WGS - GIHSN report of activity as of April 4th, 2025

1 - Description of the network

GIHSN is collecting clinical and virological information from hospitalized cases through a network of sites located in different regions of the world (figure1). This combined clinical and virological surveillance allows the identification of viruses responsible for severe influenza. This severity is assessed by the oxygen requirement of cases registered by the sites. In this report, viruses detected and sequenced from cases requiring oxygen supplementation are identified in the phylogenetic trees provided, to determine if specific lineages or clades are associated with more frequent severe presentation.

For the 2024-2025 surveillance in GIHSN, influenza activity was detected from September 1st, 2024, with a co-circulation of A/H1N1, A/H3N2 and B viruses in different relative proportions.

This report collates the sequencing data of hospitalized patients from 10 sites reporting 220 sequences available in the GISAID database on 2025/03/17: *Brazil (1), Cote d'Ivoire (7), Kenya (1), Mexico (2), USA (14), Pakistan (78), Romania (20), Senegal (27), Spain (46) Ukraine (24).* Samples were collected between W37-2024 and W08-2025.

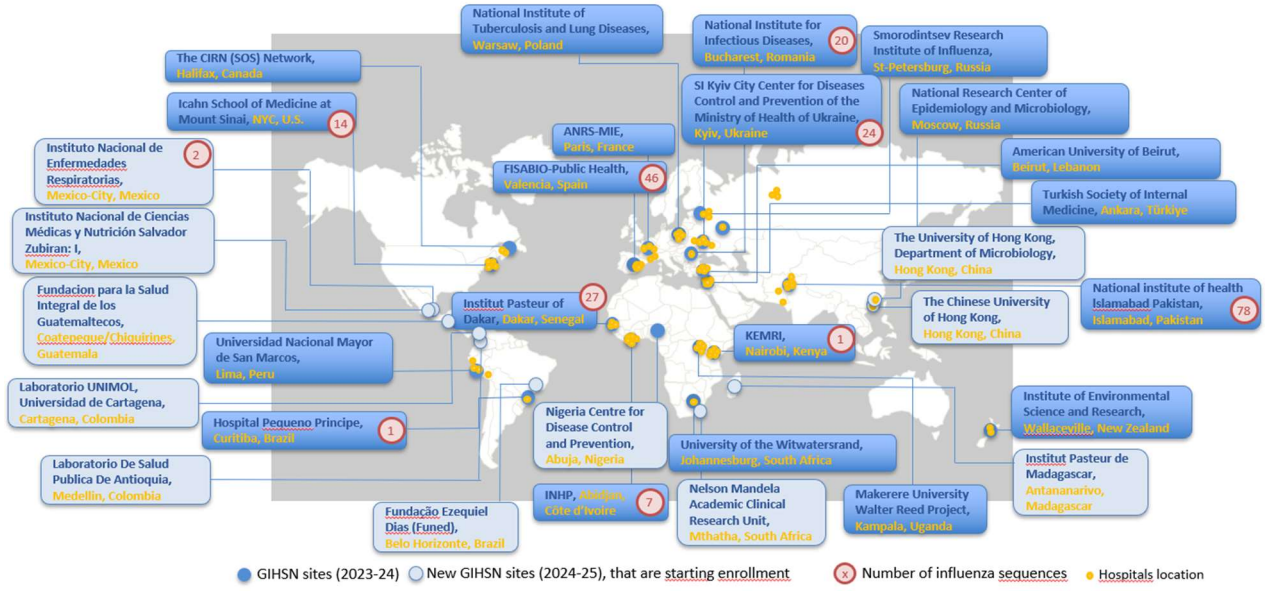

Fig. 1 Map showing the repartition of the participating countries, between September 1st, 2024 and March 18th, 2025, with the number of influenza sequences shared by sites. Eleven new sites (in pale blue) have joined the GIHSN for the 2024-2025 season but just started implementation.

2 - Description of the virus sequenced in the GIHSN

2.1 - Influenza A viruses

A(H1N1)pdm09 viruses

A(H1N1)pdm09 viruses were detected in most part of the world and predominated in Asia. A(H1N1)pdm09 viruses sequenced from the GIHSN network (n=132) were collected between W37-2024 and W8-2025, and were collected mainly from Pakistan (78/132, 59%).

Sequencing results indicated that 18% of these viruses (24/132) belonged to 6B.1A.5a.2a.1 clade close to reference strain A/Victoria/4897/2022, while 78% (103/132) belonged to 6B.1A.5a.2a clade (Fig. 2).

Most 5a.2a.1 viruses were detected in Pakistan (18/24), while the diversity of origin of 5a.2a viruses was larger (37/103 from Pakistan, 34/103 from Spain, 15/42 from Ukraine, 10/103 from Romania, 4/42 from USA, 1/103 from Cote d'Ivoire), 1/103 from Kenya.

Among 5a.2a clade, most viruses (82/103, 80%) belonged to C.1.9.3 subclade characterized by HA1: S83P substitution. In addition, 16/103 (15%) viruses belonged to C.1.9 subclade.

Among 5a.2a.1 clade, most viruses (18/24) belonged to D3 subclade characterized by the HA1:T216A substitution also found in A/Victoria/4897/2022 reference strain, and additional HA1:T120A substitution.

No specific lineage or clade could be associated with oxygen supplementation. (Fig. 2).

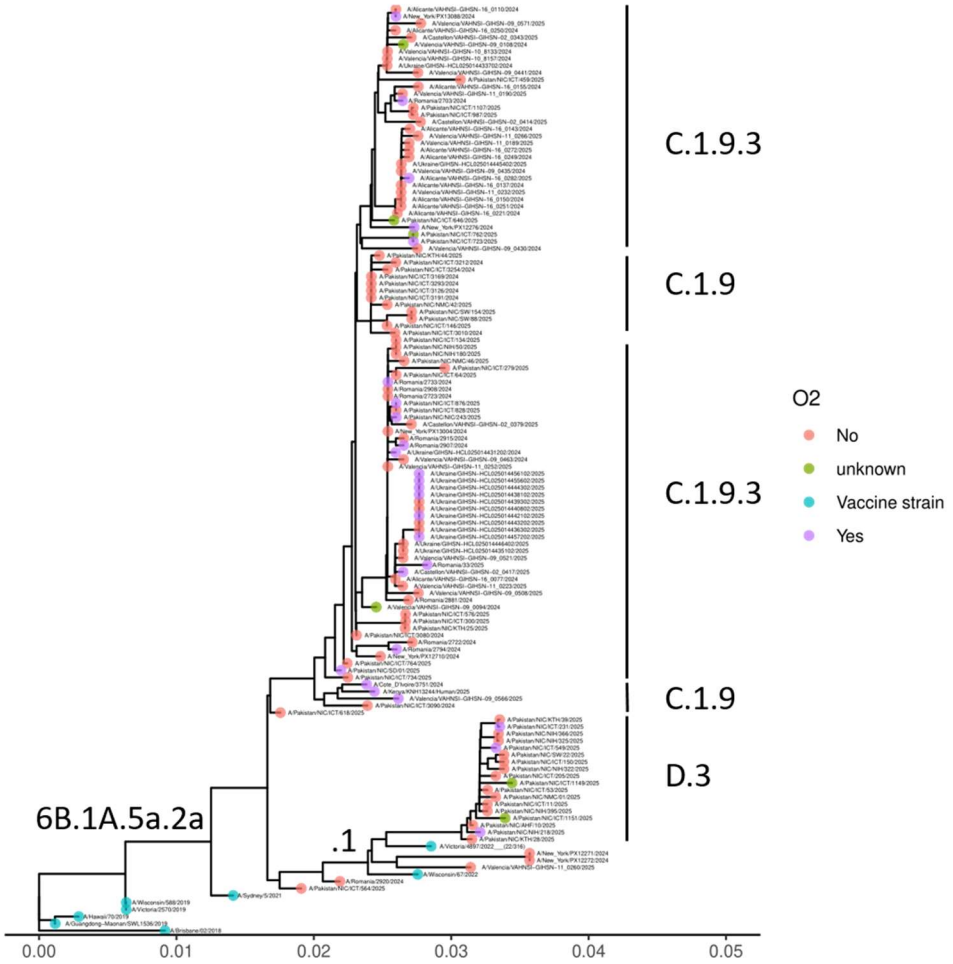

Fig 2: Phylogenetic tree of the A(H1N1pdm09) viruses analyzed between 1st of September 2024 and 23th of February 2025. The phylogeny has been inferred using a Neighbor Joining approach (Seaview). Visualization was displayed using ggtree in R. Tips (samples) colors correspond to Oxygen supplementation (yes: purple; red:no; green: unknown) with vaccine reference strains displayed in black.

A(H3N2) viruses

Circulation of A(H3N2) viruses was more limited in countries participating in the GIHSN network during the 2024-2025 season, with only 43 sequences generated. All viruses belonged to 3C.2a1b.2a.2a.3a.1 clade, with A/Massachusetts/18/2022, A/Thailand/8/2022, A/Croatia/10136RV/2023 and A/DistrictOfColumbia/27/2023 as reference viruses (Fig. 3).

Most viruses (24/43) belonged to J2 subclade characterized by the HA1:K276E substitution also found in A/Croatia/10136RV/2023 and A/DistrictOfColumbia/27/2023 reference strains, and a variety of additional substitutions related to each cluster.

3 cases requiring oxygen supplementation were detected in the J2 subclade with HA1: D104N, which warrant further analysis on a larger cohort to investigate a potential association between severity and this subclade (Fig. 3).

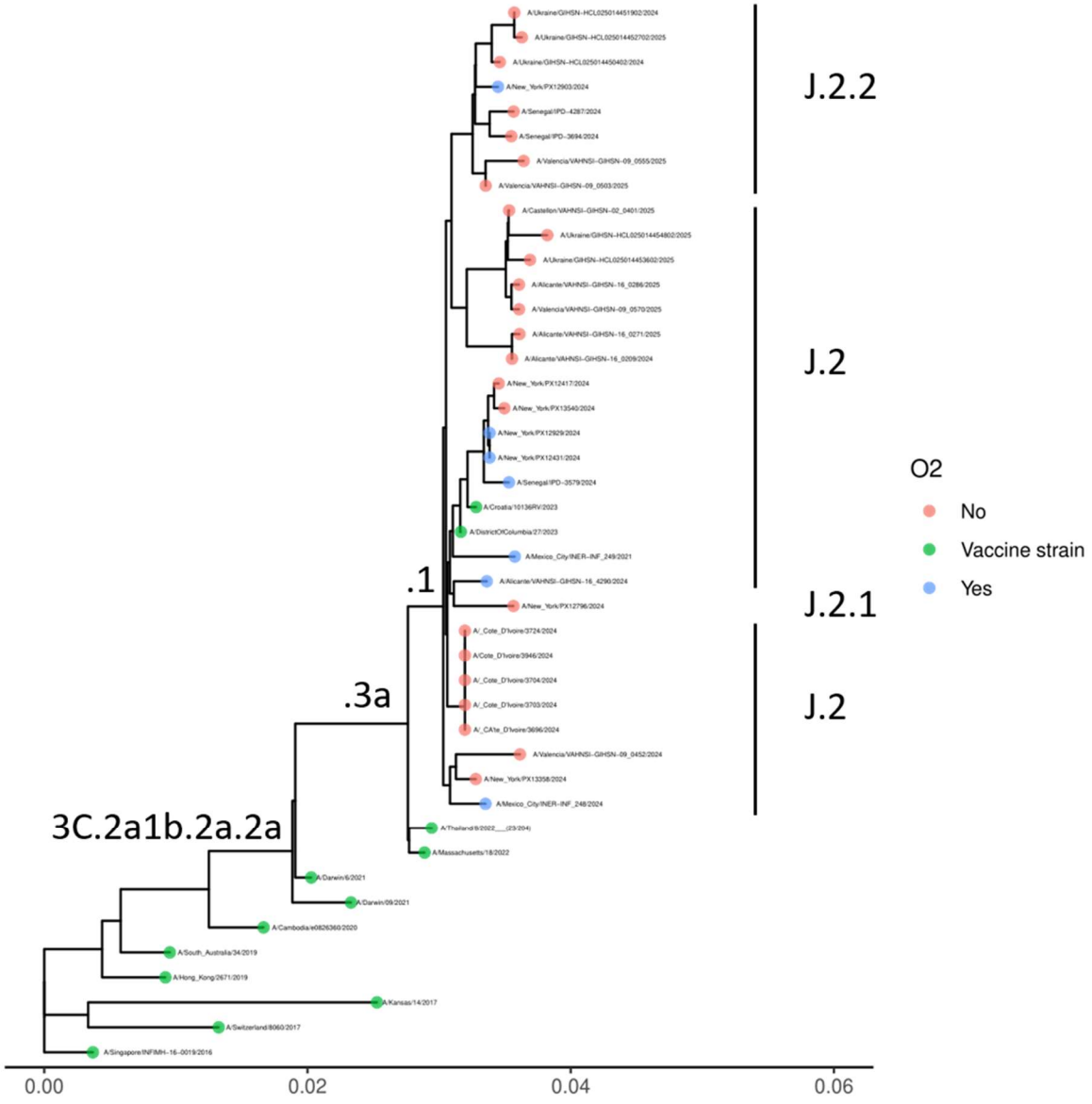

Fig 3: Phylogenetic tree of the A(H3N2) viruses analyzed between 1st of September 2024 and 23th of February 2025. The phylogeny has been inferred using a Neighbor Joining approach (Seaview). Visualization was displayed using ggtree in R. Tips (samples) colors correspond to Oxygen supplementation (yes: blue; red:no) with vaccine reference strains displayed in black.

2.2 - Influenza B viruses

B/Victoria Lineage

Influenza B viruses co-circulated with Influenza A viruses in most part of the world during the 2024-2025 season. All Influenza B viruses sequenced within the GIHSN network belonged to the V1A.3a.2 clade, with B/Austria/1359417/2021 as reference virus (Fig. 4).

Most of the sequences belonged to C.5.* subclades characterized by HA1:D197E substitution compared with B/Austria/1359417/2021 reference strain, with 5/50 viruses in C.5 subclade, 32/50 viruses in C.5.6 subclade, and 10/50 viruses in C.5.7 subclade.

Seven sequences belonged to the C.3 subclade characterized by HA1:S208P and originated from Pakistan.

Cases requiring oxygen supplementation were detected in the C.5.6, C.5.1 and C.5.7 subclades with no significant association (Fig. 4).

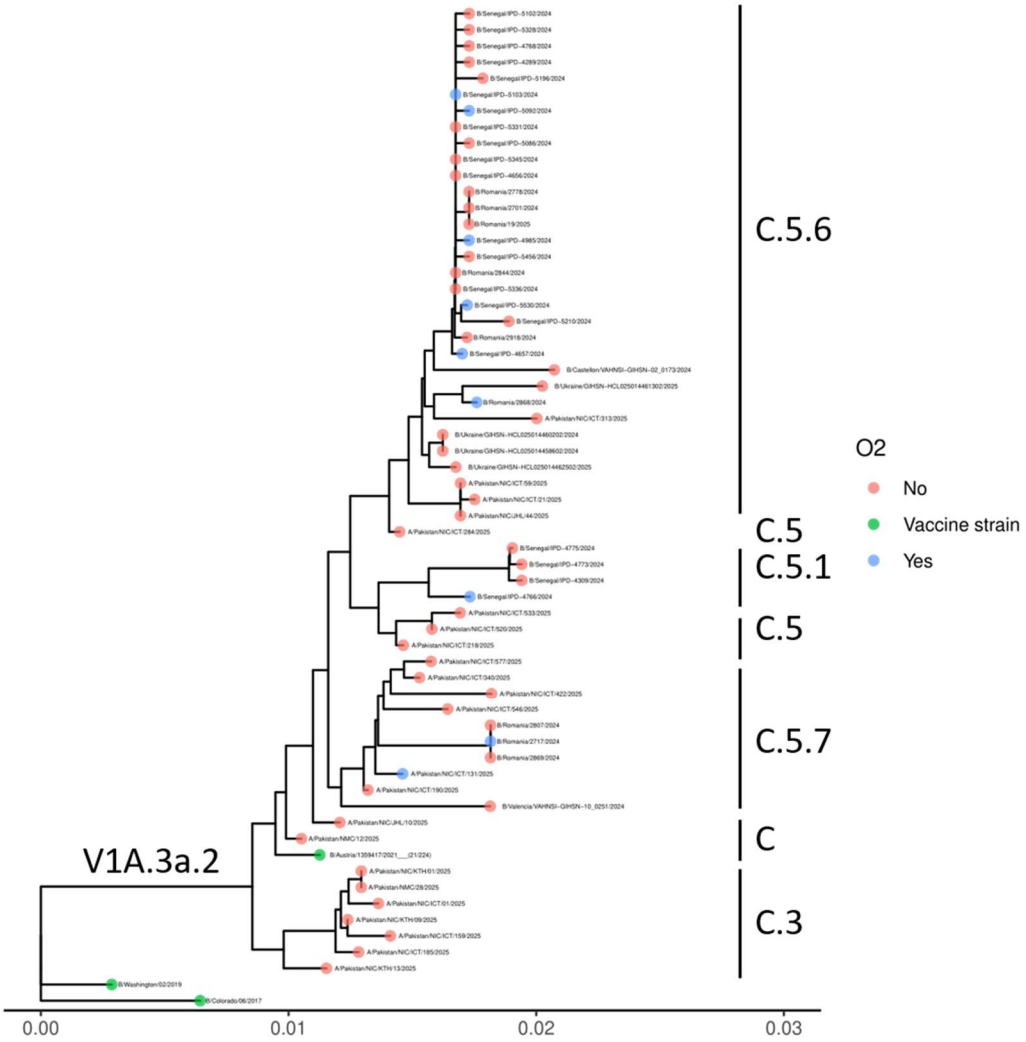

Fig 4: Phylogenetic tree of the B/Victoria viruses analyzed between 1st of September 2024 and 23th of February 2025. The phylogeny has been inferred using a Neighbor Joining approach (Seaview). Visualization was displayed using ggtree in R. Tips (samples) colors correspond to Oxygen supplementation (yes: blue; red:no) with vaccine reference strains displayed in black.

B/Yamagata viruses

No B/Yamagata/16/88 viruses have been detected.

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