5/21	214191723/21	9/21	14/17
SIAT	Cell	SIAT	Egg	SIAT	SIAT	SIAT	Egg	SIAT				
Ferret number												
Genetic group												
REFERENCE VIRUSES												
A/Denmark/3264/2019	3C.2a1b.1a	2019-10-25	SIAT3/SIAT4	320	160	640	320	320	160	40	320	160
A/Hong Kong/2671/2019	3C.2a1b.1b	2019-06-17	MDCK1/SIAT4	320	320	640	160	320	80	40	160	160
A/Cambodia/925256/2020	3C.2a1b.2a.1	2020-09-25	SIAT5	160	160	640	320	320	160	40	320	160
A/Cambodia/e0826360/2020	3C.2a1b.2a.1	2020-07-16	E5/E2	160	<	80	1280	320	160	160	160	80
A/Bangladesh/4005/2020	3C.2a1b.2a.2	2020-10-04	SIAT3	160	40	160	320	640	640	640	640	160
A/Stockholm/5/2021	3C.2a1b.2a.2	2021-04-16	S0/S3	80	<	80	160	320	640	320	640	80
A/England/214191723/2021	3C.2a1b.2a.2	2021-10-12	MDCK1/SIAT3	40	<	80	160	160	320	1280	640	40
A/Darwin/9/2021	3C.2a1b.2a.2	2021-04-17	E3/E4	160	<	80	640	640	1280	640	1280	160
A/Kansas/14/2017	3C.3a.1	2017-12-14	SIAT3/SIAT2	40	<	80	80	80	80	80	80	640
TEST VIRUSES												
A/Slovenia/9362/2022	3C.2a1b.2a.2	2022-03-04	MDCK1/SIAT1	160	<	80	320	320	640	640	640	80
A/Slovenia/9449/2022	3C.2a1b.2a.2	2022-03-08	SIATx/SIAT4	80	<	40	80	160	320	320	320	<
A/Slovenia/9450/2022	3C.2a1b.2a.2	2022-03-08	MDCKx/SIAT1	80	<	40	80	160	320	320	320	40
A/Slovenia/9454/2022	3C.2a1b.2a.2	2022-03-08	SIAT1/SIAT1	40	<	40	40	160	160	160	160	<
A/Slovenia/9456/2022	3C.2a1b.2a.2	2022-03-08	SIATx/SIAT2	80	<	40	80	160	320	320	320	40
A/Slovenia/9528/2022	3C.2a1b.2a.2	2022-03-08	SIATx/SIAT1	160	<	80	320	320	640	640	640	80
A/Slovenia/9448/2022	3C.2a1b.2a.2	2022-03-09	MDCKx/SIAT1	80	<	40	80	160	320	320	320	40
A/Slovenia/9558/2022	3C.2a1b.2a.2	2022-03-10	SIAT1/SIAT1	40	<	40	40	160	160	160	160	<
A/Slovenia/9565/2022	3C.2a1b.2a.2	2022-03-11	SIAT1/SIAT1	80	<	40	80	320	320	320	320	40
A/Slovenia/9560/2022	3C.2a1b.2a.2	2022-03-14	SIAT1/SIAT1	80	<	40	80	160	320	320	320	40
A/Slovenia/9562/2022	3C.2a1b.2a.2	2022-03-14	SIAT1/SIAT1	160	<	80	320	320	640	640	640	80
A/Slovenia/9579/2022	3C.2a1b.2a.2	2022-03-15	SIAT1/SIAT1	160	<	80	320	320	640	640	640	80
A/Slovenia/9599/2022	3C.2a1b.2a.2	2022-03-15	MDCK1/SIAT1	80	<	40	80	160	320	320	320	40
A/Slovenia/9614/2022	3C.2a1b.2a.2	2022-03-17	MDCKx/SIAT1	80	<	40	40	160	320	320	320	<
A/Slovenia/9623/2022	3C.2a1b.2a.2	2022-03-17	MDCKx/SIAT1	40	<	40	40	160	320	320	320	<
A/Slovenia/9624/2022	3C.2a1b.2a.2	2022-03-17	MDCKx/SIAT1	80	<	40	80	160	320	320	320	40
A/Slovenia/9626/2022	3C.2a1b.2a.2	2022-03-17	SIATx/SIAT1	40	<	40	40	160	320	160	320	<
A/Slovenia/9633/2022	3C.2a1b.2a.2	2022-03-21	MDCK1/SIAT1	40	<	40	80	320	320	320	320	40
A/Slovenia/9644/2022	3C.2a1b.2a.2	2022-03-21	MDCKx/SIAT1	40	<	40	40	160	320	160	320	40
A/Slovenia/9641/2022	3C.2a1b.2a.2	2022-03-22	MDCKx/SIAT2	40	<	40	40	160	320	320	320	40
A/Slovenia/9670/2022	3C.2a1b.2a.2	2022-03-22	MDCKx/SIAT1	40	<	40	40	160	320	160	160	40
A/Slovenia/9659/2022	3C.2a1b.2a.2	2022-03-23	SIAT1/SIAT1	80	<	40	80	160	320	320	640	40
A/Slovenia/9668/2022	3C.2a1b.2a.2	2022-03-23	SIATx/SIAT1	80	<	40	80	160	320	320	320	40
A/Slovenia/9706/2022	3C.2a1b.2a.2	2022-03-23	SIATx/SIAT2	40	<	40	40	160	320	160	320	40
A/Slovenia/9707/2022	3C.2a1b.2a.2	2022-03-23	MDCKx/SIAT1	40	<	40	80	160	320	320	320	40
A/Slovenia/9671/2022	3C.2a1b.2a.2	2022-03-24	SIATx/SIAT1	40	<	40	80	160	320	160	320	40
A/Slovenia/9675/2022	3C.2a1b.2a.2	2022-03-24	SIATx/SIAT1	160	<	80	160	320	640	640	640	80
A/Slovenia/9676/2022	3C.2a1b.2a.2	2022-03-24	SIATx/SIAT1	40	<	40	40	160	320	320	320	40
A/Slovenia/9705/2022	3C.2a1b.2a.2	2022-03-24	SIATx/SIAT1	40	<	40	40	160	320	320	320	40
A/Slovenia/9708/2022	3C.2a1b.2a.2	2022-03-24	SIATx/SIAT1	80	<	40	80	160	320	320	320	40
A/Slovenia/9726/2022	3C.2a1b.2a.2	2022-03-25	SIATx/SIAT2	40	<	40	80	160	320	320	320	40
A/Slovenia/9728/2022	3C.2a1b.2a.2	2022-03-25	MDCKx/SIAT1	40	<	40	80	320	320	320	320	40
A/Slovenia/9736/2022	3C.2a1b.2a.2	2022-03-28	SIATx/SIAT2	40	<	40	80	160	320	320	320	40
A/Slovenia/9737/2022	3C.2a1b.2a.2	2022-03-28	MDCKx/SIAT1	40	<	40	40	160	160	320	320	40
A/Slovenia/9739/2022	3C.2a1b.2a.2	2022-03-29	SIAT1/SIAT1	80	<	40	80	160	320	320	320	40
A/Slovenia/9740/2022	3C.2a1b.2a.2	2022-03-29	SIATx/SIAT1	160	<	80	320	320	640	640	640	80
A/Spain/1059/2022	3C.2a1b.2a.2	2022-04-22	SIAT1	40	<	40	40	80	160	320	160	40
A/Spain/1127/2022	3C.2a1b.2a.2	2022-05-03	SIAT1	40	<	40	40	160	320	320	320	40
A/Spain/1097/2022	3C.2a1b.2a.2	2022-05-03	SIAT1	40	<	40	40	160	320	320	320	40
A/Spain/1126/2022	3C.2a1b.2a.2	2022-05-04	SIAT1	40	<	40	80	160	320	320	320	40
A/Spain/1105/2022	3C.2a1b.2a.2	2022-05-04	SIAT1	80	<	40	80	160	320	320	320	40
A/Spain/1100/2022	3C.2a1b.2a.2	2022-05-04	SIAT1	40	<	40	80	160	320	320	320	40
A/Spain/1099/2022	3C.2a1b.2a.2	2022-05-04	SIAT1	80	<	40	80	160	320	320	320	40
A/Spain/1098/2022	3C.2a1b.2a.2	2022-05-04	SIAT1	40	<	40	80	160	320	320	320	40
A/Spain/1091/2022	3C.2a1b.2a.2	2022-05-04	SIAT1	40	<	40	80	160	320	320	320	40
A/Spain/1109/2022	3C.2a1b.2a.2	2022-05-05	SIAT1	80	<	40	80	160	320	320	320	40
A/Spain/1108/2022	3C.2a1b.2a.2	2022-05-05	SIAT1	80	<	40	80	160	320	320	320	40

*Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used)
1 <= <40, ND = Not Done

Vaccine
NH 2021-22

Vaccine
SH 2022
NH 2022-23

Table 5-9. Antigenic analysis of influenza A(H3N2) viruses by HI

Other information	Collection date	Passage history	Haemagglutination inhibition titre								
			Post-infection ferret antisera								
			A/Denmark 3264/19 SIAT	A/HK 2671/19 Cell St Judes F21/20 ¹	A/Camb 925256/20 SIAT	A/Camb e0826360/20 Egg F10/21 ¹	A/Bang 4005/20 SIAT	A/Stock 5/21 SIAT	A/Eng 214191723/21 SIAT	A/Darwin 9/21 Egg F39/21 ¹	A/Kansas 14/17 SIAT
F19/20 ¹	F03/21 ¹	F07/21 ¹	F35/21 ¹	F07/22 ¹	F39/21 ¹	F17/19 ¹					
Passage history	Genetic group	3C.2a1b.1a	3C.2a1b.1b	3C.2a1b.2a.1	3C.2a1b.2a.1	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.3a.1	
3C.2a1b.1a	2019-10-25	SIAT3/SIAT4	640	160	640	320	320	160	40	320	160
3C.2a1b.1b	2019-06-17	MDCK1/SIAT4	320	640	640	160	320	80	40	160	160
3C.2a1b.2a.1	2020-09-25	SIAT5	160	160	640	320	320	160	40	320	160
3C.2a1b.2a.1	2020-07-16	E5/E2	160	<	80	2560	320	160	160	160	80
3C.2a1b.2a.2	2020-10-04	SIAT3	160	40	160	320	640	640	640	640	160
3C.2a1b.2a.2	2021-04-16	SIAT0/SIAT3	80	<	80	160	320	640	320	640	80
3C.2a1b.2a.2	2021-10-12	MDCK1/SIAT3	40	<	80	160	160	320	640	640	40
3C.2a1b.2a.2	2021-04-17	E3/E4	160	<	80	640	640	1280	640	2560	160
3C.3a.1	2017-12-14	SIAT3/SIAT2	40	<	80	80	80	80	80	80	320
3C.2a1b.2a.2	2021-12-22	SIAT2	80	<	<	160	320	640	640	640	40
3C.2a1b.2a.2	2022-02-22	SIAT2	80	<	40	160	320	640	320	640	40
3C.2a1b.2a.2	2022-03-05	SIAT1/SIAT1	40	<	40	80	160	320	640	320	<
3C.2a1b.2a.2	2022-03-09	SIAT1/SIAT2	80	80	80	80	160	320	320	640	40
3C.2a1b.2a.2	2022-03-10	SIAT1/SIAT2	40	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-03-14	SIAT1	80	<	40	80	320	320	320	320	<
3C.2a1b.2a.2	2022-03-14	SIAT1	40	<	40	80	320	320	320	320	<
3C.2a1b.2a.2	2022-03-15	Px/SIAT2	80	<	40	80	160	320	320	640	<
3C.2a1b.2a.2	2022-03-15	Px/SIAT2	40	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-03-16	Px/SIAT2	80	<	40	80	320	320	320	640	<
3C.2a1b.2a.2	2022-03-16	Px/SIAT2	40	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-03-18	SIAT1/SIAT2	80	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-03-21	SIAT1	80	<	40	80	320	640	640	640	<
3C.2a1b.2a.2	2022-03-22	SIAT1/SIAT2	80	<	40	80	160	320	320	640	<
3C.2a1b.2a.2	2022-03-23	SIAT1/SIAT2	80	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-03-23	SIAT1/SIAT1	80	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-03-23	SIAT1/SIAT1	80	<	40	160	160	160	320	320	40
3C.2a1b.2a.2	2022-03-24	SIAT1	40	<	40	160	160	320	640	320	40
3C.2a1b.2a.2	2022-03-25	SIAT1/SIAT1	40	<	40	40	160	320	160	320	<
3C.2a1b.2a.2	2022-03-25	SIAT1/SIAT1	160	<	80	160	320	320	320	320	80
3C.2a1b.2a.2	2022-03-25	SIAT1/SIAT1	80	<	40	80	320	160	160	160	40
3C.2a1b.2a.2	2022-03-26	SIAT1/SIAT1	40	<	40	80	80	160	320	320	<
3C.2a1b.2a.2	2022-03-26	SIAT1/SIAT1	80	<	40	80	160	160	160	320	40
3C.2a1b.2a.2	2022-03-28	SIAT1/SIAT1	80	<	40	80	320	320	160	160	80
3C.2a1b.2a.2	2022-03-28	SIAT1/SIAT1	<	<	40	40	80	160	320	320	<
3C.2a1b.2a.2	2022-03-28	SIAT1/SIAT1	40	<	40	40	160	320	320	320	<
3C.2a1b.2a.2	2022-03-30	SIAT1	80	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-03-30	SIAT1/SIAT1	40	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-03-31	Px/SIAT2	40	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-03-31	SIAT1/SIAT1	40	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-04-01	SIAT1/SIAT1	40	<	40	80	160	320	320	640	40
3C.2a1b.2a.2	2022-04-02	SIAT1/SIAT1	40	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-04-04	SIAT1/SIAT1	80	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-04-04	SIAT1/SIAT1	80	<	40	160	320	320	320	160	80
3C.2a1b.2a.2	2022-04-04	SIAT1/SIAT1	160	<	40	320	320	640	640	640	80
3C.2a1b.2a.2	2022-04-05	SIAT2/SIAT1	40	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-04-05	SIAT1/SIAT1	80	<	40	320	320	160	160	160	80
3C.2a1b.2a.2	2022-04-06	SIAT1	160	<	80	320	320	640	640	640	80
3C.2a1b.2a.2	2022-04-06	SIAT1/SIAT2	40	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-04-06	SIAT1/SIAT1	80	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-04-06	SIAT1/SIAT1	40	<	40	80	160	320	320	640	<
3C.2a1b.2a.2	2022-04-06	SIAT1/SIAT1	80	<	40	80	160	160	160	320	<
3C.2a1b.2a.2	2022-04-07	SIAT1/SIAT1	80	<	40	160	320	640	320	640	40
3C.2a1b.2a.2	2022-04-13	SIAT2	160	<	80	320	320	320	640	640	80
3C.2a1b.2a.2	2022-04-13	SIAT1	40	<	40	40	160	160	320	320	<
3C.2a1b.2a.2	2022-04-14	SIAT1	<	<	40	80	160	160	640	640	<
3C.2a1b.2a.2	2022-04-14	SIAT1	40	<	40	40	160	160	320	320	<
3C.2a1b.2a.2	2022-04-18	SIAT1/SIAT1	80	<	40	80	160	640	320	640	40
3C.2a1b.2a.2	2022-04-18	SIAT1/SIAT1	40	<	40	80	160	320	320	320	<
3C.2a1b.2a.2	2022-04-18	SIAT2/SIAT1	40	<	40	40	160	160	640	320	<
3C.2a1b.2a.2	2022-04-23	SIAT1	80	<	40	80	160	320	320	320	<

parties (< relates to the lowest dilution of antiserum used)

Vaccine
NH 2021-22

Vaccine
SH 2022
NH 2022-23

Table 5-10. Antigenic analysis of influenza A(H3N2) viruses by HI - Summary

Viruses	Haemagglutination inhibition titre													
	Passage history							Post-infection ferret antisera						
Passage history	A/Denmark	A/HK	A/Camb	A/Camb	A/Bang	A/Stock	A/Eng	A/Darwin	A/Slo	A/Slo	A/Slo	A/Slo	A/Wyom	A/Kansas
Passage history	326/19	2671/19	925256/20	e0826360/20	4005/20	5/21	214191723/21	9/21	8720/22	9218/22	9318/22	01/21	14/17	
Ferret number	F19/20 ¹	St. Jude's F21/20 ¹	F03/21 ¹	F10/21 ¹	F07/21 ¹	F35/21 ¹	F07/22 ¹	F39/21 ¹	F25/22 ¹	F26/22 ¹	F27/22 ¹	F20/22 ¹	F17/19 ¹	
Genetic group	3C.2a1b.1a	3C.2a1b.1b	3C.2a1b.2a.1	3C.2a1b.2a.1	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.3a.1	
REFERENCE VIRUSES														
A/Denmark/326/4/2019	320	160	640	320	320	160	40	320	40	<	<	<	<	160
A/Hong Kong/2671/2019	320	320	640	160	320	80	40	160	40	<	<	<	<	160
A/Cambodia/925256/2020	160	160	1280	320	320	160	40	320	40	<	<	<	<	160
A/Cambodia/e0826360/2020	160	<	80	1280	320	160	160	160	80	80	80	40	40	80
A/Bangladesh/4005/2020	160	40	160	320	640	640	640	640	320	160	160	80	80	160
A/Stockholm/5/2021	80	<	80	160	320	640	320	640	320	160	320	320	80	80
A/England/214191723/2021	40	<	80	160	160	320	640	640	320	160	160	160	160	40
A/Darwin/9/2021	160	160	80	640	640	1280	640	1280	1280	320	640	640	640	160
A/Slovenia/8720/2022	160	<	80	320	320	640	640	640	640	320	640	ND	ND	80
A/Slovenia/9216/2022	80	<	40	320	320	320	320	640	640	320	640	ND	ND	80
A/Slovenia/9318/2022	160	<	80	640	320	640	640	640	1280	640	640	640	640	80
A/Wyoming/01/2021	160	<	80	320	320	640	160	1280	ND	ND	ND	1280	80	80
A/Kansas/14/2017	40	<	80	80	80	80	80	80	<	<	80	<	<	640
TEST VIRUSES														
Number tested	396	396	396	396	396	396	396	396	11	11	11	10	396	0
No. with titre reduction ≤2-fold	54	0	0	8	143	329	256	176	9	9	8	2	0	0
%	13.6	0	0	2.1	36.1	83.1	64.6	44.4	81.8	81.8	72.7	20.0	0	0
No. with titre reduction =4-fold	183	0	5	37	247	66	129	126	1	1	1	8	24	24
%	46.2	0	1.3	9.3	62.4	16.7	32.6	31.8	9.1	9.1	9.1	80.0	6.1	6.1
No. with titre reduction ≥8-fold	159	396	391	351	6	1	11	94	1	1	2	0	372	372
%	40.2	100	98.7	88.6	1.5	0.2	2.8	23.8	9.1	9.1	16.2	0	93.9	93.9
Number tested	3	3	3	3	3	3	3	3	3	3	3	3	3	3
No. with titre reduction ≤2-fold	3	3	3	2	2	0	0	0	0	0	0	0	0	0
No. with titre reduction =4-fold	0	0	0	0	1	3	0	0	0	0	0	0	0	0
No. with titre reduction ≥8-fold	0	0	0	1	0	0	3	3	0	0	0	0	0	3
*Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used)														
1 <= <40, ND = Not Done														
Reference virus results are taken from an individual table as an example. Summaries for each antiserum are based on fold-reductions observed on the days that HI assays were performed.														
Vaccine SH 2022 NH 2022-23														
Vaccine NH 2021-22														

Influenza B virus analyses

Influenza B/Victoria-lineage

All recently circulating B/Victoria-lineage viruses have fallen in genetic clade **V1A**, represented by **B/Brisbane/60/2008**, a former vaccine virus, but with additional **HA1** amino acid substitutions of **I117V** and **N129D** (e.g., **B/Ireland/3154/2016**). Viruses retaining full-length HAs remained antigenically similar to B/Brisbane/60/2008. However, three genetic groups (described below with amino acid substitutions/deletions relative to B/Brisbane/60/2008 indicated) containing deletions of HA gene codons emerged. Viruses in these groups were/are antigenically distinct from B/Brisbane/60/2008 and each other (as noted in the September 2018 characterization report⁴ and earlier ones), such that four antigenically distinguishable groups had been circulating:

- A group with double deletion of **HA1** residues **162** and **163** (subclade **V1A.1**) with amino acid substitutions of **D129G** and **I180V**, and **HA2 R151K** that spread worldwide and is represented by a previous vaccine virus, **B/Colorado/06/2017**. No detections of viruses in this group have been reported recently.
- A group with triple deletion of **HA1** residues **162** to **164** (subclade **V1A.2**) first detected in Asia, with amino acid substitutions of **I180T** and **K209N** that showed limited geographic spread, represented by **B/Hong Kong/269/2017**. No detections of viruses in this group have been reported recently.
- A group with triple deletion of **HA1** residues **162** to **164** (subclade **V1A.3**) first detected in Africa, with amino acid substitution **K136E** often with **G133R** that showed geographic spread and became dominant, represented by **B/Washington/02/2019** the vaccine virus recommended after the WHO VCM in February 2021 [1].

The phylogeny generated for the June report, based on sequences from viruses with collection dates after 31 December 2021, contained just 21 new sequences that were submitted to GISAID after May of 2022 (Figure 4a). All viruses were **V1A.3** subclade represented by **B/Washington/02/2019**. Overall, the great majority of viruses fell in the **V1A.3a** group characterized by **HA1 N150K**, **G184E**, **N197D** (resulting in loss of a glycosylation site) and **R279K**, with this group splitting into two subgroups designated **V1A.3a.1** (characterized by **HA1 V220M** and **P241Q** substitutions, detected in China) and **V1A.3a.2** (characterized by **HA1 A127T**, **P144L** and **K203R**, often with additional substitutions, which has spread worldwide and is represented by the **B/Austria/1359417/2021** vaccine virus). Sequences submitted by the Netherlands split between the **V1A.3a.2** subgroup and subclade **V1A.3**, with the latter viruses being similar to those from Kenya having **HA1 K75E**, **E128K**, **T155A** and **G230N** substitutions, but with an additional **HA1 G184R** substitution sometimes with **D129N** (Figure 4a). **V1A.3** viruses from Guatemala had **HA1 T73I** and **N233K** (resulting in loss of a glycosylation site) substitutions. Among the **V1A.3a.2** subgroup viruses a cluster of five viruses reported by Luxembourg appeared to have 'repaired' the three amino acid deletion at **HA1** residues **162** to **164** (Figure 4a), something that has not been confirmed at the WIC.

The phylogeny generated for this report contains mostly recently released HA sequences, but for those from the Netherlands, and shows a similar profile (Figure 4b). All but one of the recently submitted/released sequences fall in the **V1A.3a.2** subgroup with a batch of sequences from China carrying **HA1 H122Q** amino acid substitution. HA sequence for a single **V1A.3a.1** subgroup virus, detected in China in May, was released. No sequences from subclade **V1A.3** viruses were released since the June report, possibly indicating that viruses in this subclade with **HA1 G184R** amino acid substitution have not been detected outside of the Netherlands.

The WHO Collaborating Centres for Influenza Research and Response have shown the **V.1A.3a** group viruses with additional **HA1** substitutions to be antigenically distinct from one another. While relatively few B/Victoria-lineage viruses have been available for detailed antigenic characterization, those characterized earlier in the 2021-2022 season were subgroup **V1A.3a.2** viruses which were recognised poorly by post-infection ferret antiserum raised against **B/Washington/02/2019**, the 2021-2022 northern hemisphere vaccine virus [1]. However, the **V1A.3a.2** viruses were recognised well (with HI titres of at least 320 with the antiserum raised against the egg-propagated variant with **HA1 G141R** substitution) by antisera raised against **B/Austria/1359417/2021**, the recommended vaccine virus for southern hemisphere 2022 and northern hemisphere 2022-2023 influenza seasons [2, 3]. This was observed for the 45 subgroup **V1A.3a.2** viruses characterized antigenically since the June report (Tables 6-1 and 6-2). All but one test virus were recognised well, within twofold of the homologous titres, by post-infection ferret antisera raised against cell culture-propagated and egg-propagated **B/Austria/1359417/2021** viruses carrying **HA1 G141**. B/FVG-Trieste/01/2022 had a **HA1 E184K** amino acid substitution and showed fourfold reductions compared to the homologous titres. In contrast, the **B/Austria/1359417/2021** vaccine virus, which

⁴ Influenza virus characterisation, summary Europe, September 2018. Stockholm: European Centre for Disease Prevention and Control; 2018. (<https://ecdc.europa.eu/sites/portal/files/documents/ECDC-Flu-Characterisation-Report-Sep-2018.pdf>, accessed 19 October 2022).

has an 'egg-adaptation' **HA1 G141R** amino acid substitution induced a high homologous titre (5120) antiserum and all test viruses showed a drop in recognition of at least eightfold compared to the homologous titre, but all test viruses (including B/FVG-Trieste/01/2022) reacted with a titre of at least 160, well above the threshold of 40 that has been determined as the cut-off for a protective effect. The eight subclade **V1A.3** viruses from the Netherlands, all of which contained a **HA1 G184R** amino acid substitution, were not recognised by any of the post-infection ferret antisera, and were poorly recognised by the hyperimmune sheep serum raised against B/Brisbane/60/2008.

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 is GISAID as of 15 August 2022. Figure 5 is repeated from the September 2021 report. All sequences fell in genetic clade **Y3**, the B/Wisconsin/1/2010–B/Phuket/3073/2013 clade, within a subgroup defined by **HA1 L172Q** and **M251V** amino acid substitutions compared to B/Phuket/3073/2013 which is recommended for inclusion in quadrivalent vaccines for the 2021-2022 northern, 2022 southern and 2022-2023 northern hemisphere seasons [1, 2, 3]. Some sub-clustering of sequences, defined by specific amino acid substitutions (e.g., **HA1 N164K**, **K211R**, **D229N** or **D232N** [introducing a potential N-linked glycosylation site] sometimes with **R48K**), had occurred. As noted in previous characterization reports, none of these amino acid substitutions have any obvious antigenic effects based on HI assays using post-infection ferret antisera raised against egg-propagated B/Phuket/3073/2013. Of the four samples shared with WIC by the United Kingdom (Scotland: Table 3) only one yielded good sequence which showed it to be associated with Live Attenuated Influenza Vaccine (LAIV).

A concerted 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.

Figure 4a. Phylogenetic comparison of B/Victoria-lineage HA genes (GISAID/WIC, June 2022)

Vaccine viruses
Reference viruses

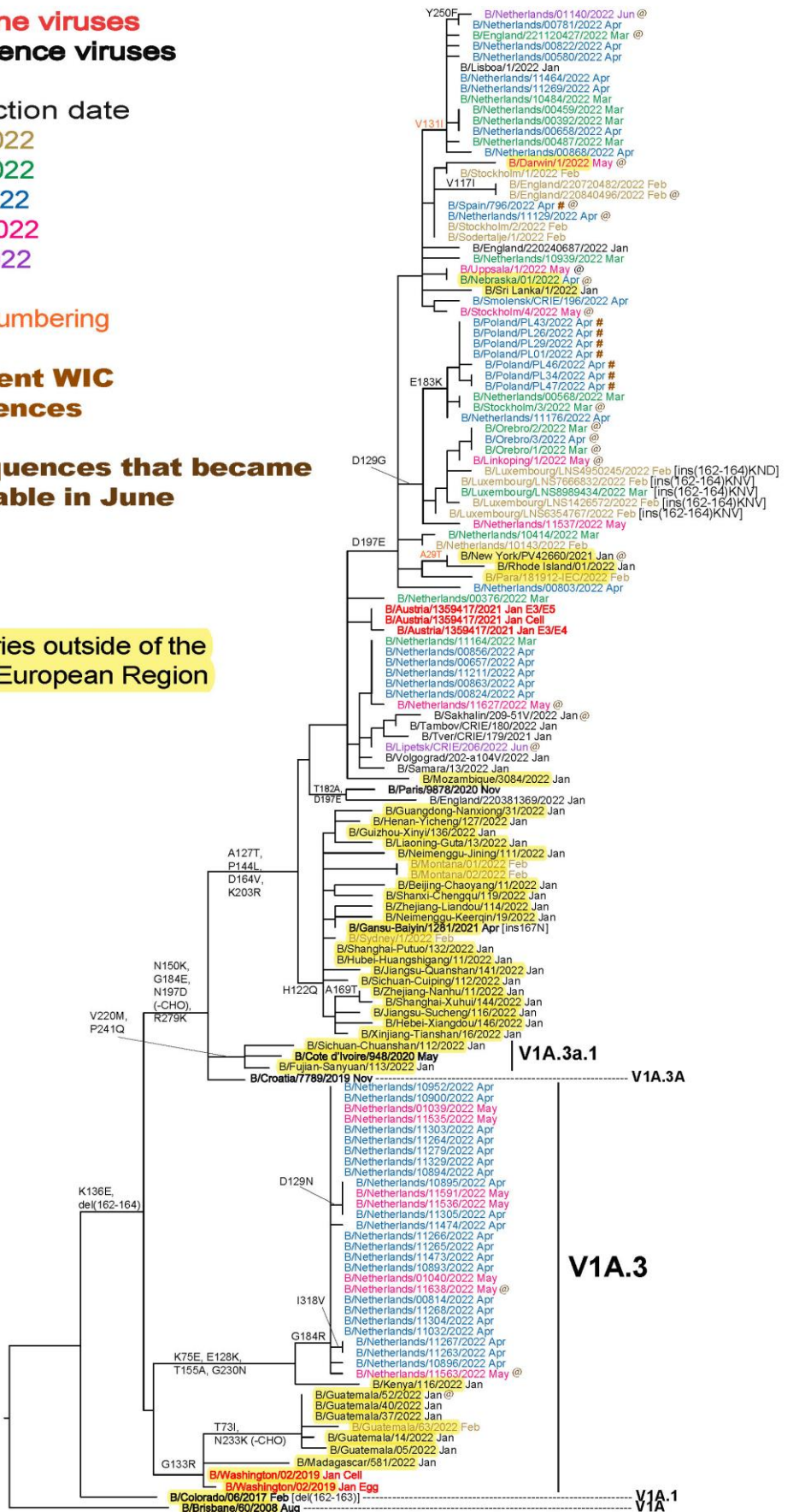
Collection date
Feb 2022
Mar 2022
Apr 2022
May 2022
Jun 2022

HA2 numbering

recent WIC sequences

@ sequences that became available in June

Countries outside of the WHO European Region



V1A.3a.2

V1A.3a.1

V1A.3A

V1A.3

V1A.1

0.07

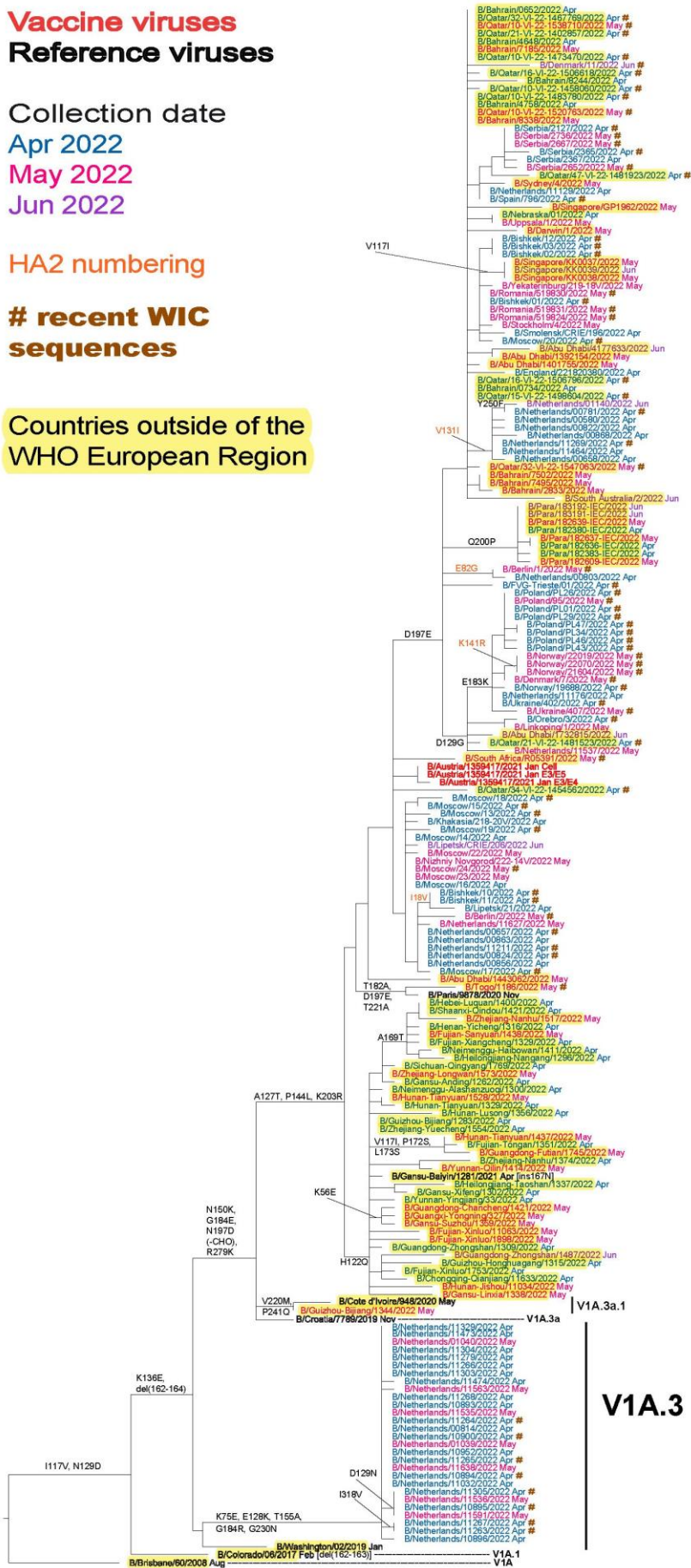
Figure 4b. Phylogenetic comparison of B/Victoria-lineage HA genes (GISAID/WIC, July 2022)

Vaccine viruses
Reference viruses

Collection date
Apr 2022
May 2022
Jun 2022

HA2 numbering
recent WIC sequences

Countries outside of the WHO European Region



V1A.3a.2

V1A.3

Table 6-2. Antigenic analysis of influenza B/Victoria-lineage viruses by HI

Viruses	Other information	Passage history	Collection date	Passage history	Haemagglutination inhibition titre										
					Post-infection ferret antiserum					NEW					
					B/CIV 948/20 MDCK	B/Paris 9878/20 MDCK	B/G-Baiyin 1281/21 MDCK	B/Stock 3/22 MDCK	B/Austria 13594/17/21 MDCK	B/Austria 13594/17/21 Egg G141R	B/Austria 13594/17/21 Egg G141R				
					F08/21 ⁵	F12/21 ¹	F08/22 ¹	F28/22 ¹	NIB F01/21 ¹	F15/21 ¹	F44/21 ¹	V1A.3a.1	V1A.3a.2	V1A.3a.2	V1A.3a.2
					V1A	V1A.1	V1A.3	V1A.3	V1A.3	V1A.3a.1	V1A.3a.2	V1A.3a.2	V1A.3a.2	V1A.3a.2	V1A.3a.2
REFERENCE VIRUSES															
B/Brisbane/60/2008		E4/E4	2008-08-04		1280	80	80	80	80	<	<	<	<	<	<
B/Colorado/06/2017		E5/E2	2017-02-05		1280	320	80	80	80	<	<	<	<	<	<
B/Washington/02/2019		E3/E3	2019-01-19		640	80	160	80	80	<	<	<	<	<	<
B/Cote d'Ivoire/948/2020		MDCK4	2020-05-28		160	20	10	10	80	320	40	80	80	80	80
B/Paris/9878/2020		MDCK2	2020-11-20		320	80	80	80	640	640	640	640	640	640	320
B/Gansu-Baiyin/1281/2021		C1/C1/MDCK2	2021-04-13		320	20	20	20	320	320	320	320	320	320	320
B/Stockholm/3/2022	D197E, D126G, E183K	SIAT1/MDCK2	2022-03-22		320	80	10	80	640	640	640	1280	640	640	320
B/Austria/1359417/2021		SIAT1/MDCK4	2021-01-09		320	20	20	20	80	320	320	640	640	640	320
B/Austria/1359417/2021 Isolate 2	G141	E3/E5	2021-01-09		320	20	20	20	160	640	640	640	2560	1280	640
B/Austria/1359417/2021 Isolate 2	G141R	E3/E5	2021-01-09		320	20	20	20	160	320	320	640	1280	1280	2560
TEST VIRUSES															
B/Bishkek/04/2022		MDCK2	2022-03-09		640	20	20	20	80	640	640	640	640	640	640
B/Bishkek/05/2022		MDCK2/MDCK1	2022-03-11		640	80	80	80	80	640	640	1280	640	640	320
B/Bishkek/06/2022		MDCK2/MDCK1	2022-03-17		640	80	10	10	160	640	640	2560	1280	1280	640
B/Bishkek/07/2022		MDCK2/MDCK1	2022-03-17		640	80	10	10	160	640	640	1280	1280	1280	640
B/Spain/796/2022		MDCK1	2022-04-07		640	80	40	40	80	640	640	1280	640	640	320
B/FYG-Trieste/01/2022		MDCK3/MDCK1	2022-04-15		640	40	40	40	320	320	320	640	320	320	160
B/Poland/95/2022		MDCK1	2022-05-07		640	40	40	40	80	640	640	640	640	640	320
B/Denmark/7/2022		MDCK2/MDCK1	2022-05-16		640	40	40	40	320	320	320	640	640	640	320
B/Romania/519831/2022		MDCK2	2022-05-26		640	80	40	40	80	640	640	1280	640	640	320
B/Romania/519824/2022		MDCK3	2022-05-26		640	40	40	40	80	640	640	1280	640	640	320
B/Denmark/11/2022		MDCK2/MDCK1	2022-06-13		640	40	40	40	80	320	320	640	640	640	320
												Vaccine SH 2020	Vaccine SH 2022		
												NH 2020-21	NH 2022-23		
												SH 2021	NH 2021-22		

* Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used);
¹ < = <20; ² < = <10; ³ hyperimmune sheep serum; ⁴ < = <20; ⁵ < = <80; ND = Not Done

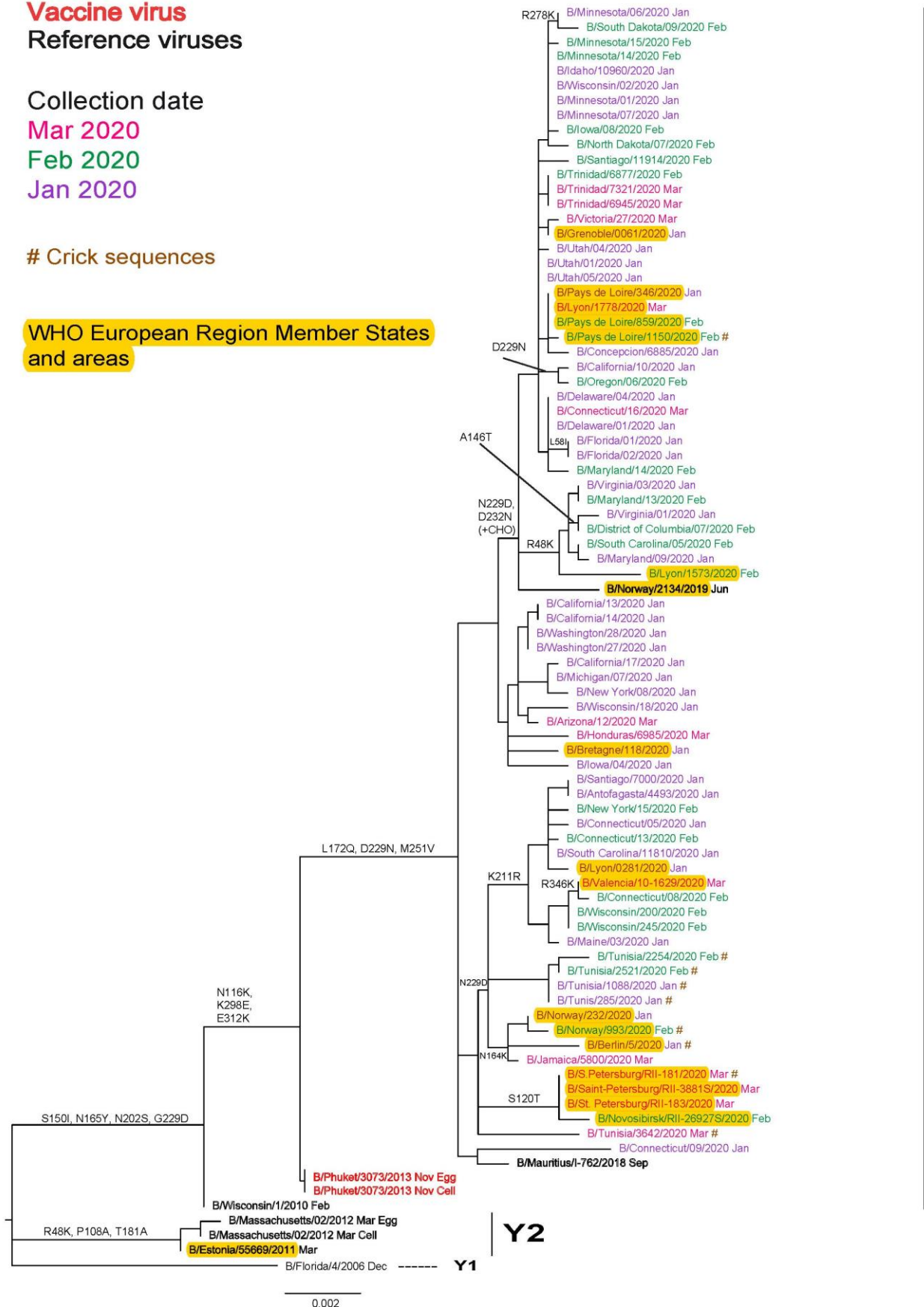
Figure 5. Phylogenetic comparison of B/Yamagata-lineage HA genes (GISAID, September 2021)

Vaccine virus
Reference viruses

Collection date
Mar 2020
Feb 2020
Jan 2020

Crick sequences

WHO European Region Member States and areas



Y3

Y2

Y1

0.002

Summaries of data submitted to TESSy

Genetic characterization

5 007 viruses detected over the course of the 2021-2022 season (weeks 40/2021-30/2022) were genetically characterized:

- Of 383 A(H1N1)pdm09 viruses, 351 belonged to clade 6B.1A.5a.1 (represented by A/Guangdong-Maonan/SWL1536/2019) and 31 belonged to clade 6B.1A.5a.2 (represented by A/Victoria/2570/2019). One was not attributed to a clade.
- Of 4 527 A(H3N2) viruses, 4 476 belonged to the 'Bangladesh-like' clade (3C.2a1b.2a.2) represented by A/Bangladesh/4005/2020, three to the 'Cambodia-like' clade (3C.2a1b.2a.1) and 20 were attributed to clade 3C.2a1b.1a (represented by A/Denmark/3264/2019). Twenty-eight were not attributed to a listed subgroup.
- Of 97 influenza B viruses, 88 were ascribed to the B/Victoria-lineage.

Antiviral susceptibility

Up to week 20/2022, 2 547 viruses were assessed for susceptibility to neuraminidase inhibitors (NAIs): 1 715 A(H3), 258 A(H1)pdm09 and 54 B virus were assessed genotypically, and 476 A(H3), 31 A(H1)pdm09 and 13 B viruses were assessed phenotypically. Susceptibility to the PA inhibitor baloxavir marboxil was assessed genotypically for 1 792 viruses: 1 528 A(H3), 227 A(H1)pdm09 and 37 B viruses. For weeks 21-30/2022 a further 18 viruses were assessed for susceptibility to NAIs and baloxavir marboxil. Phenotypically no viruses with reduced susceptibility were identified. Genotypically, two A(H3) viruses showed PA amino acid substitutions potentially associated with reduced susceptibility to baloxavir marboxil and one A(H1)pdm09 virus with potential highly reduced inhibition by oseltamivir was identified.

At the WIC, 977 influenza viruses detected within the WHO European Region during the 2021-2022 season have been assessed phenotypically against oseltamivir and zanamivir: 136 A(H1)pdm09, 763 A(H3) and 78 B/Victoria-lineage. All viruses showed normal inhibition (NI) by both NAIs and PA gene sequences from two A(H3) viruses had markers (amino acid substitutions) associated with reduced susceptibility to baloxavir marboxil, E23G and L28P respectively.

Animal influenza and zoonotic events

Influenza A(H7N9) virus

On 1 April 2013, the WHO Global Alert and Response System [4] reported that the China Health and Family Planning Commission had notified WHO of three cases of human infection with influenza A(H7N9). Increased numbers of cases were reported over the course of the following seasons, and cases were reported in 2017, including the fifth (2016-17) and largest wave to date, which included the emergence of highly pathogenic avian influenza (HPAI) strains that have caused some zoonoses, although few human cases were reported during the 2017-18 season [5]. Current risk assessments for influenza at the human-animal interface can be found on WHO's website <https://www.who.int/teams/global-influenza-programme/avian-influenza/monthly-risk-assessment-summary> (accessed 22 August 2022). The assessment published on 27 June 2022 indicated that there had been no publicly available reports from animal health authorities in China or other countries on influenza A(H7N9) virus detections in animals in recent months [6]. On 01 June 2022 the Food and Agricultural Organization of the United Nations announced that it was discontinuing monthly H7N9 updates as there had been no notifications of avian infections since October 2020. The most recent human case was detected in mid-March 2019 [7]. The latest overview of avian influenza by ECDC in collaboration with the European Food Safety Authority and the EU Reference Laboratory for Avian Influenza was approved on 30 June 2022 and can be found on ECDC's website [8].

Influenza A(H5) virus

The most recent monthly risk assessment of influenza at the human-animal interface was published by WHO on 27 June 2022. Since the previous risk assessment on 13 May 2022, two human cases of infection with A(H5N6) avian influenza viruses were reported by China [6]. The first case was in a 49-year-old male with underlying medical conditions who had disease onset on 16 April 2022, was hospitalised with severe pneumonia and passed away on 24 April. The second case was in a 58-year-old male who had disease onset on 02 June 2022, was hospitalised with severe pneumonia and was still in a severe condition at the

time of reporting. Both patients reported exposure to poultry at live poultry markets. The most recent confirmed case of human infection with an A(H5N1) virus was reported by England and a full report into the investigation of this case has been published [9].

The latest collaborative report from ECDC and the European Food Safety Authority (EFSA), reported 1 182 highly pathogenic avian influenza (HPAI) A(H5) detections between 16 March and 10 June 2022, 750 in poultry, 410 in wild birds and 22 in domestic birds [8]. Detections occurred in 28 EU/EEA countries and the United Kingdom. Of the poultry outbreaks 68% were reported by France and 24% by Hungary, while other affected countries accounted for less than 2% each. Majorities of wild bird detections were reported by Germany (n=158), the Netherlands (n=98), and the United Kingdom (n=48). Genetic analyses indicated that the circulating viruses belonged to clade 2.3.4.4b, with such viruses having been circulating in Europe since October 2020. The risk of human infection was assessed as low for the general population in EU/EEA countries, and low to medium for occupationally exposed persons. According to reports compiled by the Food and Agricultural Organization of the United Nations (FAO) as of 27 July 2022, various highly pathogenic avian influenza (HPAI) subtypes continued to be detected in wild and/or domestic birds in Africa, Americas, Asia and Europe, and since 22 June 2022 a total of 739 HPAI outbreaks (six H5Nx, 721 H5N1, three H5N2, eight H5N5 and one H5N8) and no low pathogenic avian influenza (LPAI) outbreaks had been reported [10].

Influenza A(H9N2) virus

Since the previous WHO risk assessment on 13 May 2022, China reported three cases of H9N2 infection in children (one, two and five years of age) all of whom had mild disease, were not hospitalized, and made full recoveries [6]. In one case poultry exposure was reported and investigations were taking place to identify sources of infection for the other two cases. Public Health England has published an updated risk assessment for avian influenza A(H9N2) [11]. Avian influenza A(H9N2) viruses are enzootic in poultry in Asia and increasingly reported in poultry in Africa.

Other influenza zoonotic events

Since the previous WHO update on 13 May 2022 an additional case of zoonotic infection with an avian A(H3N8) virus was reported by China involving a five-year-old boy who developed mild symptoms on 09 May 2022, did not require hospitalization and recovered. The boy had attended a live poultry market (without direct poultry contact) prior to illness onset and clinical observation, with sampling, revealed no infections or symptoms of illness in the patient's close contacts. Avian influenza A(H3N8) viruses are commonly detected in domestic and wild birds globally, but environmental samples from the poultry market were negative for A(H3) viruses.

WHO Collaborating Centre reports

A description of results generated by the London WHO Collaborating Centre at the WIC and used at the February 2022 WHO VCM (21-25 February 2022 for seasonal influenza viruses), and previous ones, can be found at <https://www.crick.ac.uk/partnerships/worldwide-influenza-centre/annual-and-interim-reports> (accessed 22 August 2022).

Note on the figures

The phylogenetic trees were constructed using [RAxML](#), drawn using [FigTree](#), and annotated using Adobe Illustrator. The bars indicate the proportion of nucleotide changes between sequences. Reference strains are viruses to which post-infection ferret antisera have been raised. The colours indicate the month(s) of sample collection. Sequences for many viruses from non-WHO Europe countries were recovered from the GISAID EpiFlu™ database. We gratefully acknowledge the authors, originating and submitting laboratories of the sequences from the GISAID EpiFlu™ database, which were downloaded for use in the preparation of this report (all submitters of data may be contacted directly via the [GISAID website](#)), along with all laboratories who submitted sequences directly to WHO CC London.

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⁵ All references except reference 10 accessed 14 September 2022.



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