

Influenza virus characteristics and update from the September 2022 Vaccine Composition Meeting

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Number of specimens positive for influenza by type/subtype/lineage

Number of virus detections BY WEEK START DATE (ISO), VIRUS TYPE NAME

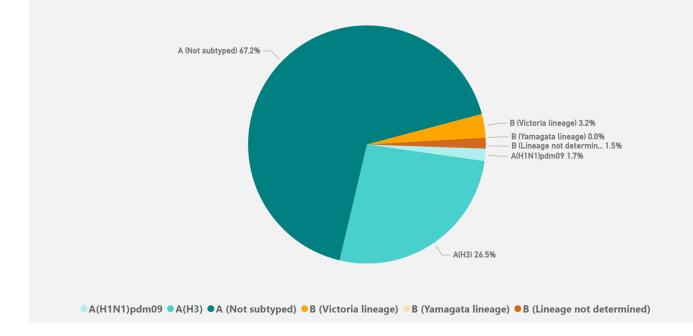
50,000 40,000 30.000 20,000 10,000 0 Jan 2020 Jul 2020 Jul 2021 Jan 2022 Jul 2022 Jan 2021 Week start date (ISO)

Virus type name
A(H1N1)pdm09 A(H3) A (Not subtyped) B (Victoria lineage) B (Vamagata lineage) B (Lineage not determined) A(H1) A(H5)





Percentage of influenza A viruses by type/subtype/lineage (Feb-Aug 22)



Data source: FluNet, (<u>www.who.int/flunet</u>), Global Influenza Surveillance and Response System (GISRS)





Countries, areas and territories that shared viruses with WHO CCs (Feb – Aug 2022)

Countries, areas and territories sharing specimens with WHO Collaborating Centres (WHO CCs) from February to August 2022



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: WHO CC reports for the WHO influenza vaccine composition consultation in September 2022 Map Production: WHO Global Influenza Programme World Health Organization



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Figure 1. Countries Sharing Influenza-positive Samples Collected after 2022-01-31 with FCI-WIC.

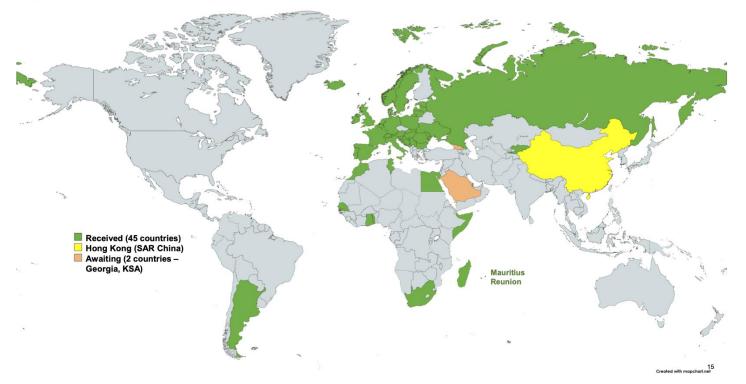
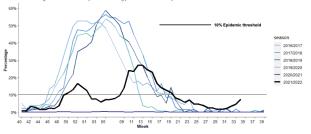




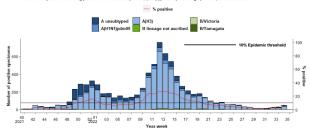


Figure E2. Seasonal influenza activity in the WHO European Region: weeks 40/2021-34/2022

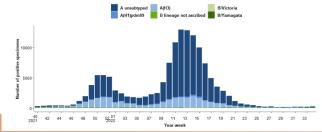
A. Percentage of sentinel ILI/ARI specimens testing positive for influenza by season



B. Sentinel specimens testing positive for influenza by week, (sub)type and percentage positive, 2021/22 season



C. Non-sentinel specimens testing positive for influenza by week, (sub)type and percentage positive, 2021/22 season

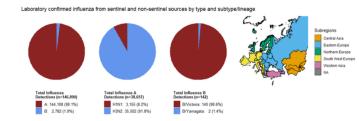






Distribution of viruses

Table E2. Distribution of Influenza Detections in the WHO European Region^a, weeks 40/2021-34/2022



a WHO European Region Member States grouped into sub-regions according to United Nations geographic composition. Available from: (http://unstats.un.org/UNSD/METHODS/M49/M49REGIN.HTM)

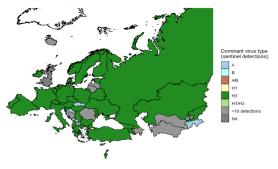
A. Laboratory confirmed influenza from sentinel and non-sentinel sources by geographic sub-region and influenza type and subtype/lineage

	-					•			
Influenza type	South West Europe	Western Europe	Eastern Europe	Northern Europe	West Asia	Central Asia	WHO European Region		
Influenza A	26,314 (99%)	47,327 (99%)	12,029 (96%)	56,711 (97%)	1,473 (100%)	254 (90%)	144,108 (98%)		
Influenza A subtyped	10,263	7,410	9,226	10,053	1,472	233	38,657		
A(H1N1)pdm09	186 (2%)	2,545 (34%)	42 (0%)	381 (4%)	1 (0%)	0 (0%)	3,155 (8%)		
A(H3N2)	10,077 (98%)	4,865 (66%)	9,184 (100%)	9,672 (96%)	1,471 (100%)	233 (100%)	35,502 (92%)		
Influenza B	219 (1%)	454 (1%)	452 (4%)	1,622 (3%)	6 (0%)	29 (10%)	2,782 (2%)		
Influenza B lineage determined	10	82	0	48 1 1		142			
B/Yamagata- lineage	0 (0%)	2 (2%)	0	0 (0%)	0	0	2 (1%)		
B/Victoria- lineage	10 (100%)	80 (98%)	0	48 (100%) 1 1		140 (99%)			
Total	26,533	47,781	12,481	58,333	1,479	283	146,890		

B. Laboratory confirmed influenza from sentinel sources by geographic subregion and influenza type and subtype/lineage

Influenza type	South- West Europe	Western Europe	Eastern Europe	Northern Europe	West Asia	Central Asia	WHO European Region	
Influenza A	2,516 (99%)	2,051 (98%)	824 (98%)	1,314 (98%)	878 (100%)	201 (98%)	7,784 (99%)	
Influenza A subtyped	1,795	1,852	627	1,261	878	180	6,593	
A(H1N1)pdm09	44 (2%)	337 (18%)	11 (2%)	24 (2%)	1 (0%)	0 (0%)	417 (6%)	
A(H3N2)	1,751 (98%)	1,515 (82%)	616 (98%)	1,237 (98%)	877 (100%)	180 (100%)	6,176 (94%)	
Influenza B	21 (1%)	35 (2%)	21 (2%)	31 (2%)	4 (0%)	4 (2%)	116 (1%)	
Influenza B lineage determined	3	10	0	8	1	1	23	
B/Yamagata- lineage	0	0 (0%)	0	0	0	0	0 (0%)	
B/Victoria- lineage	3	10 (100%)	0	8	3 1 1		23 (100%)	
Total	2,537	2,086	845 1,345		882 205		7,900	

Figure E1. Influenza circulation^b in the WHO European Region by (sub)type and Country, territory or area, 2021-2022 season



^b Dominance of (sub)type is based on at least 60% of detections and co-dominance is based on between 40% and 60% of detections. Calculations are only considered valid if at least 10 viruses were detected

- 146,890 detections
- Context of increased numbers of samples from ILI and/or ARI criteria
- A:B 98%:2% across region except Central Asia (283 detections)
- H3:H1 92%:8% across region except Western Europe (66%:34%)
- B: 99% Bvic; 1% Byam reported but unconfirmed.
 (? LAIV-associated based on timing, patient age and limited HA sequence data)

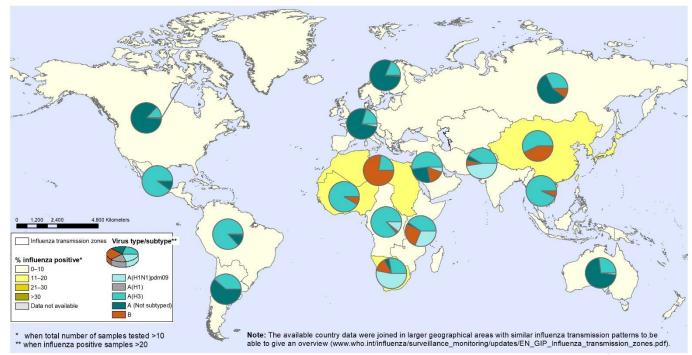
Table B: Restriction to sentinel sources:

Similar regional distribution, Type A (99%), of this 94% H3N2, of the Type B all BVic.



Influenza activity – (Feb – Aug 22)

Distribution of influenza virus type/subtype by influenza transmission zone, between February and August 2022



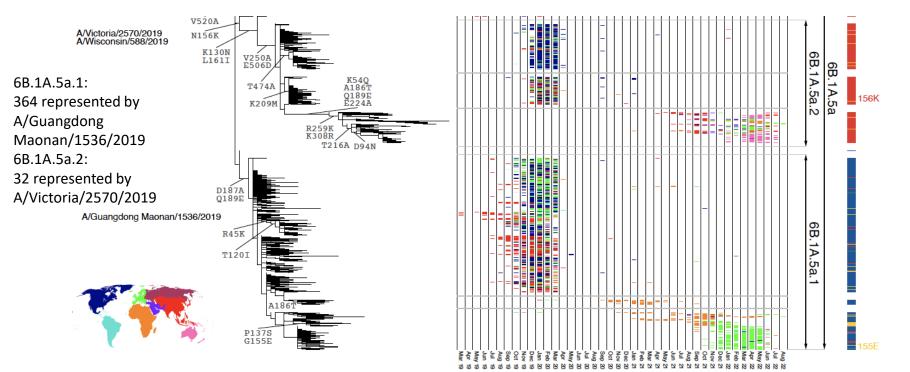
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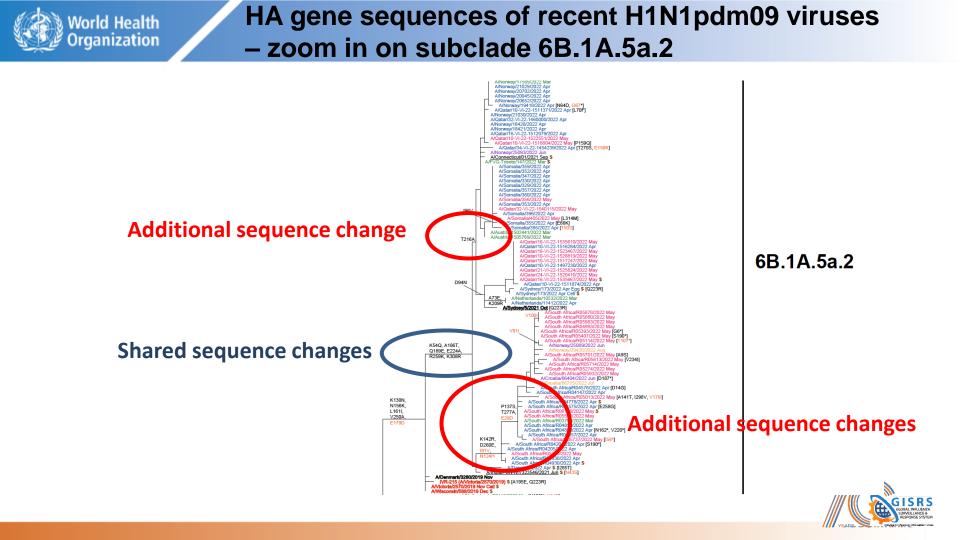


HA gene sequencing of recent H1N1pdm09 viruses



Phylogenetic tree of HA genes from Prof. Derek Smith and Dr Sarah James, University of Cambridge







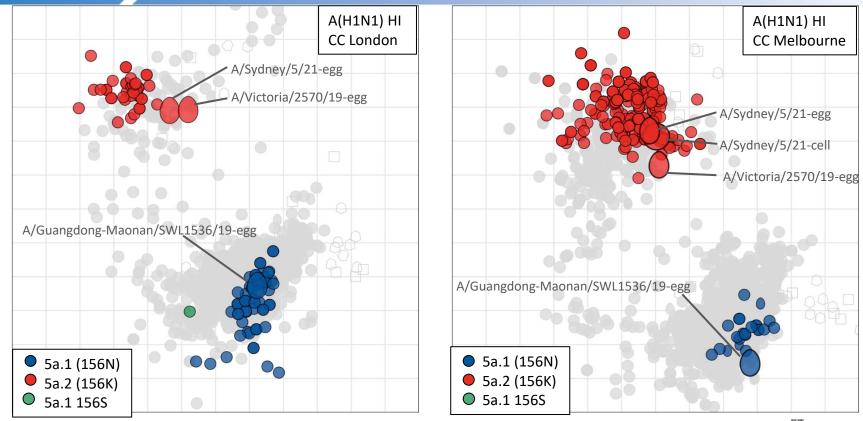
viruses

HI analysis of recent H1N1pdm09 viruses

HI analysis				Haemagglutination inhibition titres						
111 01101 9315			Post-infection ferret antisera						-	
with post-		Virus passage	Ferret	E4	SIAT1	S3, MDCK1		E4	E3	human
-		details	Antiserum	Guang/SWL1536	Vic2455	Togo881	Vic2570	Vic2570	Syd5	sera
infection ferret	Reference viruses	۲4	Clade	A.5a.1	A.5a.1	A.5a.1	A.5a.2	A.5a.2	A.5a.2	pool
	A/Guangdong-Maonan/SWL1536/2019 A/Victoria/2455/2019	E4 MDCK3	6B.1A.5a.1	1280	2560	2560 1280	<80 <80	<80	80 80	320
antisera	A/Victoria/2455/2019 A/Togo/881/2020	S3, MDCK2	6B.1A.5a.1 6B.1A.5a.1	1280 2560	1280 2560	1280 2560	<80 <80	<80 80	80 160	640 640
	A/Victoria/2570/2019	MDCK1	6B.1A.5a.1	80	2300 80	2300 <80	<80 320	320	320	160
	A/Victoria/2570/2019 A/Victoria/2570/2019	E6	6B.1A.5a.2	80	80 80	<80 <80	1280	1280	1280	640
	A/Sydney/5/2021	E3	6B.1A.5a.2	<80	80	<80	2560	1280	2560	640
Results from	100ydiley/3/2021	25	0 D .17 1 .3 u .2	<00	00	<00	2500	1200	2500	040
	Test viruses									
VIDRL show	A/Sydney/894/2022	MDCK1	6B.1A.5a.2	<80	<80	<80	1280	1280	1280	320
	A/Perth/184/2022	MDCK1, MDCK1	6B.1A.5a.2	<80	<80	<80	640	1280	1280	320
the distinct	A/Canberra/222/2022	MDCK1	6B.1A.5a.2	<80	<80	<80	1280	1280	2560	320
	A/Darwin/488/2022	SIAT2	6B.1A.5a.2	<80	<80	<80	640	1280	1280	320
recognition by	A/South Africa/R05765/2022	MDCK1, MDCK1	6B.1A.5a.2	<80	<80	<80	640	640	640	80
anticara raicad	A/South Africa/R05258/2022	MDCK1, MDCK1	6B.1A.5a.2	<80	<80	<80	1280	1280	1280	160
antisera raised	A/South Africa/R04994/2022	MDCK1, MDCK1	6B.1A.5a.2	<80	<80	<80	1280	1280	2560	160
against	A/South Africa/R03645/2022	MDCK1, MDCK1	6B.1A.5a.2	<80	<80	<80	1280	1280	2560	160
against	A (C. 1. (077 /0000	ND CHI	(D 1 4 5 1	1200	25.00	25.00	00	00	00	640
6B.1A.5a.1	A/Sydney/877/2022	MDCK1 MDCK1	6B.1A.5a.1 6B.1A.5a.1	1280 2560	2560 2560	2560 2560	<80 <80	<80 80	80 80	640 640
	A/Sydney/866/2022 A/Sydney/869/2022	MDCK1 MDCK1	6B.1A.5a.1	2560 2560	2360 2560	2560 2560	<80 <80	80 <80	80 80	640 640
and	A/Sydney/809/2022 A/South Africa/R05655/2022	MDCK1 MDCK1, MDCK1	6B.1A.5a.1	1280	1280	2300 1280	<80 <80	<80 <80	~80 <80	320
anu	A/South Africa/R05558/2022	MDCK1, MDCK1	6B.1A.5a.1	1280	2560	1280	<80	<80	80	320
6B.1A.5a.2	A/South Africa/R05539/2022	,	6B.1A.5a.1	1280	2560 2560	1280	<80	<80	80	640



Antigenic cartography of A(H1N1)pdm09 HI results



Antigenic cartography from Prof. Derek Smith and Dr Sarah James, University of Cambridge

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Since March 2022 (older viruses in grey)





Seven panels of post-vaccination antisera were used for the analysis of recent circulating viruses:

Egg-propagated vaccines (children, adult and elderly): A/Victoria/2570/2019 (6B.1A.5a.2)

Cell culture-based vaccines (children and adults): A/Wisconsin/588/2019 (6B.1A.5a.2)





A(H1N1)pdm09 – Summary (1)

- Globally, relatively few A(H1N1) pdm09 viruses with collection dates after January 2022 have been detected
- All of those A(H1N1)pdm09 viruses characterised genetically have fallen within HA clade 6B.1A.5a (5a)
- Two **5a** subclades have circulated in **2022**
- Subclade 6B.1A.5a.1 (5a.1 predominantly circulating in Europe) defined by HA1 amino acid substitutions D187A, Q189E
- Subclade 6B.1A.5a.2 (5a.2 more general global circulation) defined by HA1 amino acid substitutions K130N, N156K, L161I, V250A
- **5a.2** viruses have evolved further with all recently circulating viruses having HA1 amino acid substitutions **K54Q**, **A186T**, **Q189E**, **E224A**, **R259K**, **K308R**





A(H1N1)pdm09 – Summary (2)

- Post-infection ferret antisera raised against 5a.1 viruses (A/Guangdong-Maonan/SWL1536/2019-like) showed good recognition of circulating 5a.1 viruses but recognised 5a.2 viruses poorly
- Post-infection ferret antisera raised against 5a.2 viruses (A/Victoria/2570/2029-like) showed good recognition
 of circulating 5a.2 viruses but recognised 5a.1 viruses poorly
- A number of genetic groups defined by different HA amino acid substitutions have emerged among **5a.2** viruses
- Viruses in some of these 5a.2 groups are recognised less well by post-vaccination human sera e.g. a group of viruses recently detected in Africa, the Americas and Europe with HA1 K142R amino acid substitution, often with P137S
- Those A(H1N1)pdm09 viruses characterised (n = 607) remained susceptible to the PA inhibitor Baloxavir marboxil, while only 5/879 (0.6%) showed reduced susceptibility to at least one Neuraminidase Inhibitor

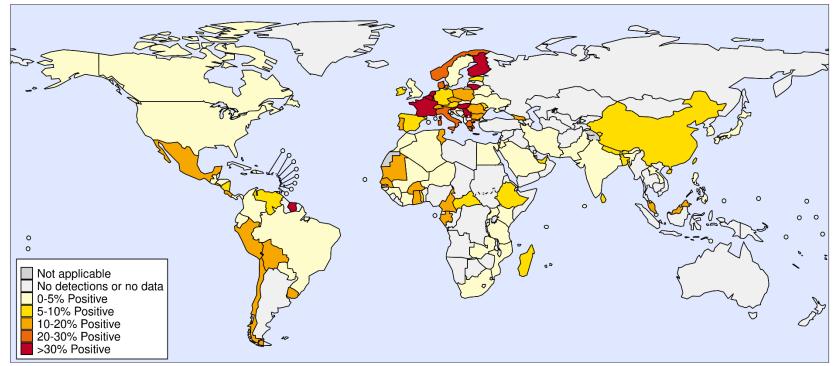


Influenza A(H3N2) activity

Influenza A(H3N2), February 2022 to August 2022, percent of all samples tested

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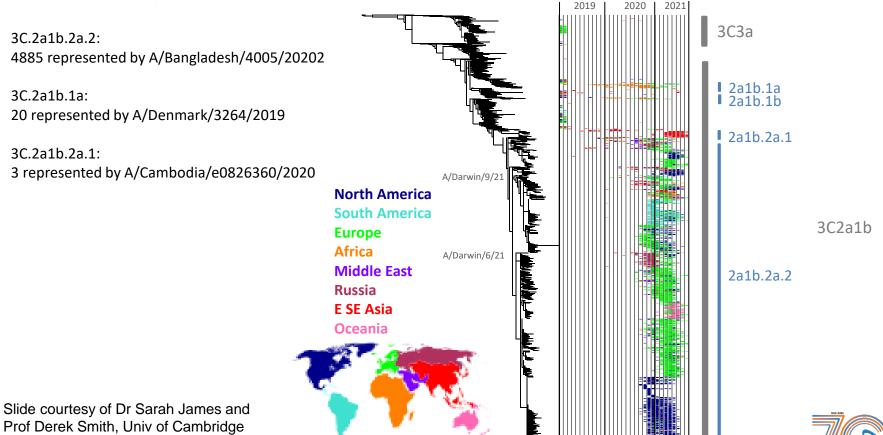
Colour intensity shows the percent of influenza A(H3N2) positive among all samples tested during this period per country

Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System (9 Sep 2022)





Phylogenetic analysis of A(H3N2) HA gene



GISRS BERRIES



Antigenic characterization (VN assay)

H3N2, FRA Test date: 25/07/2022							Fold difference <4-fold 4-fold 8-fold >8-fold
	S2 Cambe0826360 A9050−14D	S3,S1 Bang10006 A9054–14D	E3 Darwin24 A9407	S2 Darwin6 A9231–14D	E4 Darwin9 A9358-14D	Aust human serum	20-1010
	3C.2a1b.2a.1	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	pool	Clade
REFERENCE ANTIGENS							
A/Cambodia/E0826360/2020c	2560	640	<80	<80	<80	2560	3C.2a1b.2a.1
A/Bangladesh/10006/2020c	320	2560	1280	640	80	2560	3C.2a1b.2a.2
A/Darwin/24/2021	80	1280	5120	5120	1280	2560	3C.2a1b.2a.2
A/Darwin/6/2021c	<80	160	1280	1280	160	640	3C.2a1b.2a.2
A/Darwin/9/2021e	160	640	5120	5120	640	5120	3C.2a1b.2a.2
TEST ANTIGENS							
A/Timor-Leste/46/2022	2560	160	<80	80	80	1280	3C.2a1b.2a.1
A/Timor-Leste/14/2022	2560	80	<80	80	<80	1280	3C.2a1b.2a.1
A/Timor-Leste/58/2022	1280	80	<80	<80	<80	1280	3C.2a1b.2a.1
A/Timor-Leste/154/2022	80	640	2560	2560	640	2560	3C.2a1b.2a.2
A/Fiji/97/2022	<80	320	2560	2560	320	1280	3C.2a1b.2a.2
A/Singapore/GP1845/2022	<80	320	2560	2560	320	1280	3C.2a1b.2a.2
A/Singapore/KK0003/2022	<80	320	1280	2560	160	1280	3C.2a1b.2a.2
A/Singapore/KK0018/2022	<80	320	1280	1280	160	1280	3C.2a1b.2a.2
A/South Africa/R05607/2022	80	640	640	640	160	640	3C.2a1b.2a.2
A/South Africa/R03770/2022	80	1280	1280	320	160	640	3C.2a1b.2a.2
A/Newcastle/47/2022	80	1280	2560	5120	640	2560	3C.2a1b.2a.2+53G+156S
A/Darwin/62/2022	<80	640	2560	5120	320	2560	3C.2a1b.2a.2+53G+156S
A/Victoria/4004/2022	80	640	2560	5120	320	2560	3C.2a1b.2a.2+53G+156S
A/Dunedin/14/2022	<80	640	1280	2560	320	1280	3C.2a1b.2a.2+53G+156S
A/New Caledonia/56/2022	80	1280	2560	2560	640	1280	3C.2a1b.2a.2+53N+156S
A/New Caledonia/53/2022	80	320	1280	2560	320	1280	3C.2a1b.2a.2+53N+156S
A/New Caledonia/60/2022	<80	640	2560	2560	320	1280	3C.2a1b.2a.2+53N+156S

Source: WHO CC VIDRL



A(H3N2) Summary (1): Global Circulation

- □ Influenza A(H3N2) viruses predominated globally
- □ HA phylogenetics:
 - A majority of circulating A(H3N2) viruses in this period belonged to the 3C.2a1b.2a.2 (2a.2) subclade, with shared HA1 substitutions Y159N, T160I (resulting in the loss of a glycosylation site), L164Q, G186D, D190N, F193S and Y195F.
 - 2a.2 viruses have diversified into genetic groups that typically encode:
 - H156Q
 - H156S and D53G
 - H156S and D53N
 - D53G
 - Viruses belonging to 3C.2a1b.2a.1 (2a.1) with shared HA1 substitutions G186S, F193S, Y195F and S198P, predominated in China. Some viruses had additional substitutions K171N and I48T in HA1.





A(H3N2) Summary (2): Antigenic Characteristics

- **2a.2** viruses are antigenically distinct from **2a.1** viruses
- Ferret antisera to:
 - A/Darwin/6/2021 (SH 22 Cell) and A/Darwin/9/2021 (SH Egg) 2a.2
 - Recognized 2a.2 viruses with the HA1 substitution H156S well
 - Reacted less well with 2a.2 viruses without the H156S substitution
 - Reacted poorly with 2a.1 viruses
 - A/Cambodia/e0826360/2020 (NH 21-22 Cell) 2a.1
 - Reacted well with 2a.1 viruses but poorly with 2a.2 viruses





A(H3N2) Summary (3)

Human serology studies with serum panels from individuals vaccinated with A/Darwin/9/2021-like (2a.2) viruses:

- Geometric mean HI and VN titers against recent representative A(H3N2) **2a.2** and **2a.1** viruses were not significantly reduced compared to titers against cell culture-propagated A/Darwin/6/2021
- Reductions of VN GMTs were more pronounced when compared to egg-propagated A/Darwin/9/2021-like reference viruses

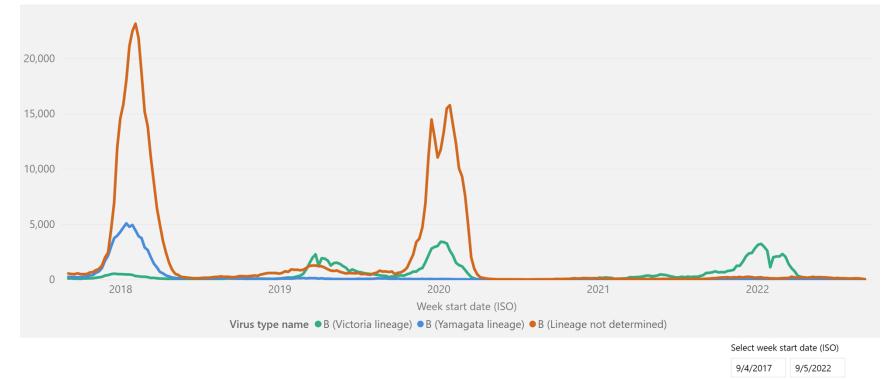
Antiviral Susceptibility

- □ Genetic and/or phenotypic testing showed that none of the 4,577 A(H3N2) viruses collected since 1 February 2022 showed reduced inhibition to neuraminidase inhibitors.
- □ Of 3,250 A(H3N2) viruses collected and analyzed since 1 February 2022, one showed genetic evidence of reduced susceptibility to baloxavir.





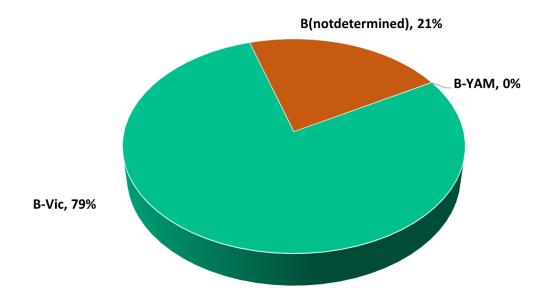
Global circulation of influenza B viruses



Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (GISRS)







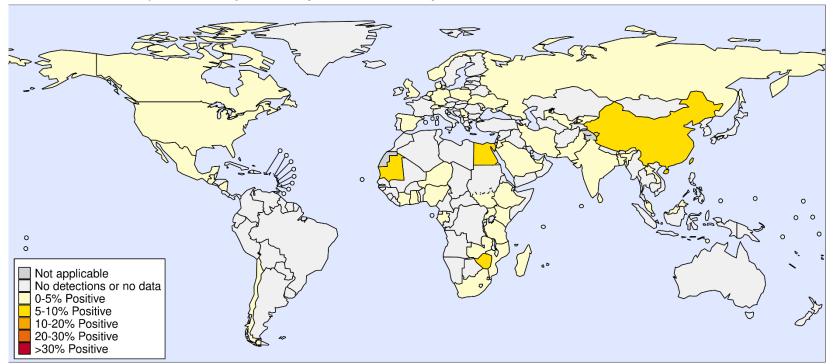


Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System (17 Sep 2022)



Influenza B viruses activity

Influenza B, February 2022 to August 2022, percent of all samples tested



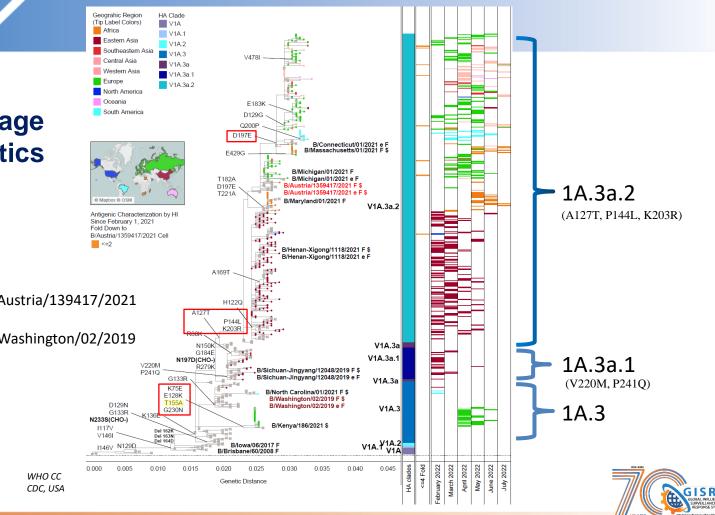
Colour intensity shows the percent of influenza B positive among all samples tested during this period per country

Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System (9 Sep 2022)





B/Victoria lineage HA phylogenetics



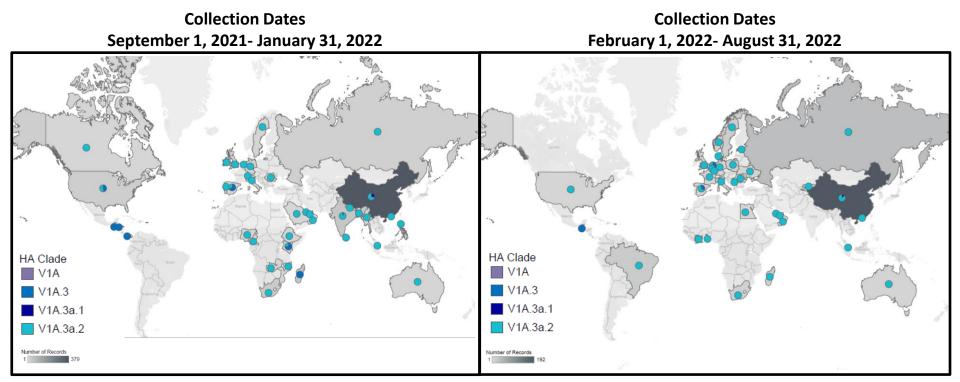
V1A.3.2:

55 viruses represented by B/Austria/139417/2021 V1A.3:

29 viruses represented by B/Washington/02/2019



Global B/Victoria HA clade diversity



Based on HA sequence availability

WHO CC CDC, USA





- There have been no confirmed detections of circulating B/Yamagata/16/88 lineage viruses after March 2020.
- No B/Yamagata/16/88 lineage viruses have been available for analysis during this period





Summary of Influenza B Viruses (1)

- Only influenza B/Victoria lineage viruses were available for analysis
- HA phylogenetics of B/Victoria lineage viruses
 - All HA genes belonged to clade **1A.3**, with a deletion of residues 162-164 and a K136E substitution in HA1
 - A small number of viruses derived from 1A.3 continue to circulate and recent viruses from Kenya and Netherlands have evolved substitutions K75E, E128K, T155A and G230N in HA1
 - Subclade 1A.3a viruses with HA genes encoding further substitutions of N150K, G184E, N197D (resulting in the loss of a glycosylation site) and R279K in HA1 have predominated
 - Two subgroups have emerged:
 - 1A.3a.1 has additional HA1 substitutions V220M and P241Q, seen exclusively in China and are decreasing in number
 - 1A.3a.2 with A127T, P144L and K203R seen in Asia, Africa, Oceania, Europe, North America and South America
 - The majority of 1A.3a.2 viruses have one additional substitution D197E in HA1





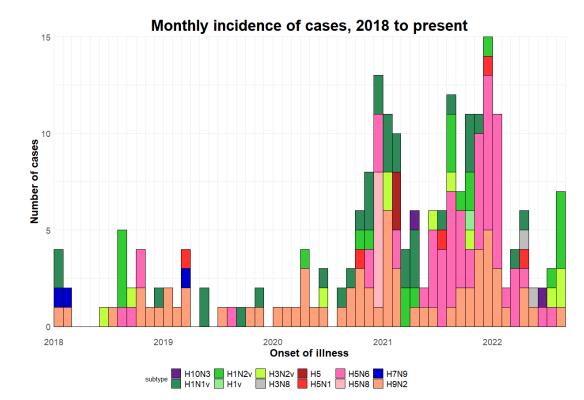
❑ Antigenic characteristics of B/Victoria lineage viruses

- Post-infection ferret antisera raised against B/Austria/1359417/2021-like viruses (1A.3a.2) inhibited the majority of recently circulating viruses well but recognized 1A.3a.1 poorly
- Subgroup 1A.3a.1 and 1A.3a.2 viruses are antigenically different
- A small number of 1A.3 viruses, detected in Kenya and the Netherlands, were not recognized well by ferret antisera raised against B/Washington/02/2019-like viruses (1A.3) and were poorly recognized by ferret antisera raised against
 B/Austria/1359417/2021-like viruses (3a.2)





27 zoonotic influenza A infections



2 (H1N1)v 5 A(H1N2)v 3 A(H3N2)v 2 A(H3N8) 1 A(H5N1) 7 A(H5N6) 6 A(H9N2)

1 A(H10N3) 0 A(H7N9)



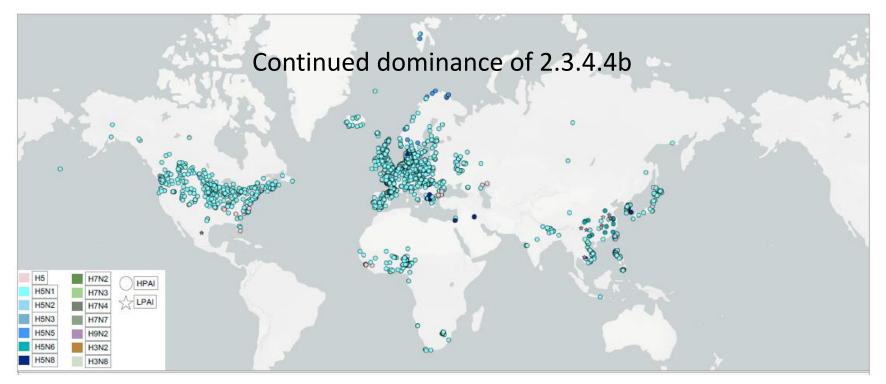


Influenza A(H5)





A(H5) activity in birds

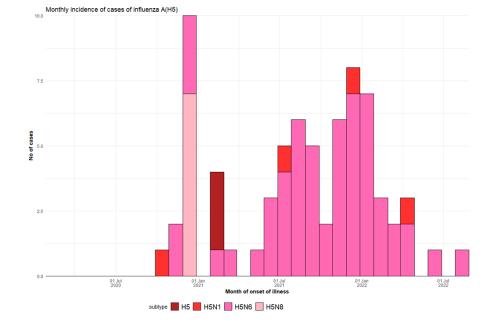






A(H5) activity in humans

- 7 A(H5N6) in China (clade 2.3.4.4b)
- 1 A(H5N1) in US (clade 2.3.4.4b)

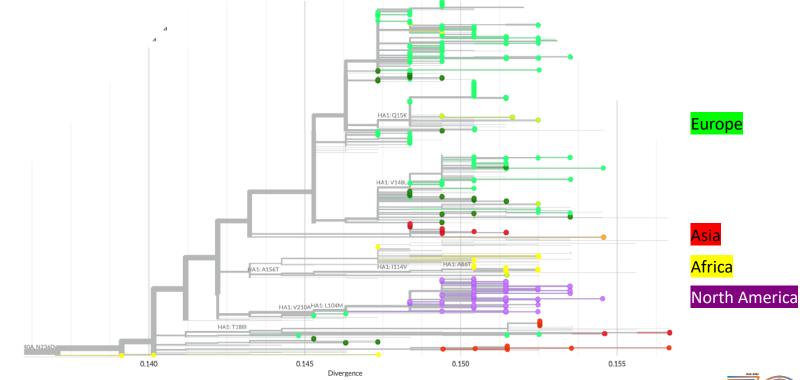


- Cumulative numbers
- 3 A(H5), 7 A(H5N8), 81 A(H5N6) and 865 A(H5N1)





Geographic clustering of 2.3.4.4b viruses





Antigenic properties of African 2.3.4.4b viruses

			A/Fujian-Sanyan	A/Astrakhan	A/chicken/Ghana	A/hen/Bulgaria
Reference Antigen	Clade	Subtyp e				
A/Fujian-Sanyan/21099/2017 xA/PR/8/1934	2.3.4.4 b	H5N6	<u>40</u>	160	1280	640
A/Astrakhan/3212/2020	2.3.4.4 b	H5N8	80	<u>160</u>	640	640
A/poultry/Niger/ET3/HALAL/21VIR2131- 33/2021	2.3.4.4 b	H5N1	10	40	320	160
A/chicken/Ghana/AVL-763/21VIR7050- 39/2021	2.3.4.4 b	H5N1	10	20	<u>320</u>	80
A/hen/Bulgaria/722-1/22VIR778-1/2021	2.3.4.4 b	H5N1	10	40	640	<u>640</u>
Test antigen						
A/laying-hen/Moldova/68-1_22VIR638-1/2022	2.3.4.4 b	H5N1	10	40	320	320
w CVV antigenically-like A/chicken/Gha	na/AVL-7	76321VII				
A/terret/Slovenia/308/22VIR777-9/2022	0		10	10	640	640

World Health Organization





Influenza A(H9N2)





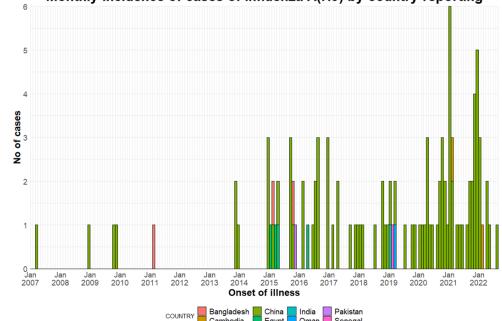
Recent A(H9N2) activity

- Human infections

- 5 in China (Y280/G9)
- 1 in Cambodia (Y280/G9)

- Avian activity

- Y280/G9 lineage viruses detected in China, Cambodia and Viet Nam
- G1 lineage viruses were detected in Bangladesh and Egypt







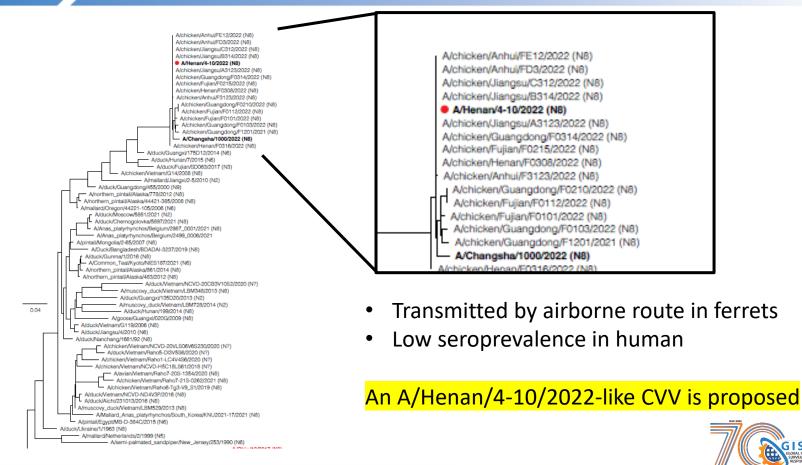


Influenza A(H3N8)





Properties of A(H3N8) viruses



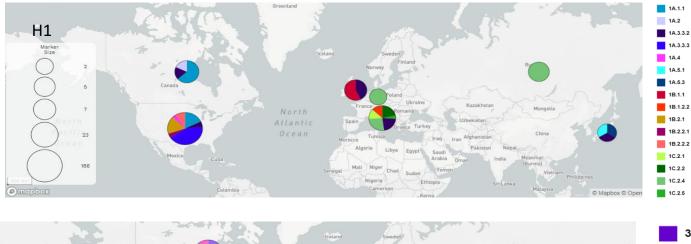


Influenza A(H1)v and A(H3)v





Influenza virus activity in swine





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Recent A(H1)v and A(H3)v activity in humans

A(H1N1)v

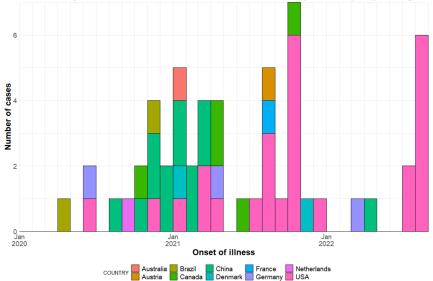
China (clade 1C.2.3) Germany (clade 1C.2.2)

A(H1N2)v

5 United States [clades 1B.2.1 (3), 1A.1.1 (1) and 1A.3.3.2 (1)]

A(H3N2)v

3 United States (clade 2010.1.)



Monthly incidence of cases of variant viruses by country reporting





Thanks are due to WHO National Influenza Centres WHO Collaborating Centres WHO HQ and WHO Regional Offices ECDC University of Cambridge Modelling groups in Germany, USA and Switzerland







