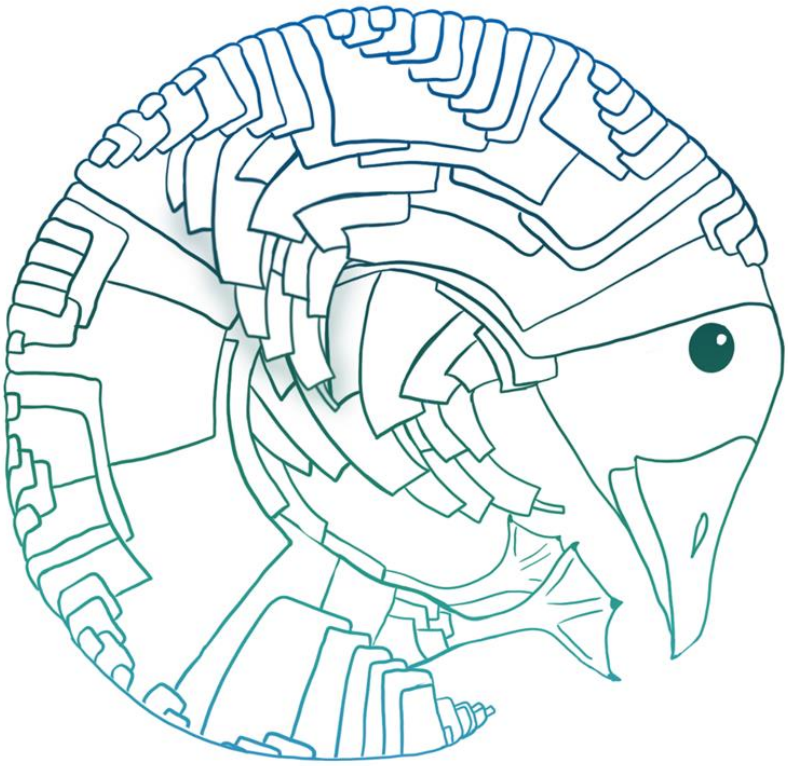
Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Hôpitaux Universitaires Genève

Influenza virus surveillance in Switzerland
Season 2022–2023

(Weeks 40/2022-16/2023)

National Reference Centre of Influenza
Laboratory of Virology
Geneva University Hospitals
4 Rue Gabrielle-Perret-Gentil
1211 GENEVA 14 – SWITZERLAND



Cover image credit and description: Digital illustration using Procreate® by Lisa Spedaliero
Phylogenetic tree representing a wild goose.
Image definition: 2000x2000 pixels

Contacts

Ms Tania Spedaliero	Tel: +41/22 372 40 82 ✉ : Tania.Spedaliero@hcuge.ch
Dr Ana Rita Gonçalves Cabecinhas	Tel: +41/22 372 40 81 ✉ : agnv@hcuge.ch
Ms Patricia Boquete-Suter	Tel: +41/22 372 40 94 ✉ : Patrica.Suter@hcuge.ch
Dr Manuel Schibler	Tel: +41/22 372 40 96 ✉ : Manuel.Schibler@hcuge.ch
Professor Laurent Kaiser	Tel: +41/22 372 98 01 ✉ : Laurent.Kaiser@hcuge.ch

Contents

Abbreviations and Acronyms

ARI	acute respiratory infection
BM	baloxavir marboxil
CDC	Centers for disease control and prevention
CDV	canine distemper virus
COVID-19	coronavirus disease 2019
CPE	cytopathic effect
Ct	cycle threshold
ECDC	European centre for disease prevention and control
EEA	European economic area
EQAP	external quality assessment programme
EU	European union
FOPH	federal office of public health
GISAID	global initiative on sharing all influenza data
HA	hemagglutinin
HAI	hemagglutinin inhibition
HAdV	human adenovirus
HBoV	human bocavirus
HCoV	human coronavirus
HEF	hemagglutinin-esterase-fusion
H/LPAI	high/low pathogenic avian influenza
HMPV	human metapneumovirus
HPIV	human parainfluenza
ILI	influenza-like illness(es)
M	matrix
MDCK	Madin-Darby canine kidney cells
MDCK-SIAT1	sialic acid-enriched MDCK cells
NA	neuraminidase
NAI	neuraminidase inhibitor
NEP	nuclear export protein
NPI	non-pharmaceutical interventions
NRCI	national reference centre of influenza
NS	non-structural
PA, PB	acidic protein, basic protein
RBC	red blood cell
RNA	ribonucleic acids
RNP	ribonucleoprotein
RV/EV	rhinoviruses/enteroviruses
RSV	respiratory syncytial virus
rRT-PCR	real-time reverse-transcription polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SPSP	Swiss pathogen surveillance platform
Vic, Yam	Victoria, Yamagata

VOC	variant of concern
VOI	variant of interest
VUM	variant under monitoring
WBE	wastewater-based epidemiology
WHO	world health organization
WIC	worldwide influenza centre
URTI	upper respiratory tract infection(s)

Acknowledgements

We would like to take this opportunity to extend our grateful thanks to:

- The Sentinel network and the participating medical practitioners.
- Jean-Luc Richard, Ornella Luminati, Rita Born, Damir Perisa, Anna Fesser, Liliane Trafelet, Hanna Hildenbrand; Federal Office of Public Health.
- Nicola Lewis, Ruth Harvey, Monica Galiano, Zheng Xiang, Christine Carr, Chandrika Halai, Karen Cross, Aine Rattigan, Burcu Ermetal, Alice Lilley, Michael Bennett, Becky Clark, and Lorin Adams; World Health Organization Collaborating Centre for Reference & Research on Influenza, the Crick Worldwide Influenza Centre, the Francis Crick Institute.
- Wenqing Zhang, Sylvie Briand, Maja Lièvre, Christian Fuster and all the members of the Global Influenza Surveillance and Response System; World Health Organization.
- The Global Initiative on Sharing All Influenza Data.Margaux Meslé, Piers Mook, Richard Pebody, and Mary Sinnathamby; World Health Organization Regional Office for Europe, and Eeva Broberg and Edoardo Colzani; European Centre for Disease Prevention and Control.
- Erik Boehm and Pauline Vetter; Geneva Centre for Emerging Viral Diseases, Geneva University Hospitals and Faculty of Medicine.
- All members of the National Reference Centre for Emerging Viral Infections and the Centre for Emerging Viral Diseases, Geneva University Hospitals.
- All members of the Laboratory of Virology, Geneva University Hospitals.

Résumé – Zusammenfassung – Summary

Résumé de la surveillance de l'activité grippale 2022/2023

Pour la troisième année consécutive au sein du réseau de surveillance Sentinelle, les prélèvements nasopharyngés reçus au Centre National de Référence de l'influenza, ont non seulement été dépistés pour les virus de la grippe mais aussi pour le SARS-CoV-2, RSV A et B, HCoV NL63, HCoV HKU1, HCoV OC43, HCoV 229E, HPIV1-4, HBoV, HAdV, RV/EV et HMPV. Parmi les 1936 échantillons analysés, 1376 se sont révélés positifs pour au moins un virus respiratoire. Les virus du SARS-CoV-2 de l'influenza A et B, ainsi que le RSV et les RV/EV étaient les plus fréquemment détectés durant cette saison (semaines 40/2022 à 16/2023).

La grippe a refait son apparition au sein du réseau Sentinelle dès la semaine 40/2022. Sur les 1936 échantillons dépistés, 472, soit 34.3%, étaient positifs pour un virus grippal. En Suisse, les virus de l'influenza ont été mis en évidence au cours de deux vagues successives. La première, et la plus importante, observée dès la semaine 40/2022 regroupait majoritairement des virus de type A, à dominance A(H3N2). La seconde a suivi dès la semaine 48/2022 et était dominée par les virus influenza de la lignée B/Victoria/2/87 et dans une moindre mesure par des influenza A(H1N1)pdm09.

Les virus influenza A de sous-type A(H3N2) détectés en Suisse appartenaient aux sous-clades 2a.3a.1, 2a.3b, 2a.2a.1 et 2a.2a.1b du groupe génétique 3C.2a1b.2a. Ces isolats étaient majoritairement bien reconnus par l'antisérum dirigé contre la souche vaccinale recommandée pour l'hémisphère nord pour 2022/2023, soit A/Darwin/9/2021 (3C.2a1b.2a.2). Les virus de sous-type A(H1N1)pdm09 appartenaient tous au groupe 6B.1A.5a.2a, dont la moitié appartenait au sous-groupe 5a.2a.1. Les isolats A(H1N1)pdm09 antigéniquement caractérisés étaient proches de la souche vaccinale recommandée pour l'hémisphère nord 2022/2023, soit A/Victoria/2570/2019. Une minorité de virus était mieux reconnue par l'antisérum dirigé contre la souche de référence A/Denmark/3280/2019. Quant aux virus de l'influenza B, tous appartenaient au clade V1A.3a.2 et tous étaient antigéniquement proches de la souche vaccinale recommandée pour l'hémisphère nord 2022/2023 B/Austria/1359417/2021.

L'activité grippale de 2022/2023 a été marquée par le retour d'un niveau de détection quasi similaire aux saisons précédant l'émergence du SARS-CoV-2, mais avec un pic de positivité plus précoce.

A ce jour, et bien que le virus aviaire A(H5N2) soit détecté en Suisse chez les oiseaux sauvages, aucune infection grippale zoonotique n'a été recensée.

Chez les oiseaux sauvages, ainsi que chez la volaille, l'activité grippale reste particulièrement élevée dans plusieurs pays d'Europe, d'Amériques et d'Asie. L'extension de la transmission de la souche H5N1 (clade 2.3.4.4b) à de nouvelles espèces aviaires et la multiplication des épisodes de transmission à des mammifères justifient une surveillance accrue du risque du passage à l'être humain

Zusammenfassung der Grippeüberwachung 2022/2023

Im dritten Jahr in Folge wurden im Rahmen des Sentinella-Überwachungsnetzes die im beim NRZI eingegangenen Nasopharynxproben nicht nur auf Influenzaviren, sondern auch auf SARS-CoV-2, RSV A und B, HCoV NL63, HCoV HKU1, HCoV OC43, HCoV 229E, HPIV1-4, HBoV, HAdV, RV/EV und HMPV getestet. Von den 1936 untersuchten Proben waren 1376 positiv für mindestens ein respiratorisches Virus. Am häufigsten wurden in dieser Saison SARS-CoV-2-Influenza-A- und -B-Viren sowie RSV und RV/EV nachgewiesen.

In der Woche 40/2022 trat die Grippe zum ersten Mal im Sentinella-Netzwerk auf. Von den 1936 getesteten Proben waren 472 Influenzaviren nach, was etwa 34.3% der positiven Proben entspricht. In der Schweiz wurden die Influenzaviren in zwei aufeinanderfolgenden Wellen nachgewiesen. Die erste und wichtigste Welle umfasste mehrheitlich Influenza-A-Viren, mit einer Dominanz vom Subtyp A(H3N2). Die zweite folgte ab Woche 48/2022 und wurde von Influenzaviren der Linie B/Victoria/2/87 und in geringerem Maße von Influenzaviren vom Subtyps A(H1N1)pdm09 dominiert. Die in der Schweiz nachgewiesenen Influenza-A-Viren des Subtyps A(H3N2) gehörten den Subkladen 2a.3a.1, 2a.3b, 2a.2a.1 und 2a.2a.1b der genetischen Gruppe 3C.2a1b.2a an. Diese Isolate wurden überwiegend gut von dem Antiserum erkannt, das gegen den Impfstamm 2022/2023 der nördlichen Hemisphäre A/Darwin/9/2021 (3C.2a1b.2a.2) gerichtet war. Die Viren des Subtyps A(H1N1)pdm09 gehörten alle zur Gruppe 6B.1A.5a.2a, wobei die Hälfte davon zur Untergruppe 5a.2a.1 gehörte. Die antigenetisch charakterisierten A(H1N1)pdm09 Isolate standen dem empfohlenen Impfstamm für die nördliche Hemisphäre 2022/2023 nahe, nämlich A/Victoria/2570/2019. Eine Minderheit der Viren wurde durch das Antiserum, das gegen den Referenzstamm A/Denmark/3280/2019 gerichtet war, besser erkannt. Was die Influenza-B-Viren betrifft, so gehörten alle zur Klade V1A.3a.2 und alle waren antigenetisch eng mit dem für die nördliche Hemisphäre empfohlenen Impfstamm 2022/2023 B/Austria/1359417/2021 verwandt.

Die Influenza-Aktivität 2022/2023 war durch die Rückkehr eines fast ähnlichen Nachweisniveaus wie in den Saisons vor dem Auftreten von SARS-CoV-2 gekennzeichnet, jedoch mit einer früheren Spitze der Positivität.

Obwohl das Vogelgrippevirus A(H5N2) in der Schweiz bei Wildvögeln nachgewiesen wurde, sind bis heute keine zoonotischen Influenzainfektionen aufgetreten.

Bei Wildvögeln sowie bei Geflügel ist die Influenza-Aktivität in mehreren Ländern Europas, Amerikas und Asiens weiterhin besonders hoch. Die Ausweitung der Übertragung des H5N1-Stamms (Klade 2.3.4.4b) auf neue Vogelarten und die Zunahme der Übertragungsepisoden auf Säugetiere rechtfertigen eine verstärkte Überwachung des Risikos des Übergangs auf den Menschen.

Summary of surveillance of influenza activity 2022/2023

For the third year running within the Sentinelle surveillance network, nasopharyngeal samples received at the National Influenza Reference Centre were screened not only for influenza viruses, but also for SARS-CoV-2, RSV A and B, HCoV NL63, HCoV HKU1, HCoV OC43, HCoV 229E, HPIV1-4, HBoV, HAdV, RV/EV and HMPV. Of the 1,936 samples analysed, 1,376 tested positive for at least one respiratory virus. The SARS-CoV-2 influenza A and B viruses, as well as RSV and RV/EV, were the most frequently detected during this season.

Influenza returned to the Sentinelle network in week 40/2022. Of the 1936 samples screened, 472, or 34.3%, were positive for an influenza virus. In Switzerland, influenza viruses were detected in two successive waves. The first, and most important, wave, observed from week 40/2022 onwards, consisted mainly of type A viruses, predominantly A(H3N2). The second wave, which began in week 48/2022, was dominated by influenza viruses of the B/Victoria/2/87 lineage and, to a lesser extent, influenza A(H1N1)pdm09.

The influenza A viruses of subtype A(H3N2) detected in Switzerland belonged to subclades 2a.3a.1, 2a.3b, 2a.2a.1 and 2a.2a.1b of the 3C.2a1b.2a genetic group. The majority of these isolates were well recognised by the antiserum directed against the vaccine strain recommended for the northern hemisphere for 2022/2023, i.e. A/Darwin/9/2021 (3C.2a1b.2a.2). The A(H1N1)pdm09 subtype viruses all belonged to group 6B.1A.5a.2a, half of which belonged to subgroup 5a.2a.1. The antigenically characterised A(H1N1)pdm09 isolates were close to the 2022/2023 northern hemisphere recommended vaccine strain, A/Victoria/2570/2019. A minority of viruses were better recognised by antiserum directed against the reference strain A/Denmark/3280/2019. As for the influenza B viruses, all belonged to the V1A.3a.2 clade and all were antigenically close to the recommended vaccine strain for the northern hemisphere 2022/2023 B/Austria/13594.

Influenza activity in 2022/2023 was marked by a return to a level of detection almost similar to the seasons preceding the emergence of SARS-CoV-2, but with an earlier peak in positivity.

To date, although the avian A(H5N2) virus has been detected in wild birds in Switzerland, no zoonotic influenza infections have been recorded.

Influenza activity in wild birds and poultry remains particularly high in several countries in Europe, the Americas and Asia. The extension of the transmission of the H5N1 strain (clade 2.3.4.4b) to new avian species and the increasing number of transmission episodes involving mammals justify increased surveillance of the risk of the virus spreading to humans.

1. Introduction

Influenza virus infections are a major clinical and economic burden worldwide.[1] In Switzerland, the sentinel surveillance system (Sentinella) is a community-based network of primary care medical practitioners who report influenza-like illnesses (ILI) or coronavirus disease 2019 (COVID-19) cases to the Federal Office of Public Health (FOPH). A subgroup of sentinel practitioners also collects respiratory samples, which are sent to the National Reference Centre of Influenza (NRCI) for further characterization.

Since week 40 of the year 2020, in addition to influenza, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus (RSV), human coronavirus (HCoV) (NL63/HKU1/OC43/229E), human parainfluenza (HPIV) 1-4 viruses, human bocavirus (HBoV), human adenovirus (HAdV), human rhinovirus/enterovirus (RV/EV) and human metapneumovirus (HMPV) screening has performed during the annual surveillance.

This report summarizes the demographic, epidemiological and virological data gathered from samples processed and analysed by the NRCI from the 1rt of October 2022 to 21st of April 2023 (week 40/2022 to week 16/2023).

2. Influenza viruses

Influenza viruses are Orthomyxoviruses, a family of enveloped, negative, single-stranded ribonucleic acid (RNA) viruses (Figure 1), known to be causative agents of respiratory tract infections referred to as influenza disease or “flu”. Influenza viruses are divided into four types, A, B, C and D. They are mainly transmitted via respiratory and contact routes.[1,2]

Influenza A viruses have a wide host tropism, while influenza B viruses are mainly found in humans[3] and seals[4]. These two influenza types are responsible for the annual influenza epidemics, known as A(H3N2) and A(H1N1)pdm09 subtypes and B/Victoria/2/87 and B/Yamagata/16/88 lineages. This latter lineage has not been detected since March 2020 worldwide. Influenza C viruses can be isolated from swine and humans in whom they mostly cause limited mild to moderate symptoms, particularly in children. Influenza C’s epidemiological pattern has not been well studied. Influenza D viruses are mainly found in swine and cattle.[5] Even if the

pathogenic potential of influenza D virus in humans remains unknown, specific influenza D antibodies can be found in high proportions in individuals regularly in contact with cattle [6] and can cross-react with influenza C virus.[7] In addition influenza D has also been found in human nasal washes.[8]

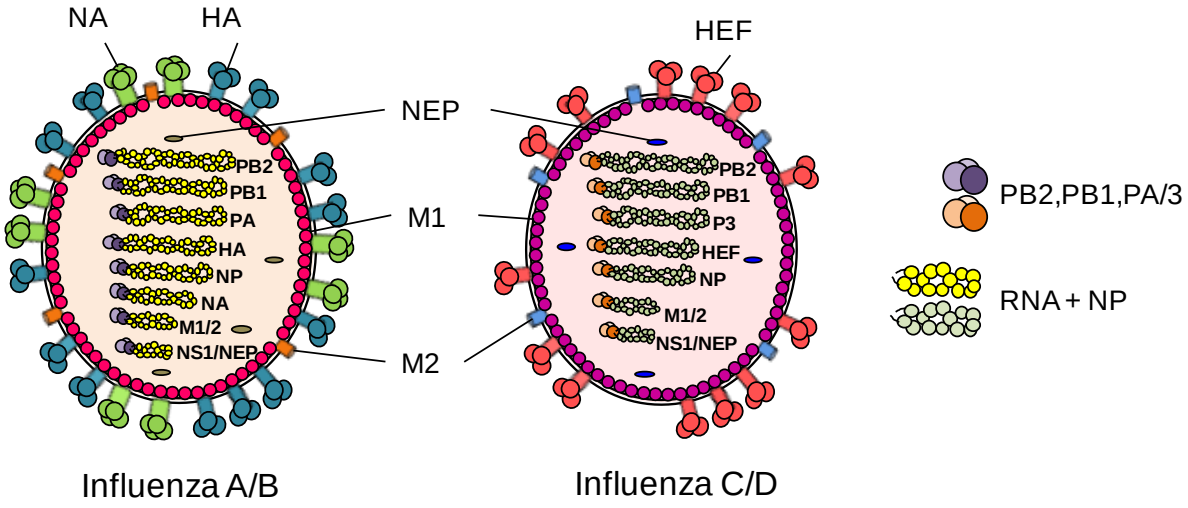


Figure 1. The structure of influenza viral particles. Basic protein 2 (PB2), 1 (PB1) and acidic protein or 3 (PA or P3) form a complex that corresponds to the RNA-dependent polymerase. The hemagglutinin (HA) and the hemagglutinin-esterase-fusion (HEF) play a role in virus attachment to sialic acids present at the surface of host cells and in fusion. The neuraminidase (NA) is crucial for virion detachment from the cellular surface by cleaving the HA on the virus surface. In influenza B, the NA gene also encodes the NB ion channel (not shown). The matrix protein 1 (M1) protein forms the viral capsid. The ion channel M2 allows virion acidification required for fusion. The nuclear export protein (NEP), also named "non-structural (NS) protein 2", is implicated in the export of the virus polymerase + RNA + nucleoprotein (NP) complex to the cell nucleus. The RNA + NP is also called ribonucleoprotein (RNP). The RNA segments PB1, PB2, PA/3, HA or HEF, NP, NA (not present in influenza C and D), M and NS are present inside the viral capsid, protected by NPs. Only non-structural protein 1 is not present in the viral particle, but it is expressed upon infection of the host cell. Influenza D is structurally closer to influenza C than to A and B.

Influenza viruses are known to evolve rapidly through two major mechanisms called antigenic drift and shift. The first is the consequence of the accumulation of mutations in the hemagglutinin (HA) and neuraminidase (NA) genes encoding the two major surface glycoproteins targeted by neutralizing antibodies produced against the virus. The antigenic drift drives the annual evolution of the virus and is therefore responsible for the need to regularly adapt the seasonal influenza vaccine strains. The antigenic shift results from the exchange (reassortment) of the influenza A HA and NA genes from different non-human species. It drives the emergence of new variants with high pandemic potential.[9]

Human infection with seasonal influenza A and B viruses can be asymptomatic or cause mild to severe diseases, which can be lethal. These viruses are of major concern in vulnerable individuals, such as the elderly (≥65 years old), pregnant

women, persons with underlying chronic diseases and young children, in whom they represent an important health threat.

3. Other respiratory viruses

Most respiratory viruses other than influenza are often associated with mild or moderate acute respiratory diseases. Nevertheless, they can also be linked to more severe syndromes and increased morbidity[10] in particular subpopulations.

3.1 Respiratory syncytial virus (RSV)

RSV A and B, as well as their multiple respective genotypes[11] , belong to the *Pneumoviridae* family, genus *Orthopneumovirus*. This enveloped viruses contain a non-segmented, single-stranded, negative sense RNA genome of ten genes coding for 11 proteins.[12] RSV is considered to be the most frequently causative agent of respiratory infections for children under 5 years old, but also an important threat for adults with underlying medical conditions, the immunocompromised[13], and the elderly.[14] Each year, RSV infections are estimated to be responsible for more than 3 million hospitalizations and more than 118'000 deaths globally[15], a large proportion in low income countries. Considering the high public health impact of RSV, the WHO has launched a study pilot actually on phase II on a global RSV surveillance programme similar to the one already existing for influenza.[16,17] During RSV upper respiratory tract infections (URTI), clinical manifestations are generally mild with symptoms such as runny nose, cough, nasal congestion, low-grade fever and decreased appetite. Most infants with RSV will develop an URTI, whereas 20-30% will develop potentially severe lower respiratory tract infection such as bronchiolitis, pneumonia, sometimes leading to respiratory failure. RSV infections at early age are also suspected to be linked to the development of asthma. Older children mostly present URTI symptoms. In adults and elderly, RSV symptoms can be similar to those caused by influenza virus.[14] Cases of RSV associated encephalitis[18], myocarditis[19,20], and hepatitis[21] have also been reported. Monoclonal antibodies are used in high-risk neonates as prevention therapy. New vaccines have been licenced by the U.S Federal Drug Administration (FDA) in 2023 as prevention for neonates in pregnant women and for the elderlies aiming to decrease the burden of the disease.[22] However, this countermeasure is not yet available in Switzerland.

3.2 Human metapneumovirus (HMPV)

Like RSV, HMPV are enveloped single-stranded, negative-sense non-segmented RNA viruses, which belong to the *Pneumoviridae* family, albeit to a distinct genus, namely the *Metapneumovirus*. Their 13kbp genome encodes for eight genes encoding for nine proteins. HMPV are divided in two genotypes and two sub-genotypes.[23]

HMPV infections are prevalent in young children <5 years old; and are second in terms of association with a hospitalisation requirement after RSV infection. Reinfection throughout life is common but the disease is generally milder in young adults. HMPV has a tropism for the upper, rather than lower respiratory tracts, and can lead to bronchiolitis, pneumonia, as well as acute asthma and chronic obstructive pulmonary disease exacerbations in adults. HMPV infections, as well as all the respiratory viruses described above, can be a major threat in vulnerable individuals such as the elderly, in whom they can also be fatal.[23]

3.3 Human coronaviruses (HCoVs)

Human coronaviruses are enveloped, single-strand, positive-sense 5′-capped and 3′-polyadenylated RNA viruses belonging to the subfamily *Orthocoronavirinae* of the Coronaviridae family. Their 30kb genome encodes more than 20 proteins.[24] *Orthocoronavirinae* are divided in four genera *: α-coronavirus, β-coronavirus, γ-coronavirus* and *δ-coronavirus. Alpha-* and *β-coronaviruses* infect mammalian species while *γ-* and *δ*-coronaviruses are avian viruses.[25]

Before the emergence of SARS-CoV-2 in 2019, four coronaviruses were known to cause, generally mild to moderate diseases in humans: HCoV 229E, NL63, OC43, and HKU1; while two were associated with more severe lower respiratory tract infections: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Most HCoV seem to peak during winter[26] and to display biannual epidemic patterns.[27]

The first cases of SARS-CoV and MERS-CoV were respectively identified in 2002 and 2012. SARS-CoV is currently not circulating in the human population, while sporadic laboratory-confirmed MERS-CoV infections continue to be reported to the WHO as of May 2023.[28,29]

HCoV 229E, NL63, OC43, and HKU1 can infect the upper and lower respiratory tracts of both adults and children, and are, as many other respiratory viruses, often associated with common colds of mild to moderate intensity depending on the viral species. Nevertheless, in vulnerable individuals, both in children and adults, HCoV 229E, NL63, OC43, and HKU1 may exhibit more severe diseases as bronchiolitis and pneumonia.[27] Neurological manifestations have also been reported.[30]

SARS-CoV-2 is a *β-coronavirus* responsible for the current coronavirus disease pandemic (COVID-19) that emerged in China in December 2019.[31] Most of the first identified cases of COVID-19 were linked to Huanan Seafood Wholesale Market in Wuhan city where live-wild animals were also traded. However, the origin of the index case(s) remains unknown[32] and the virus "emergence process" in the human population remains controversial.[33]

Clinical manifestations of SARS-CoV-2 range from mild to severe diseases with non-specific symptoms similar to those caused by other respiratory viruses. Children usually manifest mild symptoms and the risk of hospitalisation or mortality is very low[34], while the burden of disease varies with age, comorbidities, and depends on sex. Females are at slightly higher risk of severe outcomes than males.[35] Asymptomatic cases have also been described.[24] Some individuals experience long COVID or Post-Covid conditions defined by the WHO as "the condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19, with symptoms that last for at least two months and cannot be explained by an alternative diagnosis".[36] Other manifestations concern neuropsychiatric and cognitive symptoms, kidneys, heart, and blood vessels.[37-41]

As of 20 August 2023, 4'430'563 laboratory-confirmed cases (769'806'130 worldwide, as of 16 August 2023) and as of 13 August 2023 14'125 deaths (6'955'497 worldwide, as of 2 August 2023) have been reported in Switzerland and Lieschtenstein[42,43]

SARS-CoV-2 can be transmitted from human-to-human via respiratory droplets, fomites and by aerosols.[44] SARS-CoV-2 RNA has also been detected in blood[45], urine and faeces.[46] Some studies have observed viral RNA fragments in breast milk, raising the concern regarding the possibility of mother to child transmission via

breastfeeding.[47] Wild and domestic animal infections by human SARS-CoV-2 have also been observed.[48-50]

The SARS-CoV-2 virus continuously evolves into different genetic clades and subclades. Some genetic lineages were specifically identified as higher public health threats and classified in four risk groups, i.e. variant of concern (VOC), variant of interest (VOI) and variant under monitoring (VUM). VOI is defined by the WHO as “a variant with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, virulence, antibody evasion susceptibility to therapeutics or detectability, and identified to have a growth advantage over other variants, with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global health”. VOC variant is defined as a VOI and shares additional characteristics at a global public health scale such as “detrimental change in clinical disease severity, in COVID-19 epidemiology causig substantial impact on health system requiring major public health interventions or significant decrease in the effectiveness of available vaccines in protecting against severe disease.” “The VUM definition is “a variant with genetic changes that are suspected to affect virus characteristics and early signals of growth advantage relative to other circulating variants, but evidence of phenotypic or epidemiological impact is unclear, requiring enhanced monitoring and repeat assessment pending new evidence. This includes variants with unusually large number of antigenic mutations but with very few sequences and/or it is not possible to estimate its relative growth advantage.”[51]

3.4 Human parainfluenza (HPIV)

HPIV are enveloped, non-segmented, single-stranded, negative-sense RNA viruses belonging to the *Paramyxoviridae* family. Their 15’000 base-pair genome only encodes six proteins. HPIV viruses are divided in four genotypes. Genotype 4 is further subdivided into a and b genotypes. HPIV 1 and 3 belong to the *Respirovirus* genus, while HPIV 2 and 4 to the *Rubulavirus* genus.

HPIV can infect both the upper and lower respiratory tracts of children, often <5 years old, and adults. HPIV, along with RSV, infections are major causes of morbidity and mortality in young children worldwide.[52] Even if they are generally considered as mild in healthy individuals, HPIV infections can also result in more severe respiratory

diseases in immunocompromised individuals as well as in children.[53] HPIV-1 and HPIV-2 cause croup and cold-like symptoms, while HPIV-3 often results in bronchiolitis, bronchitis and pneumonia.[54] HPIV-4 is less well studied but seems to exhibit symptoms similar to HPIV-3 in children.[55] HPIV types may occur at specific seasons annually. HPIV-1 and -2 appear commonly in the fall. Although HPIV-2 is less detected it occurs especially when the detection of HPIV-1 is low. HPIV-3 occurs in spring and early summer and is particularly high when the detection of HPIV-1 and -2 is low. The seasonal patterns of HIPV subtypes 4a and 4b are not well defined though they seem to occur in fall and winter yearly.[56]

3.5 Human bocaviruses (HBoV)

Human bocaviruses (HBoV) 1 to 4 are non-enveloped, non-segmented, single-stranded DNA viruses belonging to the family *Parvoviridae,* subfamily within the *Parvovirinae* family. Their approximately 5'000 base-pair genome encodes at least eight proteins.[57]

After parvovirus B19, HBoV is the second parvovirus known to be pathogenic to humans. HBoV-1 considered as a causative agent for acute respiratory infection (ARI) is more commonly found in respiratory specimens of young children[57], in whom disseminated infection can be observed, but it can also be detected in adults.[58] HBoV-2, -3 and -4 are commonly identified in stool samples.[59] They are also often found as co-infections. Their clinical presentation is similar to other respiratory viruses leading to either asymptomatic or mild URTI with HBoV1. However more severe clinical manifestations as encephalitis, myocarditis[60], idiopathic lung fibrosis, as well as yet to be confirmed carcinogenesis have also been associated with HBoV, particularly type 1.[61]

3.6 Human adenoviruses (HAdV)

Adenoviruses are non-enveloped, double-stranded DNA viruses of more than 26'000 base-pairs encoding several non-structural and structural proteins, that infect both animals and humans. HAdV belong to the *Mastadenovirus* genus of the *Adenoviridae* family and are further divided into species A to G, within 113 genotypes and more than 50 serotypes infect humans. HAdV B and E both infect the conjunctiva as well as the upper and lower respiratory tracts, while D and C are specific to only one of

these anatomical sites, respectively. Finally, types F and G have a tropism for the gastrointestinal tract. Most HAdV infections are either asymptomatic or mild, particularly in young children. However, in vulnerable individuals (e.g. immunocompromised), the clinical manifestations are broader and more severe with possibly fatal outcomes.[62,63] Of note, HAdv has recently been suggested to be linked to acute hepatitis of unknown aetiology in children.[64] A recent study, based on a Wastewater-based epidemiology (WBE) approach has highlighted that the HADV-F40/F41 viruses could be involved in acute hepatitis cases in children.[65]

3.7 Rhinovirus/Enterovirus (RV/EV)

Picornaviruses can be pathogenic for both animals and humans. They are non-enveloped, single-stranded, positive-sense RNA viruses with genomes ranging from 7'200 to 8'500 bases long. RV (A-C) and EV (A-D) are species of the *Enterovirus* genus of the *Picornaviridae* family that are responsible for a high number of human infections annually.[66,67]

Due to their resistance to low pH and high temperatures (37°C), enteroviruses can survive the acidic gastric environment and infect the small intestine. In contrast, rhinoviruses being pH-sensitive and replicating optimally at the neutral pH and slightly lower temperature (~33°C) are found in the nasal mucosa. While rhinoviruses usually cause mild upper respiratory infections and enteroviruses usually cause non-severe diseases, such as hand, foot and mouth disease, these viruses can sometimes cause more severe manifestations as pancreatitis, hepatitis, myocarditis, encephalitis, flaccid myelitis, paralysis and even death.[66] It is notably the case of poliovirus, the causative agent of major poliomyelitis epidemics before the initiation of the Global Polio Eradication Initiative by the WHO in 1988. Of note, since 2022, France, Croatia, Italy, Spain, Sweden, and the United Kingdom of Great Britain and Northern Ireland reported 19 cases of severe enterovirus-echovirus 11 neonatal infections, some with a fatal outcome.

Rhinoviruses circulate annually seeming to peak between spring and early summer and are thus responsible for most of the ARI symptoms during this period.[68]

4. Methodology

4.1 Clinical identification of cases

A network of primary care practitioners voluntarily participate in the epidemiological national influenza surveillance on a yearly basis. Each week, they are requested to report ILI and COVID-19 suspected cases.

Within the Swiss Sentinel system, ILI cases are defined as sudden high-grade fever (>38°C) onset and cough or sore throat. The presence of other symptoms, such as malaise, myalgia, joint pain, and headache, as well as gastrointestinal symptoms is not required. Patients presenting with a secondary disease (pneumonia, bronchitis, otitis, etc.) consecutive to an unreported influenza are also expected to be reported.

COVID-19 suspected cases are defined as symptoms of acute respiratory tract disease (i.e., cough, sore throat, shortness of breath, chest pain), and/or acute confuse state or deterioration of general condition with no other aetiology in the elderly, and/or fever with no other aetiology, and/or sudden onset of anosmia, and/or ageusia. Of note, the circulation of COVID-19 still has a major impact on ILI data collection within the Sentinella network as, even though different case definitions are used, COVID-19 and influenza symptoms remain often similar. Therefore, it seems most likely that some clinically reported ILI were in fact COVID-19 cases and vice versa.

A subgroup of these sentinel practitioners collects nasopharyngeal swabs from patients fitting the ILI and COVID-19 case definitions for subsequent viral detection and further virus characterization.

4.1.1 Sentinella population

The sentinel practitioners who send samples to the NRCI are asked to complete a brief case report form. The following data are collected: patient identity, address, and phone number (necessary for mandatory reporting of COVID-19 cases only); sample type; age; gender; suspicion for a COVID-19 and/or Influenza, and Influenza and COVID-19 vaccination status.

4.2 Molecular detection of influenza viruses[1]

Nasopharyngeal swabs received at the NRCI are submitted to virus screening and subtyping tests. 400 µl of the initial respiratory specimens are extracted using the NucliSens EMAG magnetic bead system (BioMérieux, Geneva, Switzerland) and viral RNA is recovered in 75 µl of elution buffer 3. For screening, a one-step, rRT-PCR adapted from the 2009 USA Centers for Disease Prevention and Control (CDC) protocol is used to detect the presence of influenza A and B viral genomes. The duplex rRT-PCR targets are the M protein and the non-structural (NS) protein genes for influenza A and B viruses, respectively, and are combined with a custom manufactured rRT-PCR mix produced by Eurogentec. rRT-PCR reactions were performed using 5 µl of extracted RNA and 15 µl of reaction mix and run on Quantstudio 7 Pro or 5 thermocyclers.

Influenza A positive samples are subtyped using an in-house-developed quadruplex rRT-PCR targeting the HA (H1 and H3) and the NA (N1 and N2) genes discriminate between influenza A(H1N1)pdm09 and A(H3N2) strains. This new assay is a mix of already validated (in-house H1 and H3 CDC) and newly-designed ($N2_2$) rRT-PCR combinations, adapted from the one used in the study by Henritzi *et al* [69] (N1). The quadruplex detection limit is similar to that of the diagnostic rRT-PCR. The N1 combination can detect $H1N1v_3$, $swH1N1_4$ and $H5N1_5$ isolates tested during the assay validation process. The H3 and N2 rRT-PCR combinations are also able to

[1] The evaluation of the proficiency of the Laboratory of Virology at Geneva University Hospitals in performing molecular detection of influenza viruses is accessed through the World Health Organization (WHO) External Quality Assessment Programme for the Detection of Influenza Viruses by RT-PCR, and was initiated in 2007 by the WHO (https://www.who.int/influenza/gisrs_laboratory/external_quality_assessment_project/en/).

[2] Human N2 sequences from 2009-2017 were used for the N2 rRT-PCR design.

[3] H1N1v: A/Switzerland/***2244/2011 and A/Berne/****6552/2017, variants isolated from Swiss pig breeders.

[4] swH1N1 35 (2008): virus isolated from a Swiss pig.

[5] H5N1: A/Hong Kong/6841/2010 (EQAP panel 16) and A/goose/Qinghai/1A/05*A/PR8/34(INT).

detect the A/Wisconsin/12/2010 H3N2 triple reassortant (H3N2tr),[70] although the latter virus is not known to circulate in Switzerland. Nevertheless, if needed, additional tests are available at the NRCI to discriminate seasonal H3N2 from H3N2tr viruses. Influenza B/Yamagata/16/88-like (Yam) and B/Victoria/2/87-like (Vic) lineages are distinguished using a duplex rRT-PCR adapted from Schweiger et al. 2000.[71] rRT-PCR reactions were performed using 5 µl of extracted RNA and 20 µl of SuperScript™ III Platinum™ One-Step qRT-PCR Kit w/ROX (Invitrogen™) reaction mix and run on Quantstudio 5 thermocyclers.

A random selection of rRT-PCR-negative specimens is inoculated on cells for viral culture. This strategy allows the detection of influenza strains that may have "escaped" rRT-PCR detection. For example, this could be the case in the presence of viruses carrying mutations in the genomic regions targeted by rRT-PCR screening. For biosafety reasons, only negative-SARS-CoV-2 samples were submitted to cell culture.

4.3 Antigenic and genetic characterization of influenza virus

A selection of influenza viruses is submitted to phenotypic and genotypic analysis. In general, five RT-PCR positive samples with cycle threshold (Ct) values <30 are chosen per week for further characterization of samples with sufficient HA titers and are submitted to a hemagglutination inhibition (HAI) assay. The latter allows assessment of the antigenic similarity between reference and circulating influenza strains.

A subset of viruses is also sequenced to assess the phylogeny of the circulating isolates and to determine how genetically close they are to reference vaccine strains. Sequencing also allows for the detection of key mutations previously described as conferring resistance to NA inhibitors (NAIs) or Baloxavir Marboxil (BM) treatments, while M and NS genes sequencing allows to check the adequacy of rRT-PCR primers and probes used for influenza A and B screening.

4.3.1 Cell culture

Both influenza positive and negative samples are cultured on MDCK and MDCK-SIAT1 cells. This allows to ensure that a low positivity rate for influenza is not due to a rRT-PCR detection defect.

In brief, 400 µl of transport medium containing nasopharyngeal swabs are incubated at 33°C on MDCK cells and 37°C on MDCK-SIAT1. The presence of a cytopathic effect (CPE) is monitored for a period of up to 7 days. If CPE is present, samples are submitted to an hemagglutination assay. If CPE is absent or low after 7 days, the cells are screened for influenza viruses by immunofluorescence using monoclonal influenza A and B antibodies combined with mouse fluorescein isothiocyanate-conjugate (Merck-Millipore, Chemicon®, Schaffhausen, Switzerland).

4.3.2 Hemagglutination inhibition (HAI) assay

A two-fold serial dilution is performed using 50 µl of viral suspension buffer in SALK solution (5%) and 25 µl of glutaraldehyde-fixed guinea pig RBC (1.5%) are added for 1 h incubation at 4°C. The HA titer is defined as the last dilution in which the complete hemagglutination is still observed. After titer determination, HAI assay is performed as follows: 25 µl of reference antisera are added in the first two wells of a 96-well plate. Two-fold dilutions are prepared by adding 25 µl of SALK solution (5%) in the second well. 25 µl are then collected from the same well and the procedure is repeated to the end of each line. 25 µl of viral suspension containing 4 HA units are added to the antisera dilution and incubated for 1 h at room temperature. 25 µl of guinea pig RBC are then added to each well. The plates are incubated, then, for 1 h at 4°C. The HAI titer corresponds to the last antiserum dilution for which HA is still inhibited. This titer is compared to the homologous titer obtained with reference strains submitted to their corresponding antigenic antisera (antigenic table). The antigenic tables are influenza strain-specific (Figure 2) and are thereby, adjusted yearly. Since the serum is initially diluted 1/8, the titers provided in figure 2 should be multiplied by 8 to obtain the final titers.

Reference antisera and corresponding viral strains are kindly provided by the World Health Organisation (WHO) Collaborating Centre Reference Laboratory at the Francis Crick Worldwide Influenza Centre (WIC, London, UK). HAIs are performed with glutaraldehyde fixed guinea pig Red Blood Cells (RBC) (Charles River, Lyon, France).

a. H1N1pdm09	A/Brisbane/02/2018	A/Guangdong-Maonan/SWL1536/2019	A/Victoria/2570/2019	A/Denmark/3280/2019
A/Brisbane/02/2018	**64**	1024	<16	32
A/Guangdong-Maonan/SWL1536/2019	1024	**2048**	<16	16
A/Victoria/2570/2019	<16	128	**128**	512
A/Denmark/3280/2019	32	2048	256	**1024**

b. H3N2	A/England/538/2018	A/Hong Kong/2671/2019	A/Cambodia/ e0826360/2020	A/Darwin/9/2021
A/England/538/2018	**1024**	128	256	512
A/Hong Kong/2671/2019	256	**1024**	256	128
A/Cambodia/e0826360/2020	512	128	**2048**	512
A/Darwin/9/2021	256	128	512	**1024**

c. B	B/Brisbane/60/2008	B/Washington/02/2016	B/Austria/135941/2021	B/Phuket/3073/2013
B/Brisbane/60/2008	**2048**	128	<16	<16
B/Washington/02/2016	512	**512**	16	<16
B/Austria/135941/2021	128	16	**1024**	32
B/Phuket/3073/2013	64	<16	<16	**1024**

Figure 2. Antigenic tables for the 2022/23 influenza season. These tables correspond to the HI titers of reference influenza strains (first column of the tables) incubated with ferret reference antisera (first row of the tables). The HI titers correspond to the highest dilution where an inhibition is still observed. The titer obtained after incubation of a given strain with the corresponding ferret antiserum is known as the homologous titer (in bold). In red: 2022/2023 influenza vaccine strains. a, b and c correspond to A(H1N1pdm09), A(H3N2) and B (Victoria-lineage in deep blue, Yamagata-lineage in light blue) influenza virus antigenic tables, respectively.

4.3.3 Influenza genes sequencing

Positive samples, with a Ct value <30, selected for sequencing are processed as follows: 400 µl of the initial respiratory specimens are extracted using the NucliSens EMAG magnetic bead system (BioMérieux, Geneva, Switzerland) and viral RNA is recovered in 50 µl elution volume.

Whole genome sequencing of influenza is performed by Microsynth AG. Influenza A and B segments are pre-amplified using, for influenza A[72], a mix of two forward primers and a single reverse primer located in the conserved regions of the viral genome segments; and for influenza B[73], a primer cocktail of 13 different forward and reverse primers. Libraries were prepared using Illumina Nextera kits and were then run on the Illumina platform MiSeq using ≥2*150 reads. Data is quality-filtered and de-multiplexed by Microsynth AG before being sent to the NRCI for in-house sequence analysis. The best sequencing results are obtained for samples with Ct values <25.

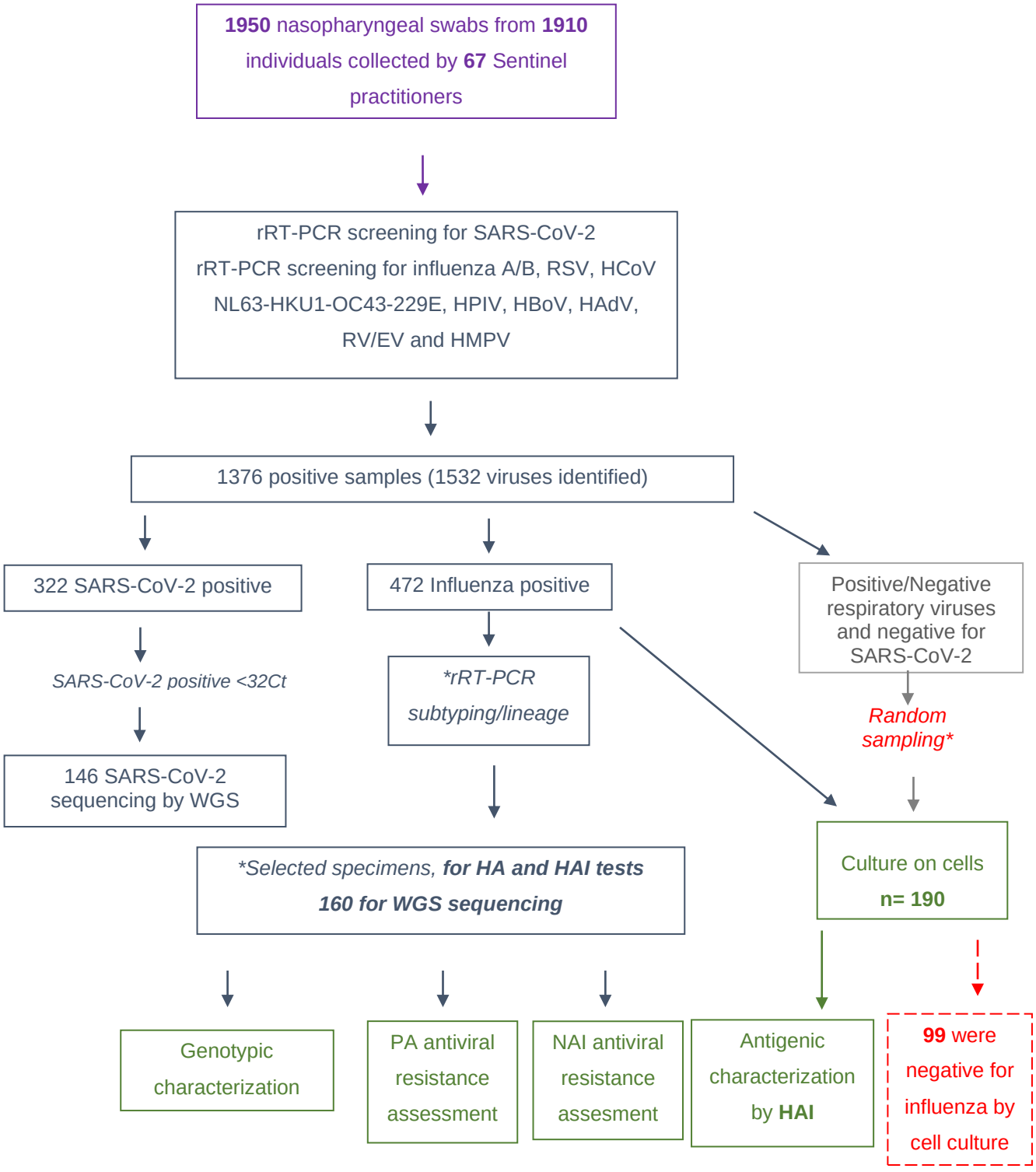


Figure 3. Flow chart of Sentinel samples collection and processing. Starting in October 2022, only influenza positive and negative samples that were also negative for SARS-CoV-2 were submitted to cell culture. Subtyping, antigenic, and genetic characterizations were only performed for influenza virus.

4.4 Molecular detection of SARS-CoV-2 viruses

SARS-CoV-2 viruses are diagnosed by PCR using the Cobas® SARS-CoV-2 reagents on a Cobas® 6800 instrument according to the manufacturer's conditions. In some rare cases GeneXpert® Xpress SARS-CoV-2 (Cepheid) test was also used.

4.4.1 Genetic characterization of SARS-CoV-2 viruses

Genetic characterization of SARS-CoV-2 is done by whole genome sequencing by the Genome Centre (Campus Biotech, Geneva, Switzerland) within the SARS-CoV-2 national genomic surveillance program. The resulting consensus sequences are shared nationally via the Swiss Pathogen Surveillance Platform (SPSP) and internationally through submission to Global Initiative on Sharing All Influenza Data (GISAID).

4.4.2 Molecular detection of respiratory viruses other than influenza and SARS-CoV-2

All nasopharyngeal swabs sent to the NRCI for influenza and SARS-CoV-2 detection are also screened for common respiratory viruses using a PCR panel already used by the Geneva University Hospitals Laboratory of Virology. RSV, HCoVs NL63/HKU1/OC43/229E, HPIV, HBoV, HAdV, RV/EV and HMPV are detected using a combination of seven custom manufactured rRT-PCR mixes produced by Eurogentec. Mixes' targets are grouped as follows:

1. RSV/ canine distemper virus (CDV, our extraction efficiency control),
2. HCoV NL63/OC43,
3. HCoV 229E/HKU1,
4. HBoV/HPIV2-4 (does not distinguish between HPIV 2 and 4),
5. HMPV/HPIV1-3 (does not distinguish between HPIV 1 and 3),
6. RV/EV, and
7. HAdV/CDV

rRT-PCR reactions are performed using 5 ul of e-Mag Nuclasens extracted RNA and 15µl of reaction mix and run on Quantstudio 7 Pro and 5 thermocyclers.

5. 2022/2023 surveillance period

Data gathered in the present report corresponds to the analysis of sentinel samples received at the NRCI from October 1st, 2022 (week 40/2022) to April 22nd, 2023 (week 16/2023). Figure 3 summarizes the flow of analysis at the NRCI.

5.1 Sentinella Population

5.1.1 Annual NRCI surveillance (2022/2023)

From week 40/2022 to week 16/2023, 67 sentinel practitioners collected nasopharyngeal samples from 1910 individuals for further screening at the NRCI. Among those, 1053 (55.1%) were female and 857 (44.9%) were male. Nineteen male and sixteen female were sampled twice. One female was tested at least 3 times during the surveillance period (Table 1).

5.1.2 Stratification by gender and age

When further stratifying the population by age groups (i.e., 0-4, 5-14, 15-29, 30-64 and ≥65 years old), a slightly higher percentage of males in the 0-4, 5-14, 30-64 years old group and of females in the >65 group could be observed (Table 1). Data on age was available for all individuals (median 41 years old, range [0 to 96 years]; 95% confidence interval (CI) 39-42 years old). Median age was 39 years old for males (range [0 days to 96 years]; 95% CI 37-40 years old) and 43 years old for females (range [0 to 94 years]; 95% CI 41-44 years old) (Figure 4).

Table 1: Age and gender distribution of the Sentinella population, from weeks 40/2022 to 16/2023

Number of individuals	*Male*	*Female*	*Totals*
	857	1053	1910
Age group distribution			
0-4	53	46	99
	6.2%	*4.4%*	*5.2%*
5-14	78	56	134
	9.1%	*5.3%*	*7.0%*
15-29	171	206	377
	20.0%	*19.6%*	*19.7%*
30-64	410	526	936
	47.8%	*50.0%*	*49.0%*
≥65	145	219	364
	16.9%	*20.8%*	*19.1%*

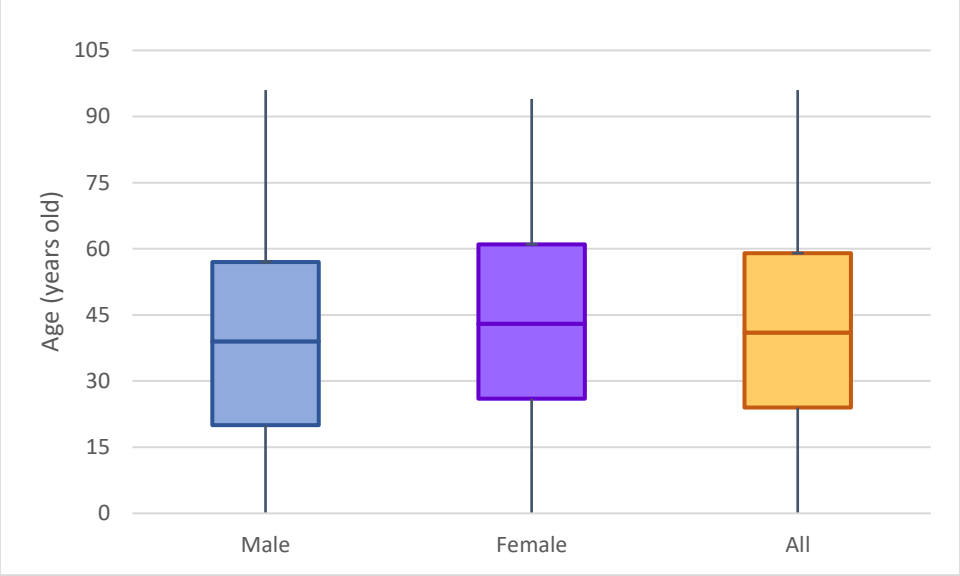


Figure 4. Age distribution by gender of the Sentinel population, from weeks 40/2022 to 16/2023. Distribution pattern for the entire population. Median ages, 25% and 75% quartiles are shown in bold lines.

5.1.3 Attribution of samples to Covid-19 and Flu suspicion criteria

As mentioned previously cases reported to, and samples tested, in the Sentinella surveillance are based on clinical suspicion of ILI and COVID-19. One thousand two hundred eleven (1211) samples originated from individuals with both COVID-19 and ILI suspicions. Four hundred and thirty-eight (438) and 141 swabs corresponded to COVID-19 and Influenza suspicions respectively. Suspicion criteria was unknown for 160 samples.

5.2 Detection of respiratory viruses in nasopharyngeal samples

From week 40/2022 to week 16/2023, a total of 1936 out of 1950 nasopharyngeal samples (NPS) were screened for influenza, SARS-CoV-2, RSV, HCoV NL63, HCoV HKU1, HCoV OC43, HCoV 229E, HPIV, HBoV, HAdV, RV/EV and HMPV. Fourteen samples were discarded from the screening due to pre-analytical issues.

One thousand three hundred and seventy-six samples (71.1%) were positive for at least one respiratory virus and 1’532 viruses in total were detected. Among these, the following pathogens were identified: SARS-CoV-2 (n= 322; 21%), influenza A virus (n=314; 20.5%), RV/EV (n= 303; 21.7%), influenza B virus (n= 158; 10.3%), RSV (n=149; 9.7%), HAdV (n=66; 4.3%), HMPV (n=63; 4.1%), HCoV OC43 (n=52; 3.4%), HPIV 1/3 (n=36; 2.3%), HCoV NL63 (n=32; 2.1%), HBoV (n=12; 0.8%), HPIV 2/4 (n=11; 0.7%), HCoV 229E (n=9; 0.6%), and HCoV HKU1 (n=5; 0.3%) (Figure 5a).

A maximum positivity rate of 88.7% was observed during week 51/2022, the latter was close to the peak of ILI consultations for 2022/2023 in Switzerland (Appendix 1). A minimum positivity rate of 56.6% could be seen during week 2/2023. The median positivity rate for this 2022/2023 season was of 69% (range [56.6 to 88.7%]; 95% CI 65.8-72.2%) (Figure 5b).

RV/EV, SARS-CoV-2, RSV, and HAdV were regularly detected throughout the surveillance period (Figure 5b). SARS-CoV-2, RV/EV and RSV were dominant at the beginning of the season. Influenza virus detection started to increase during week 40/2022 and surpassed the other respiratory viruses from week 50/2022 to week 12/2023. While HPIV2/4 and HPIV1/3 were initially sporadically detected before week 40, their prevalence increased between week 40/2022 and week 43/2022. They were also regularly detected from week 7 to week 16/2023. Detection of HMPV and human

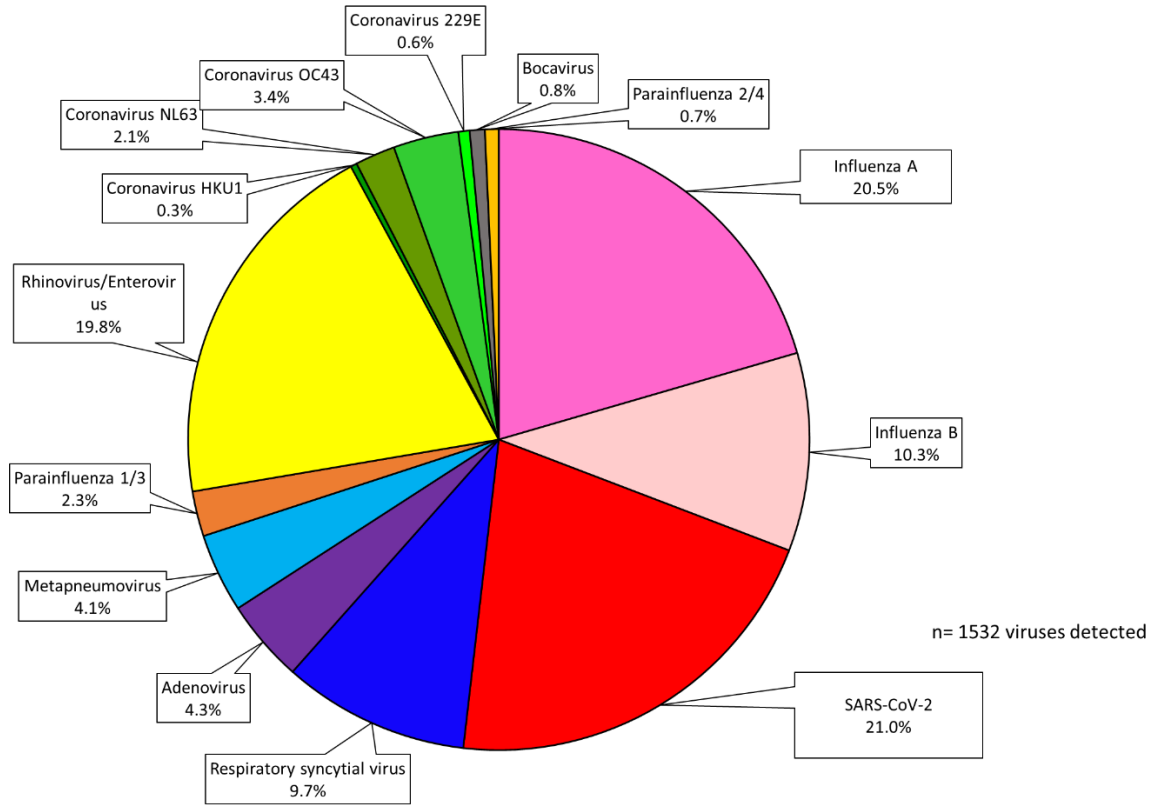
coronaviruses other than SARS-CoV- increased from week 50/2022, while RSV started to decrease (Figure 5b).

From week 40/2022 to week 16/2023, more than one virus was detected in 144 (10.5%) out of 1375 positive samples (Appendix 2). The highest number of co-detections (n=15) was observed in week 51/2022, which coincides with the highest positivity rate of the surveillance period (figure 5b). Among the 144 co-detections, 74 concerned RV/EV (51.4%); which were mainly observed with SARS-CoV-2 (23/74), RSV (19/74) or Influenza (11/74).

When stratifying positive specimens by age groups, we observed that, in the ≥ 65 year-old group, SARS-CoV-2 (n=100; 36.9%) was, as one could expect, the most prevalent virus, followed by RV/EV (n=60; 22.1%), RSV (n=35; 12.9%) and IA (n=28; 10.3%). No HKU1, nor HBOV were detected in this group (Figure 6a-b).

HBoV was detected at low levels throughout the season, and mainly in toddlers amongst the detected HBoV (n=7; 58.3%). RV/EV (n=39; 33.3%), RSV (n=23; 19.7.4%), HAdV (n=15; 12.8%) and IA (n=10; 8.5%), and) were the main viruses found in the 0-4 year-old group. (Figure 6a-b).

a



b

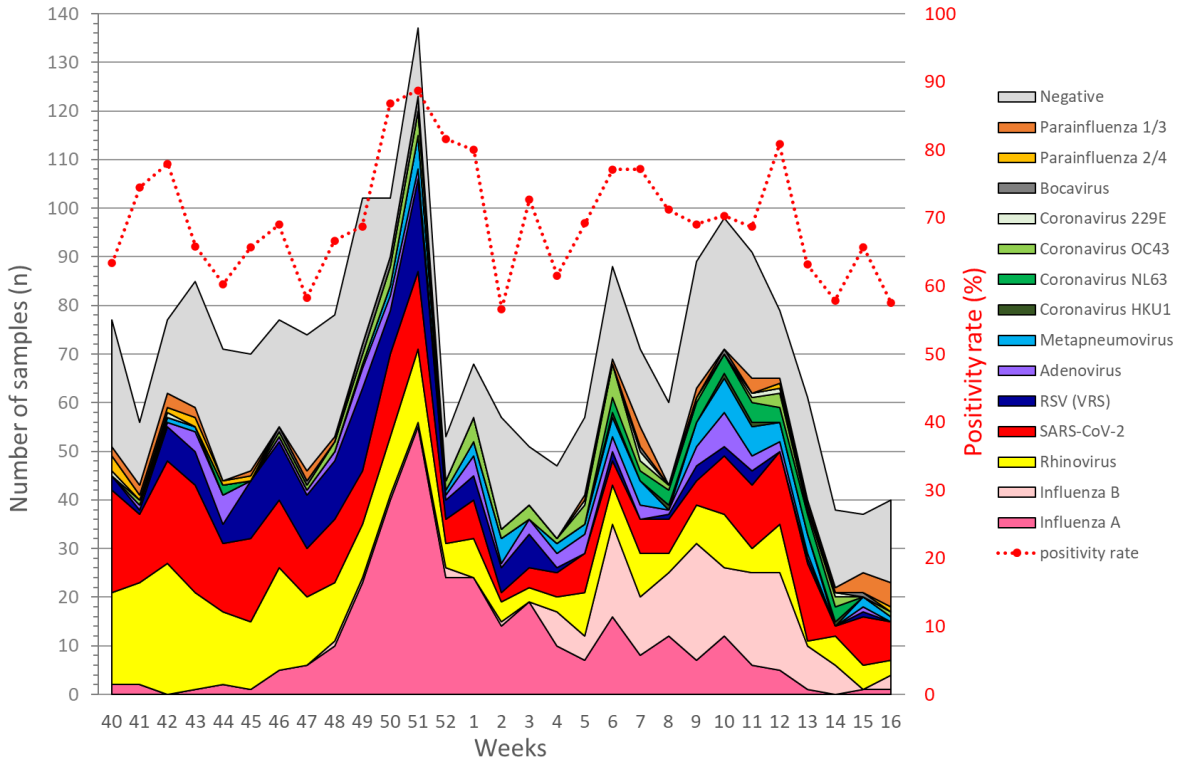
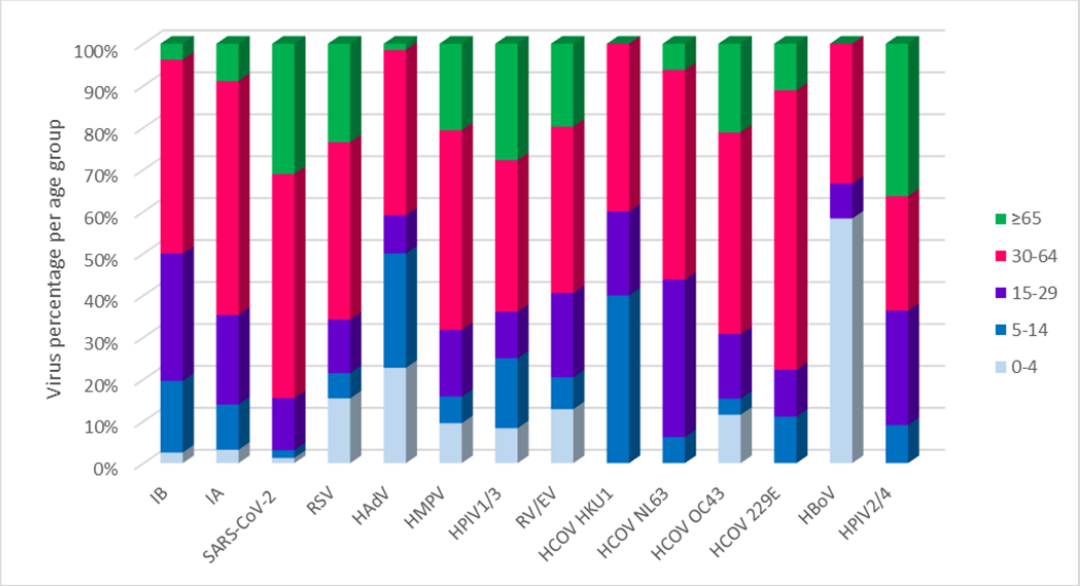
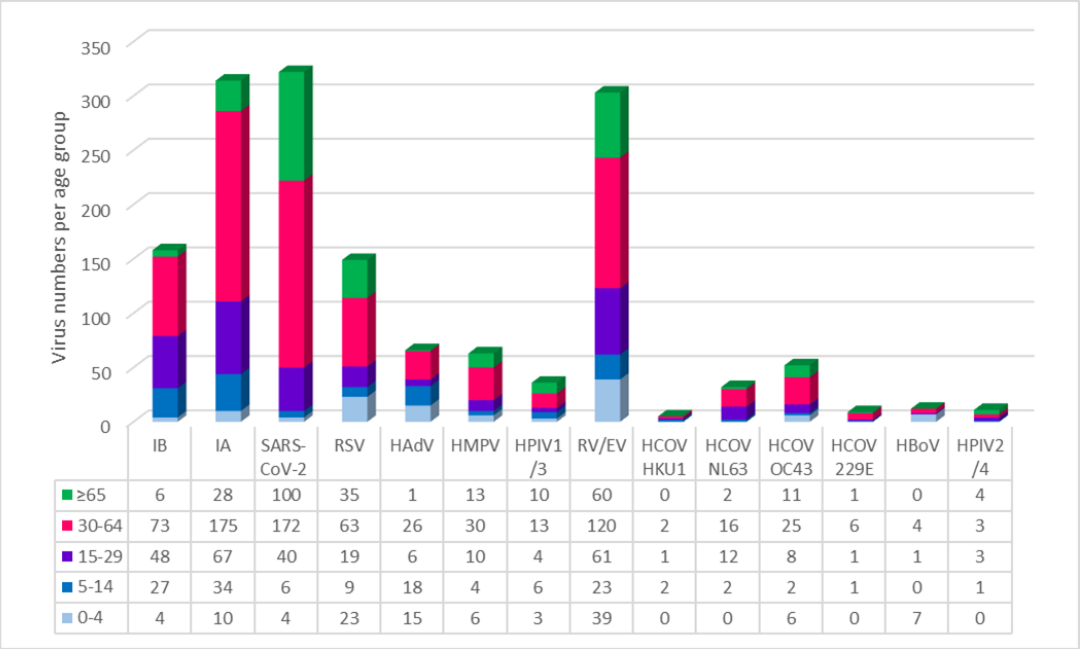


Figure 5. Percentage and temporal distribution of respiratory viruses detected in NPS collected from week 40/2022 to 16/2023. a. Percentages of the different respiratory viruses (n=1532) detected in 1936 NPS. **b**. Dynamic distribution of the samples tested and the detected pathogens throughout the surveillance period. Positivity rate is based on the number of positive samples per total number of samples received each week.

a



b



	IB	IA	SARS-CoV-2	RSV	HAdV	HMPV	HPIV1/3	RV/EV	HCOV HKU1	HCOV NL63	HCOV OC43	HCOV 229E	HBoV	HPIV2/4
≥65	6	28	100	35	1	13	10	60	0	2	11	1	0	4
30-64	73	175	172	63	26	30	13	120	2	16	25	6	4	3
15-29	48	67	40	19	6	10	4	61	1	12	8	1	1	3
5-14	27	34	6	9	18	4	6	23	2	2	2	1	0	1
0-4	4	10	4	23	15	6	3	39	0	0	6	0	7	0

Figure 6. Respiratory viruses' distribution: a. per age group in percent **b.** in absolute numbers of positive samples.

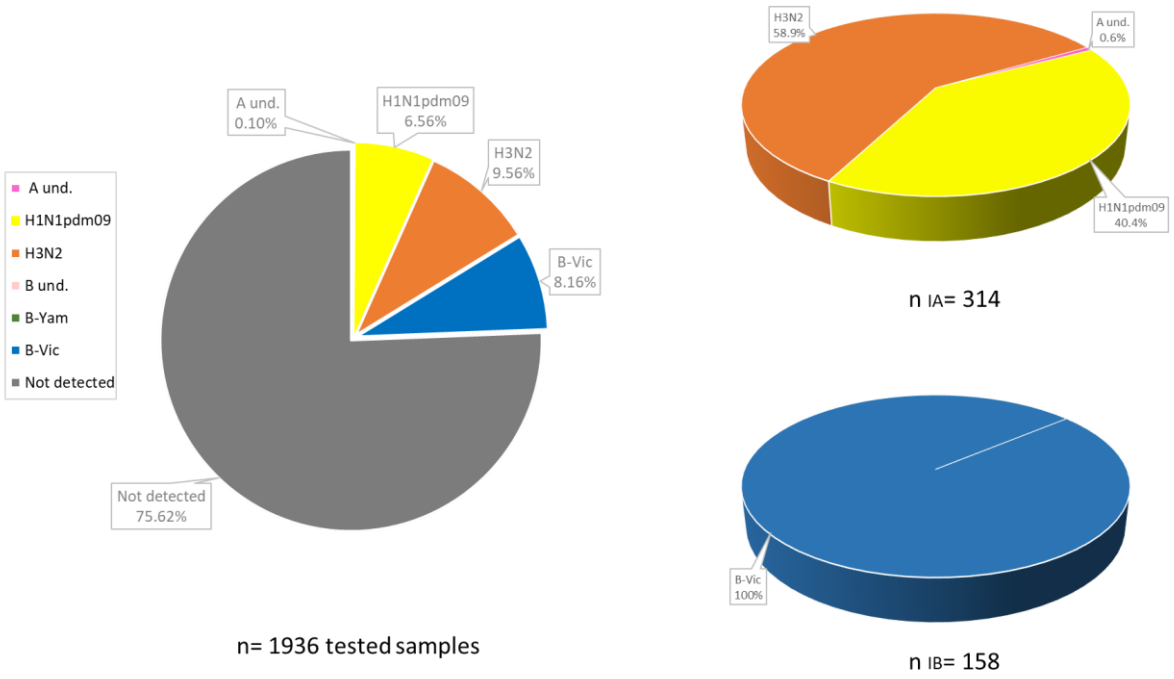
When stratifying the positive cases by age group and gender no significant difference could be observed between female and male (Figure 7).

Figure 7. Respiratory viruses' distribution by gender and age groups in absolute number. Light and dark shades represent the female and male sex respectively.

5.3 Detection of influenza in nasopharyngeal samples

Among the 1’936 samples tested, 314 influenza A viruses (16.2%) and 158 influenza B viruses (8.2%) were identified (Figure 8a). Among the influenza A viruses, a majority were subtyped as A(H3N2) (n=185; 58.9%) and 127 (40.4%) as A(H1N1)pdm09. Two (0.6%) influenza A viruses could not be subtyped due to low viral load. All the influenza B viruses identified, belonged to the B-Victoria lineage. During the sentinel surveillance, from week 40/2022 to week 16/2023, the first influenza A and B cases were detected in week 40/2022 and 48/2022, respectively (Figure 8b). The median positivity rate for influenza was of 25% (range [0 to 53.1%]; 95% CI (18.8-31.2%)) with a peak at 53.1% (n=26) during week 52/2022, which is also consistent with the maximum positivity rate for the surveillance period and close to the peak of ILI consultations in week 51/2022 (Appendix 1).

a



b

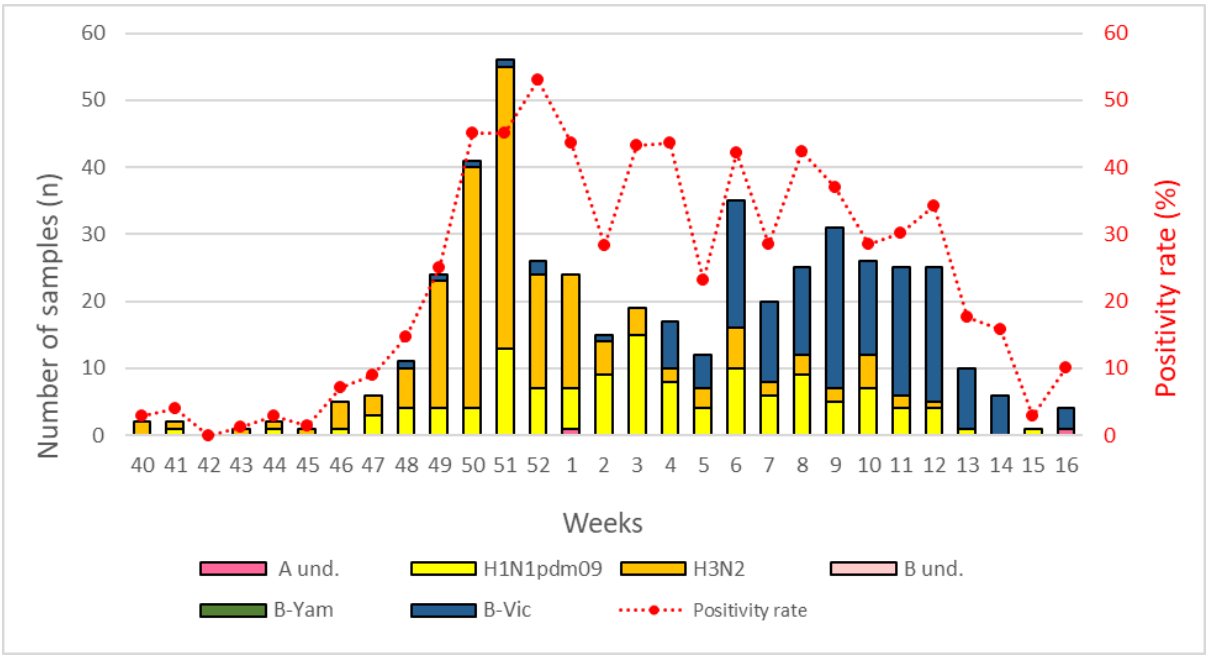


Figure 8. Percentage and temporal distribution of Influenza viruses detected in NPS collected from week 40/2022 to 16/2023. a. Percentages of influenza viruses, subtypes (FluA) and lineages (FluB). Proportion (**b.**) and distribution (**c.)** of the detected influenza viruses throughout the surveillance period. Influenza viruses typing and subtyping done by real-time rRT-PCR. A und. and B und.: influenza A and B viruses that could not be further subtyped (undefined). H1N1pdm09 and H3N2 refer to influenza A(H1N1)pdm09 and influenza A(H3N2), respectively. B-Yam: influenza B virus of Yamagata lineage. B-Vic: influenza B virus of Victoria lineage. Positivity rate is based on the number of weekly positive influenza samples per the number of samples received each week.

5.4 SARS-CoV-2 and Influenza viruses' characterisation (40/2022 to 16/2023)

This chapter describes SARS-CoV-2 genetic analysis and influenza genetic and antigenic characterisations.

5.4.1 SARS-CoV-2 variants identification and genetic analysis

One hundred and forty-six SARS-CoV-2 positive samples identified from week 40/2022 to week 16/2023, with Ct values lower than 32, were characterized by sequencing. The 140 samples that were successfully sequenced fell into 40 distinct Pangolin[74] sub-lineages of VOC Omicron (B.1.1.529+BA*) (Table 2; Appendix 3). First detected in South Africa on 9 November 2021, VOC Omicron, replaced the VOC Delta and became the major variant worldwide and the most prevalent within the Sentinel surveillance starting from week 52/2021 (Data not shown). Among the detected Omicron sub-lineages, XBB.1.5 (n =31, 22.1%) was dominant since week 5/2023 (Figure 9). Of note, during the weeks 48/2022 to 51/2022, no SARS-CoV-2 positive samples were submitted to the Genome Centre. This was during the period where the sentinella isolates were temporarily not included within the national SARS-CoV-2 genomic surveillance programme anymore, thereby not sequenced. In week 40/2022, week 2/2023 and 9/2023, no SARS-CoV-2 samples were submitted to GISAID either.

Table 2. List of SARS-CoV-2 Pangolin sub-lineages within which Sentinel isolates were distributed

Pangolin[1] sub-lineages	Number of isolates	Pangolin sub-lineages	Number of isolates
BA.5.1	7	BQ.1.1.18	1
BA.5.1.10	1	BQ.1.1.45	1
BA.5.1.21	1	BQ.1.1.47	1
BA.5.1.23	1	BQ.1.1.7	1
BA.5.1.28	1	BQ.1.10	1
BA.5.1.3	1	BQ.1.13.1	1
BA.5.1.5	2	BQ.1.18	1
BA.5.2	9	BQ.1.2	2
BA.5.2.1	7	BQ.1.21	1
BA.5.2.20	2	CH.1.1	4
BA.5.2.27	1	EG.1	1
BA.5.2.6	3	XBB.1.16	1
BA.5.2.7	1	XBB.1.5	31
BA.5.9	2	XBB.1.5.12	1
BE.1.1	2	XBB.1.5.15	1
BE.1.1.2	4	XBB.1.5.37	1
BF.10	2	XBB.1.5.7	2
BF.26	1	XBB.1.9	1
BF.7	6	XBB.1.9.1	6
BF.7.4	1	XBB.1.9.2	6
BM.1.1.3	1	XBB.2.3	1
BN.1.4	1	XBF	1
BQ.1	2	XBF.2	1
BQ.1.1	11	XBF.7.1	1
BQ.1.1.15	1		
n	140		

[1] Web-based lineage assessment: https://cov-lineages.org/lineage_list.html

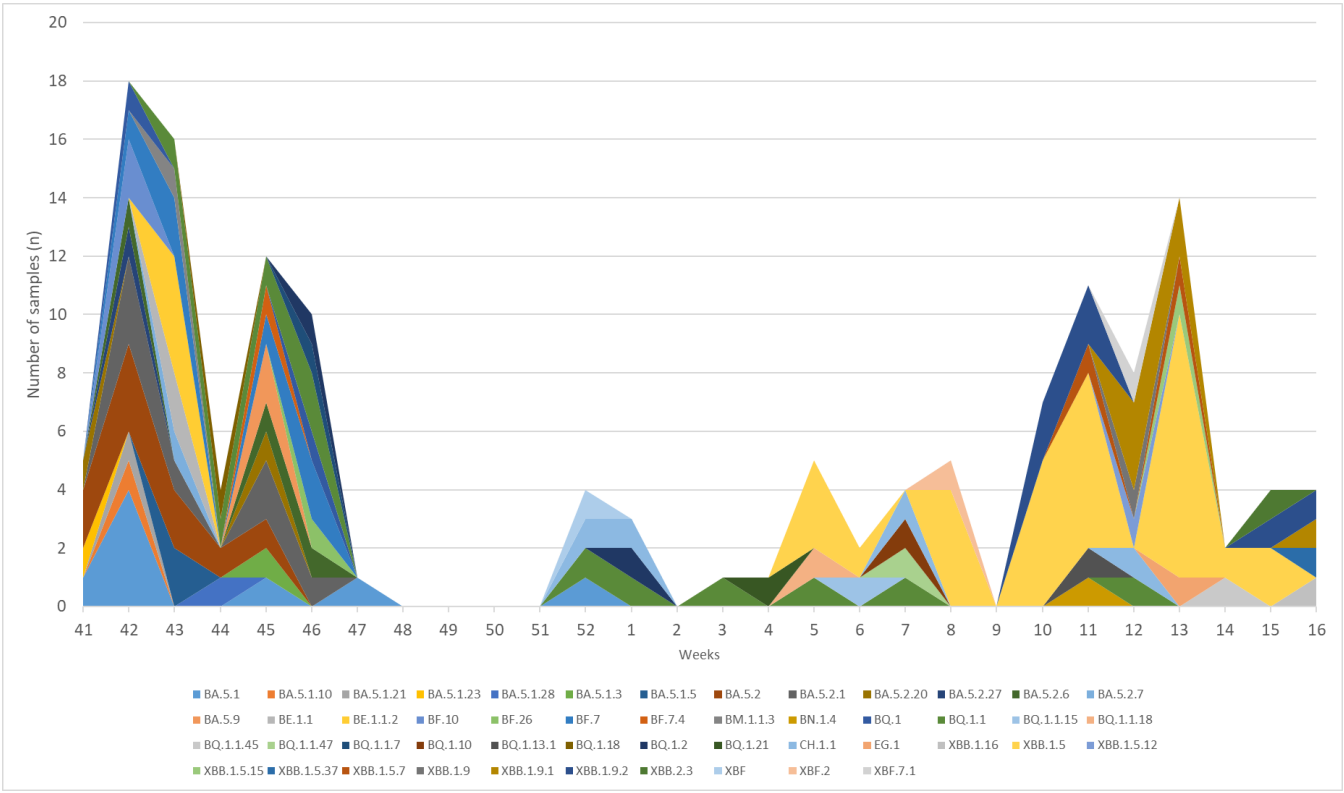


Figure 9. **Distribution of SARS-CoV-2 sub-lineages within the Sentinella surveillance (40/2022-16/2023).** Of note, no samples in week 40/2022, between the weeks 48/2022 and 51/2022, weeks 2/2023 and 9/2023 were submitted to GISAID.

5.4.2 Antigenic and genetic characterization of influenza viruses

Cell culture on MDCK and MDCK-SIAT1 cells was attempted for 190 negative-SARS-CoV-2 samples.

Among the 190 samples, 145 were influenza rRT-PCR positive (Ct values range from 13.3 to 37.9). Eighty-seven isolates underwent antigenic characterization using the HAI assay. Eighty-six (46 IA and 40 IB) out of 87 were successfully characterized. Of note, none of the negative rRT-PCR samples grew up on cell culture.

Eighty-two samples collected from October 2022 to February 2023 were submitted to genetic characterization. Eighty out of 82 HA sequences were successfully recovered. Among these, 53, 21 and 6 were from A(H3N2), A(H1N1)pdm09 and B-Victoria lineage viruses, respectively (Figures 10-12). Forty-one samples were shared with the WHO Collaborating Centre Worldwide Influenza Centre (WIC) at Francis Crick Worldwide (London) for characterization. (See appendixes 4 to 9 for

antigenic characterization and appendixes 10-12 for phylogenic analysis). A second batch of 78 sentinella isolates collected from January 2023 to May 2023 were sent to the WIC. Only sequencing results are currently available (Data not shown).

5.4.2.1 Characterization of influenza A(H3N2) viruses

A(H3N2) viruses were the dominant subtype collected since October 2022 at the NRCI, as well as in most parts of the world according to the WIC.

Twenty-four A(H3N2) (52.2%) isolates were characterized by HAI. Twenty-three isolates reacted well with the antiserum raised against A/Darwin/9/2021 (egg-based recommended vaccine strain 2022/2023). One isolate was poorly (≥8-fold titre reduction compared to the homologous) recognized by both the A/Darwin/9/2021 and A/Cambodia/e0826360/2020 reference antisera but showed good reactivity, within 2- to 4-fold the homologous titer, in presence of the antiserum raised against A/England/538/2018-like virus, a “recent” 3C.3a1 (Data not shown; Appendixes 4-6).

Fifty-three A(H3N2) samples were subjected to sequencing. All HA genes belonged to subclade 3C.2a1b.2a.2. As observed in other countries, our A(H3N2) strains have further diversified into three recent subgroups. Twenty-five viruses belonged to the subclade 3C.2a1b.2a.2b who has grown recently and characterized by amino acid E50K, F79V and I140K substitutions. Nineteen viruses belonged to the subgroup A/Slovenia/8720/2022, subclade 3C.2a1b.2a.2a.1, and characterized by the amino acid D53G, D104G, and K276R. Among the 19 isolates, 2 had additional amino acid T135A and T167S substitutions and 16 were further subcategorized into the subclade 3C.2a1b.2a.2a.1b discriminated by amino acid I140K and R299K substitutions (Figure 10; Appendix 10). One isolate was attributed to the subclade 3C.2a1b.2a.3b, characterized by the amino acid substitution I140M. The remaining 8 isolates belonged to subclade 3C.2a1b.2a.2a.3a.1 and were characterized by E50K, D53N, I140K, I192F, and I223V amino acid substitutions.

Among the 78 tested isolates from the second batch, 14 were A(H3N2) and all the HA were successfully covered. Consistent with the previous samples, all belonged to the subclade 3C.2a1b.2a.2 and were diversified into three subgroups. Four belonged to the 3C.2a1b.2a.2a.1b characterized by the amino acid substitution R299K and

additional N133D, I140K and S209N mutations. One sample was attributed to the subclade 3C.2a1b.2a.3a.1 and had additional V297I mutation. Nine tested samples were referred to the subclade 3C.2a1b.2a.2b (Data not shown).

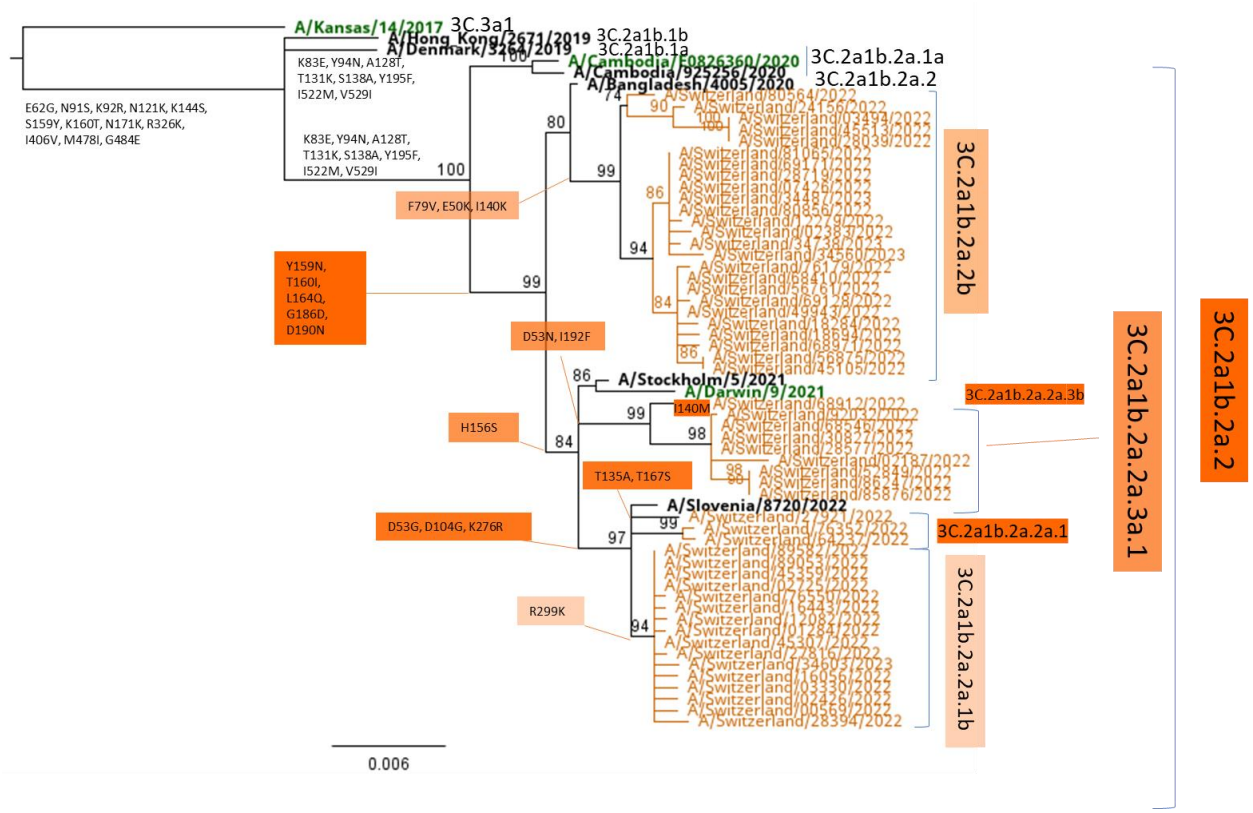


Figure 10. Phylogenetic analysis of the HA gene of A(H3N2) viruses. Orange: influenza viruses detected in the Sentinel network during the 2022/2023 season. Green: vaccine strains for 2019-20 A/Kansas/14/2017, 2021-22 A/Cambodia/E0826360/2020, 2022-23 A/Darwin/9/2021 (egg-based). Bold: reference strains. Some typical substitutions characterizing the respective clusters described by the WIC and Nexclade V.1.14.1. are displayed and highlighted in orange box. Blue: genetic groups/sub-groups. Sequences were aligned using Geneious 6.1.8 MAFT alignment (v7.017) with default settings. A consensus tree was built from 1000 original trees in maximum likelihood (70% support threshold) using Geneious prime 2022.1.1 PHYML default settings.

5.4.2.2 Characterization of influenza A(H1N1pdm09) viruses

Among the 86 isolates characterized by HAI assay, 22 were A(H1N1)pdm09 viruses (25.6%). Nineteen of these isolates were well recognized by the reference antiserum directed against the egg-based northern hemisphere vaccine strain 2022/2023 A/Victoria/2570/2019. Three isolates showed reduced reactivity to the antisera raised against A/Victoria/2570/2019 and the recommended vaccine strain 2020/2021

A/Guangdong Maonan/SWL1536/19 but were well recognized by the antiserum raised against the A/Denmark/3280/2019 strain (Data not shown; Appendixes 7-8).

Consistent with data from other European countries, sequencing results indicated that all our A(H1N1)pdm09 isolates (n=21) collected since October 2022 had HA genes belonging to the subclade 5a.2a of 6B.1A clade. A half of the A(H1N1)pdm09 viruses had additional HA1 substitutions P137S, K142R, D260E, T277A, E356D, N451H constitutive of subclade 2a.1 (Figure 11; Appendix 11).

Within the second batch of samples, 21 out of 78 were A(H1N1)pdm09. Most of the tested samples belonged to the clade 6B.1A.5a.2a (n=18). Five of them had additional HA1 mutations D94N, R113S, P137S, S143G, S190N, A261V, T216A, or K311N. Only two isolates have further diversified into the subclade 2a.1 with additional amino acid T216A or T120A substitutions (Data not shown).

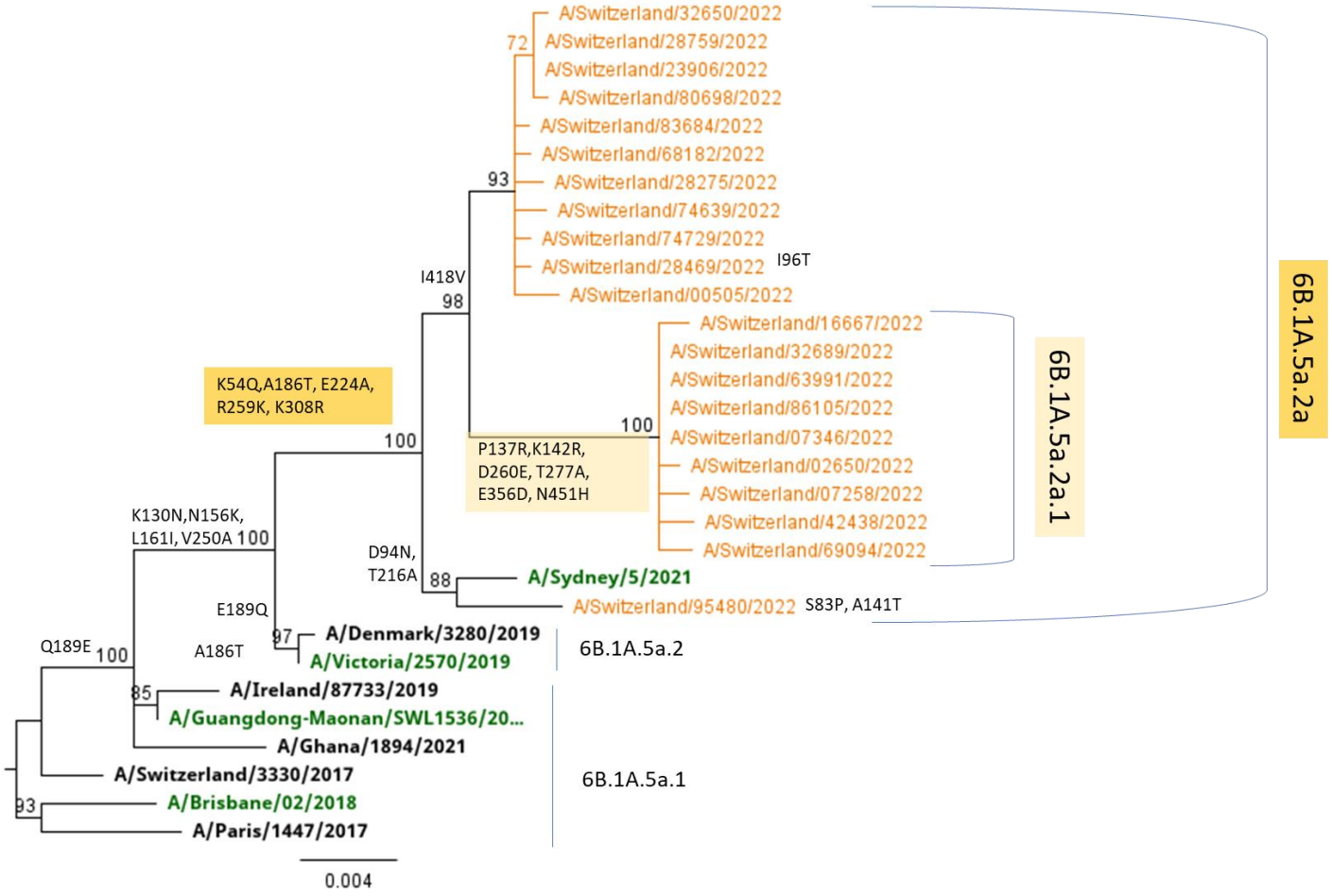


Figure 11. Phylogenetic analysis of the HA1 gene of A(H1N1)pdm09 viruses. Yellow: influenza viruses detected in the Sentinel network during the 2022/2023 season. Green: vaccine strains for 2022-23 northern hemisphere A/Victoria/2570/2019 (egg-based), 2023 A/Sydney/5/2021(cell-/egg-based). Bold: reference strains. Some typical mutations characterizing the respective clusters described by the WIC and Nexclade V.1.14.1. are displayed in yellow box. Blue: genetic groups/sub-groups. Sequences were aligned using Geneious 6.1.8 MAFT alignment (v7.017) with default settings. A consensus tree was built from 1000 original trees in maximum likelihood (70% support threshold) using Geneious prime 2022.1.1 PHYML default settings.

5.4.2.3 Characterization of influenza B(Victoria) viruses

Forty out of 41 B/Victoria/2/87 viruses were characterized by HAI assay. They all reacted well with the antiserum raised against B/Austria/1359417/2021 virus (recommended vaccine 2022/2023, subclade V1A.3a.2). One isolate was excluded from characterization due to low reaction with all antisera available at the NRCI (Data not shown; Appendix 9). This isolate was included in our regular seasonal virus shipments to the WIC.

All six influenza B/Victoria/2/87 lineage viruses, collected since October 2022, belonged to the subclade V1A.3a.2 with the substituted amino acid residues A127T, P144L, and K203R (Figure 12). Similarly, the samples from the second batch (43/78 B-Victoria lineage) were attributed to the subclade V1A.3a.2. (Figure 12). This was consistent with the data from the WIC (Appendix 12).

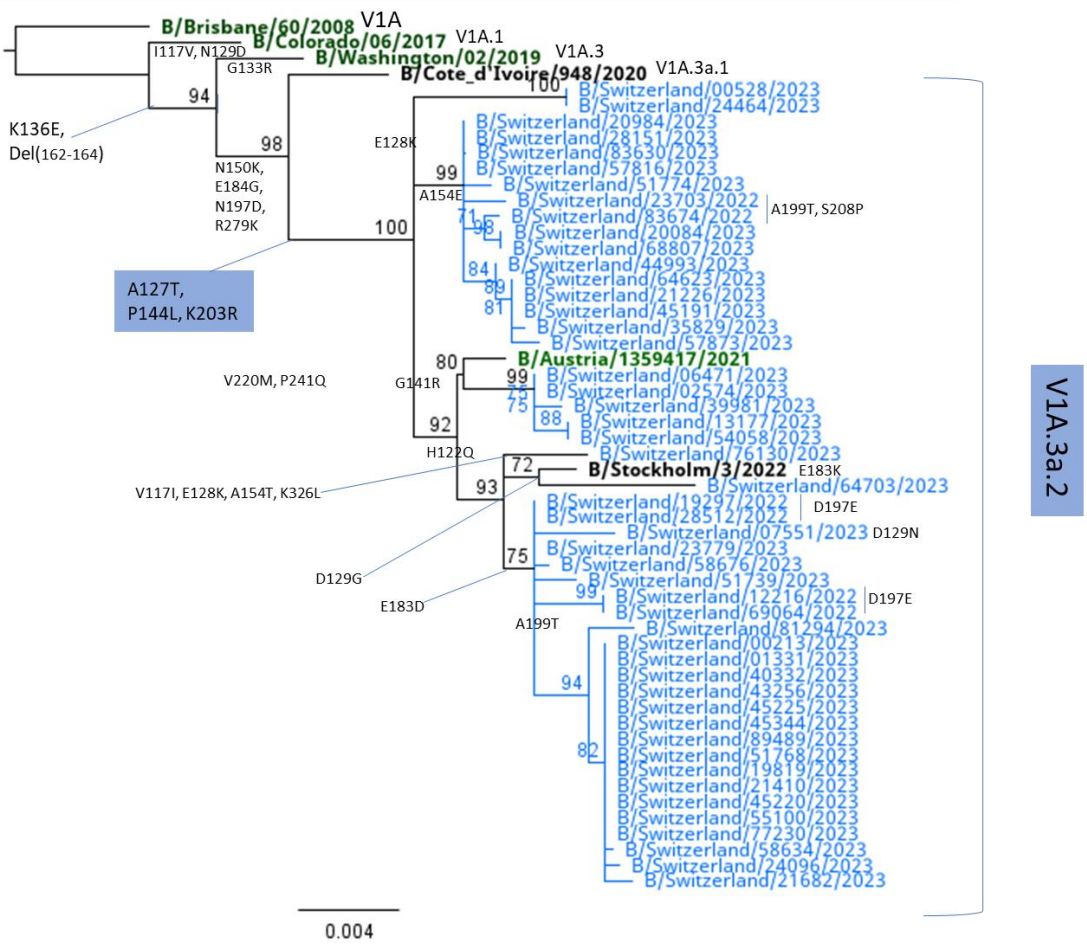


Figure 12. Phylogenetic analysis of the HA1 gene of B-Victoria viruses. Blue: influenza viruses detected in the Sentinel network during the 2022/2023 season. Green: vaccine strains for 2012-18 B/Brisbane/60/2008, 2019-20 B/Colorado/06/2017, 2020-22 B/Washington/02/2019, and 2022-23 B/Austria/1359417/2021. Bold: reference strains. Some typical mutations characterizing the respective clusters by the WIC and Nexclade V.1.14.1. are displayed in blue box. Sequences were aligned using Geneious 6.1.8 MAFT alignment (v7.017) with default settings. A consensus tree was built from 1000 original trees in maximum likelihood (70% support threshold) using Geneious 6.1.8 PHYML default settings.

5.4.2.4 Characterization of influenza B/Yamagata lineage

No influenza B virus of the B/Yamagata/16/88 was detected since January 2019 at the NRCI.

5.4.3 Antiviral resistance

Hundred fifty-seven NA sequences were successfully recovered: 66 were A(H3N2), 42 A(H1N1)pdm09, and 49 B-Victoria (Data not shown). One hundred and fifty-one PA sequences were recovered: 62 were A(H3N2), 43 A(H1N1)pdm09, and 46 B-Victoria (Data not shown).

Among the A(H1N1) isolates, one had amino acid mutation in the NA gene conferring normal inhibition to reduced inhibition to Oseltamivir (I223T). Five B-Victoria/2/87 isolates displayed the amino acid K360E substitution in the NA gene conferring highly reduced susceptibility to Peramivir[75] (Data not shown). None of the isolates displayed any markers in the PA gene associated with decreased susceptibility to Baloxavir Marboxil (Data not shown). Of note, amino acids E23, F36 and I38 were not covered for 2 influenza B isolates thus not affording the assessment for antiviral susceptibility to Baloxavir Marboxil.

Phenotypic tests for antiviral resistance assessment were not performed at the NRCI. Phenotypic and genetic testing was performed at the WIC and covered samples collected from October 2022 to January 2023. All the clinical specimens tested were susceptible to NAI and no mutations for reduced inhibition by NAIs were identified in the NA gene (Data not shown).

5.5 Influenza circulation Worldwide

The global circulation of influenza viruses across the WHO regions was about two-fold higher in 2022-2023 than during the 2021/2022 season (GISRS monitoring systems). Of note, most indicators showed influenza activity levels typically observed in pre-pandemic seasons across all WHO regions. Overall, two distinct waves could be observed between week 40/2022 and week 16/2023.

In the Northern Hemisphere, the first wave was constituted of influenza A viruses, subtype A(H3N2). It peaked in week 52/2022. The second wave started to increase in week 4/2023 and consisted in a mix of influenza B and A(H1N1)pdm09 viruses. The second peak of positivity was reached in week 10/2023.

As expected influenza activity in the northern hemisphere declined by the end of the described season, and raised from week 6/2023 up to week 23/2023 in the southern hemisphere, particularly in Australia.[76,77]

Across most of the monitoring systems a wave of influenza A (90%), subtype A(H3N2) (71%), was first observed, followed by a second wave of mainly influenza B-Victoria lineage and to a lower proportion of subtype A(H1N1)pdm09 (Appendix 14). However, influenza type B dominated in Middle Africa during weeks 46/2022 to 8/2023, in some countries of the South-East Asia (Malaysia) during week 10/2023 to week 14/2023, and in the Temperate and Tropical South America (Argentina and Brazil) regions during week 40/2022 to 50/2022 and weeks 01/2023 to 14/2023, respectively.[78]

Data collected from the WIC in February 2023 reported that the majority of influenza A, subtype A(H3N2) were attributed to the subclade 3C.2a1b.2a.2, represented by the recommended Northern Hemisphere vaccine 2022/2023 and 2023 Southern Hemisphere strain A/Darwin/9/2021 and the WHO reference strains A/Bangladesh/4005/2020, and A/Slovenia/8780/2022. Less than 1% of the viruses tested were attributed to the subclade 3C.2a1b.1a represented by A/Denmark/3264/2019 strain. Most of the influenza A viruses, subtype A(H1N1)pdm09, were attributed to the clade 6B.1A.5a.2, and subclade 5a.2a represented by the Northern Hemisphere vaccine 2022/2023 A/Victoria/2570/2019 and the Southern Hemisphere vaccine 2023 A/Sydney/5/2021, respectively. Most of the strains antigenically characterized were well-recognised by an antiserum raised against 2a.1 viruses A/Norway/25089/2022 (Cell) or the A/Norway/31694/2022 (Egg). Most of the B Victoria-lineage isolates were attributed to the subgroup V1A.3a.2 represented by B/Austria/1359417/2021, which is also the recommended strain for the Northern Hemisphere 2022/2023 and Southern Hemisphere 2023 influenza vaccines. Antigenic analyses demonstrated that almost all the viruses from the clade V1A.3a.2 (96%) were recognised to within 2- to 4-fold reductions by the antisera raised against B/Austria/1359417/2021 and -like viruses.

Antiviral resistance assessment tests did not show reduced susceptibility to NA nor PA inhibitors.

6. WHO recommendation for the composition of influenza virus vaccines for the 2022/2023 influenza season

Influenza vaccine recommendations are based on the Global Influenza Surveillance Response System network data, virus antigenic and genetic characterization data, human serology data, virus fitness forecasting data, antiviral resistance data, vaccine effectiveness, and the availability of candidate vaccine viruses.

The vaccine strains recommended for the 2023/2024 northern hemisphere influenza vaccine by the WHO experts are depicted in table 4.

Table 4. Recommended influenza vaccine composition for the 2023/2024 influenza season.
a: for egg-based vaccines. b: for cell-based vaccines

a	Vaccine strains 2023/24
A(H1N1)pdm09	A/Victoria/4897/2022 (H1N1)pdm09-like virus
A(H3N2)	A/Darwin/9/2021 (H3N2)-like virus
B/Victoria lineage	B/Austria/1359417/2021 (B/Victoria lineage)-like virus *
B/Yamagata lineage	B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

** B strain included in the trivalent vaccine*

b	Vaccine strains 2023/24
A(H1N1)pdm09	A/Wisconsin/67/2022 (H1N1)pdm09-like virus
A(H3N2)	A/Darwin/6/2021 (H3N2)-like virus
B/Victoria lineage	B/Austria/1359417/2021 (B/Victoria lineage)-like virus *
B/Yamagata lineage	B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

**B strain included in the trivalent vaccine*

7. Human infection with influenza viruses of zoonotic origin

Transmission of zoonotic influenza viruses to humans often leads to infections limited to a single individual and sometimes to their close contacts. However widespread outbreaks and pandemics are also possible in the case of efficient human-to-human transmission. Recombination events between porcine/avian and human viruses due to concomitant circulation can drive human adaptation of zoonotic strains. To allow for the early identification and rapid containment of new potential animal-to-human

transmission events, several countries, including Switzerland, have introduced regular screening of animals such as poultry, wild birds, and farm pigs for the presence of the respective influenza strains.

7.1 Swine-to-human influenza virus transmission

Human infections with influenza A viruses of porcine origin are identified as “variant” viruses and denoted with a letter “v”, such as A(H1N2)v, A(H3N2)v and A(H1N1)v.

7.1.1 In Switzerland

In 2001, the Federal Food Safety and Veterinary Office initiated a collaborative project with the Federal Office of Public Health project, the Institute of Virology of the Vetsuisse Faculty of the University of Zurich, and the Pig Health Service (SSP) of SUISAG, which aimed at monitoring the swine flu circulation in Switzerland. The project is named “Surveillance of swine influenza in pigs and humans”. In this context, specimens from farm pigs with respiratory symptoms are sent to, and analysed by, the National Veterinarian Institute (Vetvir, Zurich). In parallel, samples from pig breeders (or their employees), who have been in contact with influenza-infected animals and present with ILI symptoms, are sent to the NRCI. The latter are analysed using a rRT-PCR with the capacity to distinguish influenza A viruses of human and animal origin, both avian and porcine. Positive samples are further characterized by sequencing.

From week 40/2022 to week 16/2023, 3 non-sentinel samples originating from farmers having contacts with pigs were sent to the NRCI, all tested negative for influenza.

7.1.2 Worldwide

Since 2010, 492 [439 A(H3N2)v, 18 A(H1N1)v and 35 A(H1N2)v] human cases of variant influenza have been reported in several states in the USA. These cases were often mild with no evidence of further human-to-human transmission. One case of A(H3N2)v was reported in 2022/2023.[79]

In 2023, human A(H1N1)v and A(H1N2)v infections were also reported in two EU/EEA countries (Germany and Netherlands). Sporadic human infections with influenza virus A(H1N1)v, A(H1N2)v, and A(H3N2)v were also identified in non-EU/EEA regions such as Brazil, China, Taiwan and the United States of America (USA).[80]

7.2 Avian influenza A subtypes in human

As for porcine influenza, human cases of infection with avian viruses are sporadically reported. As of April 2023, a total of 878 cases of A(H5N1), including 458 deaths, have been reported from 23 countries since 2003.[81] Since 2022, six human cases with avian A(H5N1) have been reported to the WHO.[82-85]

The last two confirmed cases were reported in February 2023 within the Western Pacific Region in Cambodia.[83]

At the NRCI, we received one sample from a symptomatic person who had contact with an A(H5N1) positive bird. The individual tested negative for influenza A and B as well as for an H5 specific real-time RT-PCR.

Since February 2014, 86 laboratory-confirmed cases of highly pathogenic avian influenza (HPAI) A(H5N6), including 33 deaths, have been reported. The last case date back to July 2023 and was reported from China.[86]

A total of 3 cases of A(H3N8) , resulting in one death, were reported so far, all were from China.[87] The last case was reported in February 2023.

In 2022,16 human cases of avian A(H9N2) were reported in China and Cambodia out of 90 cases identified since December 2015.

No human case of avian influenza A(H7N9), A(H10N3) and A(H7N4) were reported for 2023.

8. Avian influenza A in animals[88]

The reservoirs for high/low pathogenic avian influenza A (H/LPAI) viruses are wild birds. Both virus types can cause moderate to large outbreaks in poultry worldwide.

The largest number of avian influenza outbreaks in Europe, since 2016/2017, was observed during2021/2022 season. As of April 2023, 3849 HPAI cases (1175 in domestic birds and 2674 in wild birds) were identified over 31 countries. This is 60 % less than during 2021/2022, but still higher than in 2020/2021 and previous seasons. HPAI subtypes A(H5), A(H5N1), A(H5N2), A(H5N5), A(H5N8) were the most current in Europe. A(H7N3), A(H5N6) and A(H5N4) outbreaks were observed in Mexico, Vietnam and in the USA, respectively. One LPAI avian influenza A(H5) was reported from Belize.[88,89]

The number of HPAI detections continues to increase in Europe and in Americas and it is expected to spread to Antarctic. HPAI A(H5N1) 2.3.4.4b virus transmission from birds to mammal species continues to be observed.

9. Discussion

Gender and age group distributions were comparable to previous years within the Sentinella population.

For the third consecutive year, the NRCI monitored not only influenza viruses circulating in Switzerland but also a panel of respiratory viruses, including SARS-CoV-2. The number of samples (1950) received from week 40/2022 to 16/2023 was comparable to the number (2225) received in 2021/2022 for the same period. This was not surprising considering the ongoing SARS-CoV-2 circulation and the continuation of other respiratory virus testing for the last three seasons and along the influenza screening.

The median positivity rate during week 40/2022 to week 16/2023 was comparable (69%) to the last season 2021/2022 (66%) and 2019/2020 (61.9%) but was significantly higher than for 2020/2021 (49.2%). The increase in the positivity rate observed for both 2021/2022 and 2022/2023 may be explained by the re-emergence and sustained circulation of influenza viruses, as well as the continuing detection other respiratory viruses and of new SARS-CoV-2 variants/subvariants. As a reminder only one influenza B with low viral load was detected from week 17 to week 46/2021.

As usually observed, the increase in detection at the NRCI fitted well with the increase in the number of cases identified in the Swiss population (Figure 5b; Appendix 1).

As already mentioned, rRT-PCR detection data on respiratory viruses other than influenza is only available since 2019/2020 within the Sentinel network, and the emergence of SARS-CoV-2 in 2020/2021 season was shown to significantly impact the circulation of other respiratory viruses.[90,91] During the 2022/2023 some respiratory viruses seemed to revert to seasonal patterns observed before the COVID-19 pandemic; particularly in children.[92] However, additional data are needed in order to confirm this reversion to usual circulation patterns. RSV has shown to alternate between low prevalence followed by high prevalence during annual epidemics in Switzerland.[93] In 2020/2021 season, RSV circulation was unusual as it was delayed by around 20 weeks compared to what could be expected. This phenomenon was not only observed in Switzerland but also in other countries.[94-97] During 2022/2023, RSV circulation in Switzerland was observed from week 40/2022 to week 3/2023 with a peak in week 45/2022 (17.7%; n=12), thus six weeks earlier than in 2021/2022, suggesting a probable reversion towards pre-pandemic seasonality with winter peaks[98], but in Switzerland further data are needed to confirm this trend.

HMPV epidemics began 9 weeks later than during the 2021/2022 season, starting from week 49/2022, with a peak in week 2/2023 (9.4%; n=5). This coincides with the seasonality usually observed in China, Israel and Switzerland.[99-101]

Though the number of detections was lower than during the 2021/2022 season, SARS-CoV-2 virus remained regularly detected. It represented, together with Influenza and RV/EV, the most prevalent virus, reaching a peak of detection (27.9%; n=22) in week 43/2022.

As existing variants evolve and new ones emerge, scientific knowledge on the different viruses is constantly being updated. Data from the national genomic surveillance of SARS-CoV-2, focusing on hospitalized patients (https://gisaid.org/lineage-comparison/, https://www.hug.ch/centre-maladies-virales-

emergentes/programme-sequencage-national-du-sars-cov-2/) demonstrated that Omicron BA.5 variant predominated since October 2022. This variant has rapidly split into several sub-lineages such as BQ.1, and was replaced by XBB sublineages, with XBB.1.5 (VOI) becoming the dominant variant worldwide in February 2023.

As of January 2023, literature[102] shows that XBB.1.5, a recombinant from BA.2.10.1 and BA.2.75 lineages and characterized by the amino acid substitution F486P in the spike protein, was already present in 38 countries, including Switzerland and sequences were reported from the United States of Americas, the United Kingdom, and Denmark.[102-104] There is currently no evidence of higher transmission nor immune escape properties relative to XBB.1, but according to ECDC, "its predecessors-XBB+XBB.1 showed significant reduction in the neutralising capacity of serum from vaccinated people"[105] and despite this, available vaccines "still remain effective against severe disease because of previous and current omicron variants dominant in the EU, even though there is some evidence of waning over time".[105] As of beginning March 2023 and because of no longer circulating BA.2, BA.4 and BA.5 variants, the ECDC has removed them from the list of VOCs. There are currently no SARS-CoV-2 lineages corresponding to the ECDC's VOC criteria.[106,107] A continuous update of SARS-CoV-2 variants evolution in Switzerland and in the world can be found on Covariants[108] and CoV-Spectrum.[109]

RV/EV were the third most prevalent viruses after SARS-CoV-2 during2022/2023. This is consistent with data already published for in- and out- patients in Geneva.[110] As expected RV/EV detection was consistent throughout the year with a peak of positivity reaching 41.2% at week 41/2022 (n=21).

Similarly to the last season, only HCoV OC43 was regularly detected through the seasonal surveillance. While HCoV 229E was continuously detected during the winter 2021 season, only rare detections were observed from week 40/2022 to week 16/2023. Although HCoV HKU1 was regularly detected at a low rate during the spring 2022, only sporadic cases were reported during the same period in 2023. HCoV NL63 was regularly detected during weeks 6/2023 to 14/2023 in contrast to what had been observed during the past season; with only one case detected in week 19/2021. Of note, the proportion of HCoV NL63 represented 2.1% in 2022/2023, 11.3% in

2020/2021, and 2.9% in 2019/2020 during the surveillance period. HCoVs tend to exhibit seasonal circulation, with peaks mostly in winter in the Northern Hemisphere, however the prevalence pattern of each HCoV strain varies between countries and from year to year.[111,112]

According to their seasonality pattern[56,113], HPIV1/3 and HPIV2/4 were mostly detected in spring and fall during 2022/2023 surveillance period, respectively. Interestingly, this was not the case for HPIV2/4 during 2019/2020, 2020/2021, and 2021/2022, where only sporadic cases were observed. 2022/2023 circulation pattern tend towards a return of seasonality for each serotype.[114]

Consistent with the observed prevalence in Europe[115], HBoV detection rate remained low during the three last study periods (0.8% in 2022/2023, 1.4% in 2021/2022, and 0.3 % in 2020/2021), and was mainly found in children.[116]

Co-detections accounted for 10.5%, 11.3% and 7.2% of the positive samples in 2022/2023, 2021/2022, and 2020/2021, respectively. This observation is consistent with existing literature.[117,118] The most common co-detection was RV/EV (51.4%) combined with SARS-CoV-2 (23/74), RSV (19/74) and Influenza (11/74). Consistent with what could be observed during the previous years, the coinfections tend to be more prevalent when viruses showed the highest positivity rate at their respective epidemic/circulation period.[119]

Of note, the rRT-PCR respiratory panel used at the NRCI does not target bacterial or fungal pathogens. However, the latter are also often detected along with respiratory viruses, particularly in hospitalized patients.[118]

The 2022/2023 season has been marked by the return of influenza virus activity at fairly similar levels to those observed in pre-COVID-19 pandemic seasons in the EU/EEA countries. Consistent with the ECDC data, influenza seasonal epidemic in Switzerland started (week 48/2022) and peaked earlier (53.1% positivity in week 52/2022) compared to 2021/2022 season (week 5/2022 to 15/2022; 38.3% in week 10/2022) and overall, compared to the four previous seasons.[120] In addition, as observed in other countries[121,122] , the influenza epidemic lasted longer than usual, with a positivity rate >10% from week 48/2022 to week 14/2023. In Switzerland, as in

other countries[122,123], influenza virus activity was characterized by two waves, with a dominant detection of A(H3N2) virus from week 48/2022 to 1/2023, peaking at week 51/2022 relayed by a short dominance of A(H1N1)pdm09 from week 2/2023 to week 4/2023, followed by a wave of B-Victoria from week 5/2023 to week 14/2023.

Compared with 2021/2022, antigenic and genetic data, as well as reporting of influenza cases in TESSY/ECDC appeared to increase to 5.2-fold in 2022/2023.[121] This could be due to the extended circulation of the virus, consistent with a return of a pre-COVID-19 pandemic seasonal influenza activity.

Genetic analyses from the NRCI showed that A(H3N2) isolates belonged to the subclade 3C.2a1b.2a.2 and subsequently to subclade 2a.2b, 2a.3a.1, 2a.3b, 2a.2a.1, and 2a.2a.1b characterized by new specific amino acid changes in the HA1 gene. This was consistent with the WIC analyses and the predominance of these clades globally. Most of the tested samples were well recognised by the antiserum from the Northern Hemisphere vaccine strain 2022/2023 A/Darwin/9/2021 (clade 3C.2a1b.2a.2). Furthermore, data from the WIC showed the broadest cross-recognition of viruses in different genetic groups by an antiserum raised against a 2a virus A/Stockholm/5/2021 (SIAT)- an A/Darwin/6-like virus. The isolates which were attributed to the emerging genetic subgroups (2a.2b, 2a.3a.1, 2a.3a.b, 2a.2a.1) were well recognised by antisera raised against the A/Thuringen/10/2022 virus from subclade 2a.2b, A/Norway/24873/2021 from 2a.3, A/Poland/97/2022 from 2a.2 and A/Slovenia/8720/022 from 2a.1.

Most of the A(H1N1)pdm09 isolates were well recognised by the antiserum raised against the Northern Hemisphere vaccine strain 2022/2023 A/Victoria/2570/2019 (clade 5a.2) and a few were antigenically characterized by the antiserum raised against the reference strain A/Denmark/3280/2019 (clade 5a.2). All belonged to the group 6B.1A.5a.2a and a half of them were sub-divided into the 5a.2a.1 group. The WIC reported that most of the recent 5a.2a.1 A(H1N1)pdm09 viruses tested showed variable recognition by antisera raised against the Southern Hemisphere vaccine 2023 A/Sydney/5/2021 (egg- and cell-based) (clade 5a.2a) but were well-recognised by the antisera raised against the reference strains A/Norway/25089/2022 (cell-based) or the A/Norway/31694/2022 (egg-based) (subclade 5a.2a.1). Our genetic

results were also consistent with the WIC results and the clades attributed to our samples were found in all regions of the European countries.

Except for one isolate, all B-Victoria lineage viruses were antigenically characterized by an antiserum raised against the Northern Hemisphere 2022/2023 vaccine strain B/Austria/1359417/2021, which was observed by the WIC, and all belonged to the clade V1A.3a.2 which has predominated since 1st September 2022 globally. Of note, no clade V1A.3 viruses were detected since 1st September 2022. No B-Yamagata-lineage virus has been detected since March 2020. This repeated lack of detection may suggest that the B-Yamagata-lineage may either be extinct or close to extinction.

During the 2022/2023 season, none of the viruses sequenced at the NRCI in the context of the national surveillance program exhibited mutations associated with reduced susceptibility to Baloxavir Marboxil, Oseltamivir and Zanamivir. These results were consistent with those from WHO Europe reports.[121]

Since the Covid-19 pandemic was recognized in 2020, variations in genetic and antigenic diversity to each influenza virus,[124-126] were impacted by global restrictions, other non-pharmaceutical interventions (NPI) and travels disruptions.[127-130] Indeed, the interplay between the different seasonal influenza virus subtypes and lineages may vary throughout the season and in the different regions, leading to significant variation in population immunity to each virus.[131] Even if already suspected from 2021/2022 influenza moderate circulation, 2022/2023 data from ECDC/Tessy, GISAID, GISRS and NICs may confirm the hypothesis supporting the return of influenza circulation, high genetic diversity through the emergence of new subclades and the possible extinction of lineages. Considering the confirmed return of influenza activity at similar rates to pre-COVID-19 pandemic seasons, we can speculate that the competition between SARS-CoV-2 virus, influenza viruses and the other common cold viruses, and the re-circulation of influenza virus with high genetic diversity would enable further divergence and expansion of separated lineages and more broad circulation. A study from modelling the effect of variable duration of immunity on the size of seasonal influenza epidemics found that the proportion of the population susceptible to infection by influenza after a mild or moderate season leads to a larger

outbreak in following seasons.[132] This is in line with what was observed during 2022/2023. The same study showed that when the duration of immunity in a given population is variable, namely when the exposure was low and then high, the infection rate and the epidemic peaks will be higher than when the duration of the immunity is constant, as it would be the case in the context of regular and high vaccination coverage. This illustrates well that the shapes of future epidemics are influenced by past ones and raises the questions about how to tailor vaccination. Ultimately, ongoing evolution and antigenic drift increase the risk that the antigens included in the vaccine will not represent the viruses that circulated previously, thus reducing vaccine effectiveness.[131] This emphasises the importance of regularly assessing influenza genetic and antigenic evolution.

As observed during 2022, the number of HPAI infections remained high in wild birds during 2023. This high prevalence of avian influenza may increase the risk of outbreaks in domestic birds, mainly in poultry, resulting in high mortality rates both due to natural infection and massive culling.

Since 2020 H5N1 HPAI, in particular 2.3.4.4b viruses, have emerged in and continue to spread to several animal species including, terrestrial and aquatic mammals.[133] The increased ability of those viruses with highly mutation rate to cross species barrier is very concerning as it increases the risk of transmission to humans.

After three years of the SARS-CoV-2 pandemic, which was demoted in May 2023 from its global health emergency status by the WHO, and after one year of significant decrease in detection, influenza confirmed re-emergence emphases the importance of continuing the collection and analyses of influenza viruses and associated data. It was and remains crucial to choose the most appropriated influenza vaccine strains. The goal being to mitigate as much as possible the burden linked to severe influenza cases.

To conclude, as already observed during 2021/2022, concomitant Influenza virus, SARS-CoV-2 and other respiratory viruses' circulation was observed and is expected to be seen during next season 2023/2024.

10. Collaborative projects and publications

As for 2022, the NRCI continued to support the laboratory of virology and the National Reference Centre for Emerging Viral Infections (CRIVE), especially regarding SARS-CoV-2 variant detection and genetic characterization as part of the national genomic surveillance of SARS-CoV-2.

10.1 Ongoing project

As for 2022, the NRCI continued to collaborate with the Health 2030 Genome Centre DNA Sequencing and Data Analytics and Interpretation Platforms' team in order to evaluate the illumina Respiratory oligo panel performance. The panel was initially tested using Twist Biosciences' synthetic influenza A and B, and other respiratory viruses. Giving promising results, a second experiment included 16 positive influenza A and B nasopharyngeal swabs, and 14 samples positive for other respiratory viruses. In order to assess the sequencing panel sensitivity for influenza and RSV, five 10-fold dilutions of 2 A(H1N1)pdm09, 2 A(H3N2), 2 B/Victoria, 2 B/Yamagata, 1 A(H5N1), 1 A(H7N9), 1 RSV A and 1 RSV B viruses were also tested.

All samples were prepared according to the standard respiratory virus protocol and analysis was performed using KrakenUniq v0.5.8 as in previous experiments. The reconstruction of consensus sequences was then adapted with our SARS-CoV-2 pipeline. Results were conclusive as the expected viral genomes were detected at low concentrations and with a high specificity.

Overall sensitivity and specificity of the panel are good for influenza and RSV. Consensus sequences with good coverage could be obtained from < 25-27 Ct dilutions. This was in line with what we usually obtain from Miycrosynth and what could be observed in literature.[134] Analysis process needs to be further optimized especially for influenza B. Investigation of the sequencing efficiency for other coronaviruses than SARS-CoV-2 is also ongoing.

11. References

1. Hutchinson EC, Yamauchi Y. Understanding Influenza. In: Yamauchi Y, ed. Influenza Virus: Methods and Protocols. Springer New York; 2018:1-21

2. Krammer F, Smith GJD, Fouchier RAM, et al. Influenza. *Nature Reviews Disease Primers*. 2018/06/28 2018;4(1):3. doi:10.1038/s41572-018-0002-y

3. Taubenberger JK, Morens DM. The Pathology of Influenza Virus Infections. Annual Review of Pathology: Mechanisms of Disease. 2008;3(1):499-522. doi:10.1146/annurev.pathmechdis.3.121806.154316

4. Bodewes R, Morick D, de Mutsert G, et al. Recurring Influenza B Virus Infections in Seals. *Emerging Infectious Diseases*. 2013;19(3):511-512. doi:10.3201/eid1903.120965

5. Hause BM, Collin EA, Liu R, et al. Characterization of a Novel Influenza Virus in Cattle and Swine: Proposal for a New Genus in the Orthomyxoviridae Family. *mBio*. May 1, 2014 2014;5(2)doi:10.1128/mBio.00031-14

6. Asha K, Kumar B. Emerging Influenza D Virus Threat: What We Know so Far! *J Clin Med*. 2019;8(2):192. doi:10.3390/jcm8020192

7. Su S, Fu X, Li G, Kerlin F, Veit M. Novel Influenza D virus: Epidemiology, pathology, evolution and biological characteristics. *Virulence*. Nov 17 2017;8(8):1580-1591. doi:10.1080/21505594.2017.1365216

8. Hause BM, Collin EA, Liu R, et al. Characterization of a novel influenza virus in cattle and Swine: proposal for a new genus in the Orthomyxoviridae family. *mBio*. Mar 4 2014;5(2):e00031-14. doi:10.1128/mBio.00031-14

9. Hyunsuh Kim RGW, and Richard J. Webby,. Influenza Virus: Dealing with a Drifting and Shifting Pathogen. *Viral Immunology*. 2018;31(2):174-183. doi:10.1089/vim.2017.0141

10. Mombelli M, Lang BM, Neofytos D, et al. Burden, epidemiology, and outcomes of microbiologically confirmed respiratory viral infections in solid organ transplant recipients: a nationwide, multi-season prospective cohort study. *American Journal of Transplantation*. 2021;21(5):1789-1800. doi:10.1111/ajt.16383

11. Muñoz-Escalante JC, Comas-García A, Bernal-Silva S, Noyola DE. Respiratory syncytial virus B sequence analysis reveals a novel early genotype. *Scientific reports*. 2021;11(1):3452.

12. Coultas JA, Smyth R, Openshaw PJ. Respiratory syncytial virus (RSV): a scourge from infancy to old age. *Thorax*. 2019;74(10):986-993. doi:10.1136/thoraxjnl-2018-212212

13. Chatzis O, Darbre S, Pasquier J, et al. Burden of severe RSV disease among immunocompromised children and adults: a 10 year retrospective study. *BMC Infect Dis*. 2018;18(1):111-111. doi:10.1186/s12879-018-3002-3

14. Carvajal JJ, Avellaneda AM, Salazar-Ardiles C, Maya JE, Kalergis AM, Lay MK. Host Components Contributing to Respiratory Syncytial Virus Pathogenesis. 10.3389/fimmu.2019.02152. *Frontiers in Immunology*. 2019;10:2152.

15. Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *The Lancet*. 2017/09/02/ 2017;390(10098):946-958. doi:10.1016/s0140-6736(17)30938-8

16. World Health Organization. WHO strategy for global respiratory syncytial virus surveillance project based on the influenza platform. 2019; https://cdn.who.int/media/docs/default-source/influenza/rsv-surveillance/who-rsv-surveillance-strategy-phase-26mar2021.-final.pdf?sfvrsn=d8b1c36a_9. Accessed 25.08.2023

17. Pebody R, Moyes J, Hirve S, et al. Approaches to use the WHO respiratory syncytial virus surveillance platform to estimate disease burden. *Influenza and Other Respiratory Viruses*. 2020;14(6):615-621. doi:10.1111/irv.12667

18. Robinson CP, Busl KM. Neurologic Manifestations of Severe Respiratory Viral Contagions. *Critical Care Explorations*. 2020;2(4):e0107. doi:10.1097/cce.0000000000000107

19. Milas A, Shah A, Anand N, Saunders-Kurban M, Patel S. Respiratory Syncytial Virus Associated Myocarditis Requiring Venoarterial Extracorporeal Membrane Oxygenation. *Case Reports in Infectious Diseases*. 2017/05/08 2017;2017:7074508. doi:10.1155/2017/7074508

20. Ivey KS, Edwards KM, Talbot HK. Respiratory Syncytial Virus and Associations With Cardiovascular Disease in Adults. *Journal of the American College of Cardiology*. 2018/04/10/ 2018;71(14):1574-1583. doi:10.1016/j.jacc.2018.02.013

21. Eisenhut M, Thorburn K. Hepatitis Associated with Severe Respiratory Syncytial Virus-positive Lower Respiratory Tract Infection. *Scandinavian Journal of Infectious Diseases*. 2002/01/01 2002;34(3):235-235. doi:10.1080/00365540110077191

22. Federal Drug Administration. FDA Approves First Respiratory Syncytial Virus (RSV) Vaccine. 2023.

23. Shafagati N, Williams J. Human metapneumovirus - what we know now. *F1000Res*. 2018;7:135. doi:10.12688/f1000research.12625.1

24. Long Q-X, Tang X-J, Shi Q-L, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nature Medicine*. 2020/06/18 2020;doi:10.1038/s41591-020-0965-6

25. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. *Journal of Medical Virology*. 2020;92(4):418-423. doi:101002/jmv.25681

26. Masse S, Capai L, Villechenaud N, Blanchon T, Charrel R, Falchi A. Epidemiology and Clinical Symptoms Related to Seasonal Coronavirus Identified in Patients with Acute Respiratory Infections Consulting in Primary Care over Six Influenza Seasons (2014–2020) in France. *Viruses*. 2020;12(6):630.

27. Liu DX, Liang JQ, Fung TS. Human Coronavirus-229E, -OC43, -NL63, and -HKU1 (Coronaviridae). *Encyclopedia of Virology*. 2021:428-440. doi:10.1016/b978-0-12-809633-8.21501-x

28. World Health Organization. Regional Office for the Eastern M. MERS situation update: December 2021. Cairo: World Health Organization. Regional Office for the Eastern Mediterranean. 2021.

29. World Health Organization. MERS situation update May 2023. 2023.

30. Desforges M, Le Coupanec A, Brison E, Meessen-Pinard M, Talbot PJ. Neuroinvasive and neurotropic human respiratory coronaviruses: potential neurovirulent agents in humans. *Adv Exp Med Biol*. 2014;807:75-96. doi:10.1007/978-81-322-1777-0_6

31. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *New England Journal of Medicine*. 2020;382(8):727-733. doi:10.1056/NEJMoa2001017

32. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. Mar 2020;579(7798):270-273. doi:10.1038/s41586-020-2012-7

33. Gostin LO, Gronvall GK. The Origins of Covid-19 - Why It Matters (and Why It Doesn't). *N Engl J Med*. Jun 22 2023;388(25):2305-2308. doi:10.1056/NEJMp2305081

34. Bundle N, Dave N, Pharris A, et al. COVID-19 trends and severity among symptomatic children aged 0-17 years in 10 European Union countries, 3 August 2020 to 3 October 2021. *Euro Surveill*. Dec 2021;26(50)doi:10.2807/1560-7917.ES.2021.26.50.2101098

35. Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. *Nat Med*. Apr 2021;27(4):626-631. doi:10.1038/s41591-021-01292-y

36. World Health Organization. *A clinical case definition of post COVID-19 condition by a Delphi consensus*. 2021. *COVID-19: Clinical care*. 2021; https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1. Accessed: 25.08.2023

37. Vitalakumar D, Sharma A, Kumar A, Flora SJS. Neurological Manifestations in COVID-19 Patients: A Meta-Analysis. *ACS Chem Neurosci*. Aug 4 2021;12(15):2776-2797. doi:10.1021/acschemneuro.1c00353

38. Marinho PM, Marcos AAA, Romano AC, Nascimento H, Belfort R, Jr. Retinal findings in patients with COVID-19. *Lancet*. May 23 2020;395(10237):1610. doi:10.1016/s0140-6736(20)31014-x

39. Landecho MF, Yuste JR, Gándara E, et al. COVID-19 retinal microangiopathy as an in vivo biomarker of systemic vascular disease? *J Intern Med*. Jan 2021;289(1):116-120. doi:10.1111/joim.13156

40. Riotto E, Mégevand V, Mégevand A, et al. Retinal Manifestations in Patients with COVID-19: A Prospective Cohort Study. *J Clin Med*. Mar 25 2022;11(7)doi:10.3390/jcm11071828

41. Markan A, Bansal R, Gautam N, et al. Longitudinal analysis of cotton wool spots in COVID-19 with high-resolution spectral domain optical coherence tomography and optical coherence tomography angiography. *Clin Exp Ophthalmol*. May 2021;49(4):392-395. doi:10.1111/ceo.13919

42. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/. Accessed: 25.08.2023

43. Office fédérale de la santé publique (OFSP). COVID-19 Suisse. https://www.covid19.admin.ch/fr/epidemiologic/death?sum=cumulative&epiRelDev=abs&epiRelDemo=abs&epiZoomDev=2020-03-01_2023-06-18. Accessed : 25.08.2023

44. Hamilton F, Arnold D, Bzdek BR, et al. Aerosol generating procedures: are they of relevance for transmission of SARS-CoV-2? *The Lancet Respiratory Medicine*. doi:10.1016/s2213-2600(21)00216-2

45. Cappy P, Candotti D, Sauvage V, et al. No evidence of SARS-CoV-2 transfusion transmission despite RNA detection in blood donors showing symptoms after donation. *Blood*. 2020;136(16):1888-1891. doi:10.1182/blood.2020008230

46. Jones DL, Baluja MQ, Graham DW, et al. Shedding of SARS-CoV-2 in feces and urine and its potential role in person-to-person transmission and the environment-

based spread of COVID-19. *Science of The Total Environment*. 2020/12/20/ 2020;749:141364. doi:10.1016/j.scitotenv.2020.141364

47. World Health Organization. *Breastfeeding and COVID-19*. 2020/06/23. https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci_Brief-Breastfeeding-2020.1. Accessed: 25.08.2023

48. Goryoka GW, Cossaboom CM, Gharpure R, et al. One Health Investigation of SARS-CoV-2 Infection and Seropositivity among Pets in Households with Confirmed Human COVID-19 Cases — Utah and Wisconsin, 2020. *bioRxiv*. 2021:2021.04.11.439379. doi:10.1101/2021.04.11.439379

49. Halfmann PJ, Hatta M, Chiba S, et al. Transmission of SARS-CoV-2 in Domestic Cats. *New England Journal of Medicine*. 2020;383(6):592-594. doi:10.1056/NEJMc2013400

50. Sit THC, Brackman CJ, Ip SM, et al. Infection of dogs with SARS-CoV-2. *Nature*. 2020/10/01 2020;586(7831):776-778. doi:10.1038/s41586-020-2334-5

51. World Health Organization. Tracking SARS-CoV-2 variants. 2023; https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/. Accessed: 25.08.2023

52. Rafeek RAM, Divarathna MVM, Noordeen F. A review on disease burden and epidemiology of childhood parainfluenza virus infections in Asian countries. *Rev Med Virol*. Mar 2021;31(2):e2164. doi:10.1002/rmv.2164

53. Pawełczyk M, Kowalski ML. The Role of Human Parainfluenza Virus Infections in the Immunopathology of the Respiratory Tract. *Curr Allergy Asthma Rep*. 2017;17(3):16-16. doi:10.1007/s11882-017-0685-2

54. Russell E, Ison MG. Parainfluenza Virus in the Hospitalized Adult. *Clinical Infectious Diseases*. 2017;65(9):1570-1576. doi:10.1093/cid/cix528

55. Frost HM, Robinson CC, Dominguez SR. Epidemiology and Clinical Presentation of Parainfluenza Type 4 in Children: A 3-Year Comparative Study to Parainfluenza Types 1–3. *The Journal of Infectious Diseases*. 2013;209(5):695-702. doi:10.1093/infdis/jit552

56. Centers for Disease Control and Prevention (CDC). Human Parainfluenza viruses (HPIVs). 2022; https://www.cdc.gov/parainfluenza/seasons.html. Accessed: 25.08.2023

57. Christensen A, Kesti O, Elenius V, et al. Human bocaviruses and paediatric infections. *The Lancet Child & Adolescent Health*. 2019;3(6):418-426. doi:10.1016/s2352-4642(19)30057-4

58. Lee HN, Koo HJ, Kim SH, Choi S-H, Sung H, Do K-H. Human Bocavirus Infection in Adults: Clinical Features and Radiological Findings. *Korean J Radiol*. 2019;20(7):1226-1235

59. Watanabe ASA, Luchs A, Leal É, et al. Complete Genome Sequences of Six Human Bocavirus Strains from Patients with Acute Gastroenteritis in the North Region of Brazil. *Genome Announcements*. 2018;6(17):e00235-18. doi:10.1128/genomeA.00235-18

60. Brebion A, Vanlieferinghen P, Déchelotte P, et al. Fatal Subacute Myocarditis Associated with Human Bocavirus 2 in a 13-Month-Old Child. *Journal of Clinical Microbiology*. 2014;52(3):1006-1008. doi:doi:10.1128/JCM.03013-13

61. Schildgen O, Schildgen V. The Role of the Human Bocavirus (HBoV) in Respiratory Infections. In: Tang Y-W, Stratton CW, eds. *Advanced Techniques in Diagnostic Microbiology: Volume 2: Applications*. Springer International Publishing; 2018:281-301.

62. Greber UF, Flatt JW. Adenovirus Entry: From Infection to Immunity. *Annual Review of Virology*. 2019;6(1):177-197. doi:10.1146/annurev-virology-092818-015550

63. Radke JR, Cook JL. Human adenovirus infections: update and consideration of mechanisms of viral persistence. *Current Opinion in Infectious Diseases*. 2018;31(3):251-256. doi:10.1097/qco.0000000000000451

64. Hu W, Zhang M, Xu Z, Li J, Wang F-S, Li T. Severe Acute Hepatitis of Unknown Etiology in Children: Is It Caused by Pathogens or Non-infectious Factors? *Infectious Diseases & Immunity*. 2022;2(3):200-203. doi:10.1097/id9.0000000000000060

65. Reyne MI, Allen DM, Levickas A, et al. Detection of human adenovirus F41 in wastewater and its relationship to clinical cases of acute hepatitis of unknown aetiology. *Sci Total Environ*. Jan 20 2023;857(Pt 2):159579. doi:10.1016/j.scitotenv.2022.159579

66. Tapparel C, Siegrist F, Petty TJ, Kaiser L. Picornavirus and enterovirus diversity with associated human diseases. *Infection, Genetics and Evolution*. 2013/03/01/ 2013;14:282-293. doi:10.1016/j.meegid.2012.10.016

67. Zell R. Picornaviridae—the ever-growing virus family. *Archives of Virology*. 2018/02/01 2018;163(2):299-317. doi:10.1007/s00705-017-3614-8

68. Monto AS. The seasonality of rhinovirus infections and its implications for clinical recognition. *Clin Ther*. Dec 2002;24(12):1987-97. doi:10.1016/s0149-2918(02)80093-5

69. Henritzi D, Zhao N, Starick E, et al. Rapid detection and subtyping of European swine influenza viruses in porcine clinical samples by haemagglutinin- and neuraminidase-specific tetra- and triplex real-time RT-PCRs. *Influenza and Other Respiratory Viruses*. 2016;10(6):504-517. doi:10.1111/irv.1240

70. Shu B, Garten R, Emery S, et al. Genetic analysis and antigenic characterization of swine origin influenza viruses isolated from humans in the United States, 1990–2010. *Virology*. 2012/01/05/ 2012;422(1):151-160. doi:10.1016/j.virol.2011.10.016

71. Watzinger F, Suda M, Preuner S, et al. Real-time quantitative PCR assays for detection and monitoring of pathogenic human viruses in immunosuppressed pediatric patients. *J Clin Microbiol*. Nov 2004;42(11):5189-98. doi:10.1128/jcm.42.11.5189-5198.2004

72. Zhou B, Wentworth DE. Influenza A virus molecular virology techniques. *Methods Mol Biol*. 2012;865:175-92. doi:10.1007/978-1-61779-621-0_11

73. Zhou B, Lin X, Wang W, et al. Universal Influenza B Virus Genomic Amplification Facilitates Sequencing, Diagnostics, and Reverse Genetics. *Journal of Clinical Microbiology*. 2014;52(5):1330-1337. doi:10.1128/JCM.03265-13

74. Rambaut A, Holmes EC, O'Toole Á, et al. A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic epidemiology. *Nature Microbiology*. 2020/11/01 2020;5(11):1403-1407. doi:10.1038/s41564-020-0770-5

75. Leang SK, Kwok S, Sullivan SG, et al. Peramivir and laninamivir susceptibility of circulating influenza A and B viruses. *Influenza Other Respir Viruses*. Mar 2014;8(2):135-9. doi:10.1111/irv.12187

76. World Health Organization. Influenza Update No 449. 2023; https://cdn.who.int/media/docs/default-source/influenza/influenza-updates/2023/2023_07_10_surveillance_update_449.pdf?sfvrsn=9e73ba74_1&download=true. Accessed: 25.08.2023

77. Centers for Disease Control and Prevention (CDC). Influenza Season overview. 2023; https://flunewseurope.org/SeasonOverview. Accessed: 25.08.2023

78. Worldwide Influenza Centre WHO CC for Reference & Research on Influenza. Report prepared for the WHO annual consultation on the composition of influenza vaccines for the Northern Hemisphere 2023-2024. 2023; https://www.crick.ac.uk/sites/default/files/2023-03/F2023-VCM-seasonal_web.pdf

79. Centers for Disease Control and Prevention (CDC). Novel Influenza A Virus Infections. 2022; https://gis.cdc.gov/grasp/fluview/Novel_Influenza.html. Accessed: 25.08.2023

80. European Centre for Disease Control and Prevention. Zoonotic influenza-Annual Epidemiological Report for 2022. 2023; https://www.ecdc.europa.eu/en/publications-data/zoonotic-influenza-annual-epidemiological-report-2022. Accessed: 25.08.2023

81. World Health Organization. Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO,2003-2023. 2023; https://www.who.int/publications/m/item/cumulative-number-of-confirmed-human-cases-for-avian-influenza-a(h5n1)-reported-to-who-2003-2022-5-jan-2023. Accessed: 25.08.2023

82. World Health Organization. Human infection with avian influenza A(H5) viruses. Avian Influenza Weekly Update Number 907.2023; https://cdn.who.int/media/docs/default-source/wpro---documents/emergency/surveillance/avian-influenza/ai_20230804.pdf?sfvrsn=5f006f99_118

83. European Food Safety Authority (EFSA), European Centre for Disease Control and Prevention (ECDC), et al. Avian influenza overview december 2022–march 2023. *EFSA Journal*. 2023;21(3):e07917

84. World Health Organization. Influenza at the human-animal interface, Summary and risk, from 6 to 26 January 2023. 2023; https://cdn.who.int/media/docs/default-source/influenza/human-animal-interface-risk-assessments/influenza-at-the-human-animal-interface-summary-and-assessment--from-6-to-26-january-2023.pdf?sfvrsn=abc6faf5_1&download=true

85. World Health Organization. Influenza at the human-animal interface summary and assessment, 3 March 2023. 2023; https://www.who.int/publications/m/item/influenza-at-the-human-animal-interface-summary-and-assessment-3-march-2023

86. World Health Organization. Regional Office for the Western P. Avian Influenza Weekly Update 2023. Manila: WHO Regional Office for the Western Pacific; 2023.

87. European Food Safety Authority (EFSA), European Centre for Disease Control and Prevention (ECDC), et al. Avian influenza overview march–June 2022. *EFSA Journal*. 2022;20(8):e07415.

88. European Food Safety Authority (EFSA), European Centre for Disease Control and Prevention (ECDC), Adlhoch C, et al. Avian influenza overview March–April 2023. *EFSA Journal*. 2023;21(6):e08039.

89. Food and Agriculture Organization of the United Nations (FAO). EMPRES-i. https://empres-i.apps.fao.org/#/. Accessed : 25.08.2023

90. Yum S, Hong K, Sohn S, Kim J, Chun BC. Trends in Viral Respiratory Infections During COVID-19 Pandemic, South Korea. *Emerging Infectious Disease journal*. 2021;27(6):1685. doi:10.3201/eid2706.210135

91. Agha R, Avner JR. Delayed seasonal RSV surge observed during the COVID-19 pandemic. *Pediatrics*. 2021;148(3)

92. Kuitunen I, Artama M, Haapanen M, Renko M. Respiratory virus circulation in children after relaxation of COVID-19 restrictions in fall 2021-A nationwide register study in Finland. *J Med Virol*. Sep 2022;94(9):4528-4532. doi:10.1002/jmv.27857

93. Duppenthaler A, Gorgievski-Hrisoho M, Frey U, Aebi C. Two-year periodicity of respiratory syncytial virus epidemics in Switzerland. *Infection*. Mar 2003;31(2):75-80. doi:10.1007/s15010-002-3124-8

94. Delestrain C, Danis K, Hau I, et al. Impact of COVID-19 social distancing on viral infection in France: A delayed outbreak of RSV. *Pediatr Pulmonol*. Dec 2021;56(12):3669-3673. doi:10.1002/ppul.25644

95. Foley DA, Yeoh DK, Minney-Smith CA, et al. The Interseasonal Resurgence of Respiratory Syncytial Virus in Australian Children Following the Reduction of Coronavirus Disease 2019-Related Public Health Measures. *Clin Infect Dis*. 2021/02// 2021;doi:10.1093/cid/ciaa1906

96. Center for Preparedness and Response (CPR), Centers for Disease Control and Prevention (CDC). Increased Interseasonal Respiratory Syncytial Virus (RSV) Activity in Parts of the Southern United States. 06.07.2021. 2021; https://emergency.cdc.gov/han/2021/han00443.asp. Accessed 25.08.2023

97. National Institute for Communicable Diseases (NICD).Increase in Respiratory syncitial virus (RSV) cases 2020. 2021; https://www.nicd.ac.za/increase-in-respiratory-syncytial-virus-rsv-cases-2020/. Accessed: 25.08.2023

98. Hamid S, Winn A, Parikh R, et al. Seasonality of Respiratory Syncytial Virus—United States, 2017–2023. *Morbidity and Mortality Weekly Report*. 2023;72(14):355.

99. Heininger U, Kruker AT, Bonhoeffer J, Schaad UB. Human metapneumovirus infections—biannual epidemics and clinical findings in children in the region of Basel, Switzerland. *European Journal of Pediatrics*. 2009/02/24 2009;168(12):1455. doi:10.1007/s00431-009-0949-5

100. Zhu R, Guo C, Zhao L, et al. Epidemiological and genetic characteristics of human metapneumovirus in pediatric patients across six consecutive seasons in Beijing, China. *International Journal of Infectious Diseases*. 2020/02/01/ 2020;91:137-142. doi:10.1016/j.ijid.2019.11.012

101. Fratty IS, Reznik-Balter S, Nemet I, et al. Outbreak of Influenza and Other Respiratory Viruses in Hospitalized Patients Alongside the SARS-CoV-2 Pandemic. Front *Microbiol*. 2022;13:902476. doi:10.3389/fmicb.2022.902476

102. Mahase E. Covid-19: What do we know about XBB.1.5 and should we be worried? *Bmj*. Jan 19 2023;380:153. doi:10.1136/bmj.p153

103. Mahase E. Covid-19: Is the UK still tracking the virus-and other questions answered. *Bmj*. Nov 18 2022;379:o2802. doi:10.1136/bmj.o2802

104. World Health Organization. XBB. 1.5 rapid risk assessment. 11 January 2023. 2023; https://www.who.int/docs/default-source/coronaviruse/11jan2023_xbb15_rapid_risk_assessment.pdf

105. European Centre for Disease Control and Prevention. Implications for the EU/EEA of the spread of the SARS-CoV-2 Omicron XBB. 1.5 sub-lineage. 13 January 2023. 2023; https://www.ecdc.europa.eu/sites/default/files/documents/TAB-Implications%20for%20the%20EU-EEA%20of%20the%20spread%20of%20the%20SARS-CoV-2%20Omicron%20XBB.1.5%20sub-lineage.pdf

106. European Centre for Disease Control and Prevention. *SARS-CoV-2 variants of concern as of 10 August 2023*. 2023; https://www.ecdc.europa.eu/en/covid-19/variants-concern. Accessed: 23.08.2023

107. World Health Organization, European Centre for Disease Control and Prevention. *Joint ECDC-WHO Regional Office for Europe Weekly COVID-19 Surveillance Bulletin*. 2023. *Week 07/2023 (13 February-19 February 2023)*. https://worldhealthorg.shinyapps.io/euro-covid19/_w_0f629f17/archive/ECDC-WHO-Regional-Office-for-Europe-COVID19-Bulletin-07-23-eng.pdf

108. Global Initiative on Sharing Influenza Data (GISAID). Overview of Variants in Countries. 2023; https://covariants.org/per-country?region=Switzerland. Accessed: 25.08.2023

109. Global Initiative on Sharing Influenza Data (GISAID). Detect and analyze variants of SARS-CoV-2. 2023; https://cov-spectrum.org/explore/Switzerland/AllSamples/AllTimes. Accessed: 25.08.2023

110. Ambrosioni J, Bridevaux PO, Wagner G, Mamin A, Kaiser L. Epidemiology of viral respiratory infections in a tertiary care centre in the era of molecular diagnosis, Geneva, Switzerland, 2011–2012. *Clinical Microbiology and Infection*. 2014/09/01/ 2014;20(9):O578-O584. doi:10.1111/1469-0691.12525

111. Marshall NC, Kariyawasam RM, Zelyas N, Kanji JN, Diggle MA. Broad respiratory testing to identify SARS-CoV-2 viral co-circulation and inform diagnostic

stewardship in the COVID-19 pandemic. *Virology Journal*. 2021/05/01 2021;18(1):93. doi:10.1186/s12985-021-01545-9

112. Zhang Y, Su L, Chen Y, et al. Etiology and clinical characteristics of SARS-CoV-2 and other human coronaviruses among children in Zhejiang Province, China 2017–2019. *Virology Journal*. 2021/04/30 2021;18(1):89. doi:10.1186/s12985-021-01562-8

113. DeGroote NP, Haynes AK, Taylor C, et al. Human parainfluenza virus circulation, United States, 2011-2019. *J Clin Virol*. Mar 2020;124:104261. doi:10.1016/j.jcv.2020.104261

114. Greiff DRL, Patterson-Robert A, Blyth CC, Glass K, Moore HC. Epidemiology and seasonality of human parainfluenza serotypes 1-3 in Australian children. *Influenza and Other Respiratory Viruses*. n/a(n/a)doi:10.1111/irv.12838

115. Polo D, Lema A, Gándara E, Romalde JL. Prevalence of human bocavirus infections in Europe. A systematic review and meta-analysis. *Transbound Emerg Dis*. Sep 2022;69(5):2451-2461. doi:10.1111/tbed.14233

116. Guido M, Tumolo MR, Verri T, et al. Human bocavirus: Current knowledge and future challenges. *World J Gastroenterol*. 2016;22(39):8684-8697. doi:10.3748/wjg.v22.i39.8684

117. Peci A, Winter A-L, Gubbay JB, et al. Community-acquired respiratory viruses and co-infection among patients of Ontario sentinel practices, April 2009 to February 2010. *Influenza and Other Respiratory Viruses*. 2013;7(4):559-566. doi:10.1111/j.1750-2659.2012.00418.x

118. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. *J Infect*. 2020;81(2):266-275. doi:10.1016/j.jinf.2020.05.046

119. Eldesouki RE, Uhteg K, Mostafa HH. The circulation of Non-SARS-CoV-2 respiratory viruses and coinfections with SARS-CoV-2 during the surge of the Omicron variant. *Journal of Clinical Virology*. 2022/08/01/ 2022;153:105215. doi:10.1016/j.jcv.2022.105215

120. European Centre for Disease Control and Prevention. Infographic: Influenza in Europe, 2019-2023. 2023; https://www.ecdc.europa.eu/en/publications-data/infographic-influenza-europe-2019-2023. Accessed: 25.08.2023

121. World Health Organization and European Centre for Disease Control and Prevention. *Influenza virus characterization: summary report, Europe, February 2023*. 2023; https://www.who.int/europe/publications/i/item/WHO-EURO-2023-6189-45954-68789

122. Ben Moussa M, Buckrell S, Rahal A, et al. National influenza mid-season report, 2022-2023: A rapid and early epidemic onset. *Can Commun Dis Rep*. Jan 5 2023;49(1):10-14. doi:10.14745/ccdr.v49i01a03

123. Centers for Disease Control and Prevention (CDC). 2022-2023 U.S. Flu Season: Preliminary In-Season Burden Estimates. 2023; https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm. Accessed: 25.08.2023

124. Lagacé-Wiens P, Sevenhuysen C, Lee L, Nwosu A, Smith T. Impact of nonpharmaceutical interventions on laboratory detections of influenza A and B in Canada. *Can Commun Dis Rep*. Mar 31 2021;47(3):142-148. doi:10.14745/ccdr.v47i03a04

125. Sullivan SG, Carlson S, Cheng AC, et al. Where has all the influenza gone? The impact of COVID-19 on the circulation of influenza and other respiratory viruses, Australia, March to September 2020. *Euro Surveill*. Nov 2020;25(47)doi:10.2807/1560-7917.Es.2020.25.47.2001847

126. Olsen SJ, Azziz-Baumgartner E, Budd AP, et al. Decreased influenza activity during the COVID-19 pandemic-United States, Australia, Chile, and South Africa, 2020. *Am J Transplant*. Dec 2020;20(12):3681-3685. doi:10.1111/ajt.1638

127. Baker RE, Park SW, Yang W, Vecchi GA, Metcalf CJE, Grenfell BT. The impact of COVID-19 nonpharmaceutical interventions on the future dynamics of endemic infections. *Proc Natl Acad Sci U S A*. Dec 1 2020;117(48):30547-30553. doi:10.1073/pnas.2013182117

128. Leung NHL, Chu DKW, Shiu EYC, et al. Respiratory virus shedding in exhaled breath and efficacy of face masks. *Nat Med*. May 2020;26(5):676-680. doi:10.1038/s41591-020-0843-2

129. Tang JW, Bialasiewicz S, Dwyer DE, et al. Where have all the viruses gone? Disappearance of seasonal respiratory viruses during the COVID-19 pandemic. *J Med Virol*. Jul 2021;93(7):4099-4101. doi:10.1002/jmv.26964

130. Gomez GB, Mahé C, Chaves SS. Uncertain effects of the pandemic on respiratory viruses. *Science*. Jun 4 2021;372(6546):1043-1044. doi:10.1126/science.abh3986

131. Dhanasekaran V, Sullivan S, Edwards KM, et al. Human seasonal influenza under COVID-19 and the potential consequences of influenza lineage elimination. *Nat Commun*. Mar 31 2022;13(1):1721. doi:10.1038/s41467-022-29402-5

132. Woolthuis RG, Wallinga J, van Boven M. Variation in loss of immunity shapes influenza epidemics and the impact of vaccination. *BMC Infect Dis*. Sep 19 2017;17(1):632. doi:10.1186/s12879-017-2716-y

133. World Organization for Animal Health and Food Agricultural Organization of the United Nations Network of Expertise on Animal Influenza (OFFLU). *Strategic challenges in the global control of high pathogenicity avian influenza*. *90 GS*. 2023; https://www.woah.org/app/uploads/2023/05/a-90sg-8.pdf

134. Wüthrich D, Lang D, Müller NF, Neher RA, Stadler T, Egli A. Evaluation of two workflows for whole genome sequencing-based typing of influenza A viruses. *J Virol Methods*. Apr 2019;266:30-33. doi:10.1016/j.jviromet.2019.01.009

Geneva, August 29th 2023

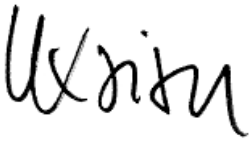
Mrs Tania Spedaliero

Dr Ana Rita Gonçalves Cabecinhas

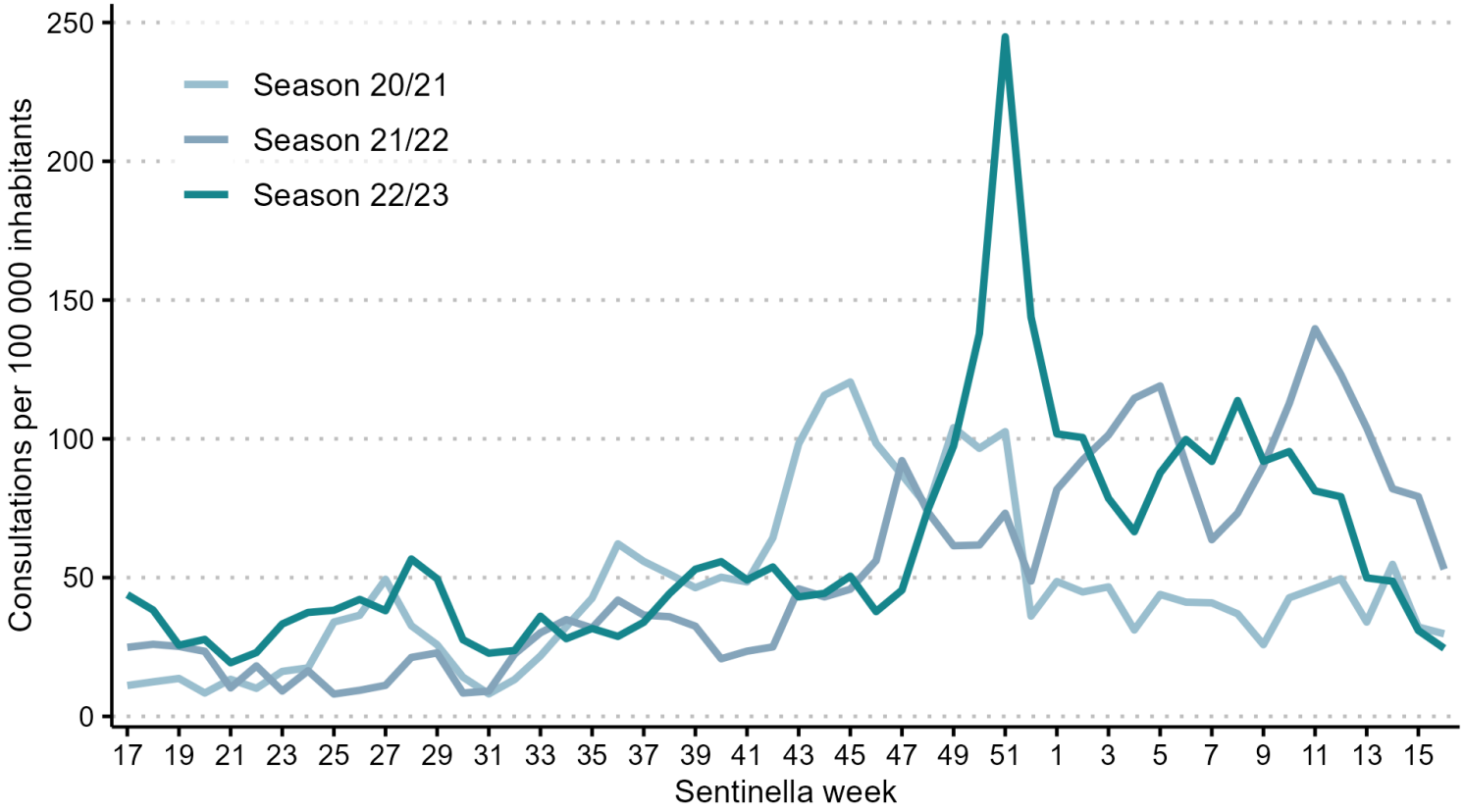
Mrs Patricia Suter-Boquete

Dr Manuel Schibler

Professor Laurent Kaiser



Appendix 1: Consultations due to influenza-like illness in Switzerland, FOPH



(https://www.bag.admin.ch/bag/fr/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/saisonale-grippe---lagebericht-schweiz.html)

Appendix 2: Detailed description of the observed co-infections (40/2022-16/2023)

Weeks	Co-detections															
40	VRS/RV-EV	RV-EV/SARS-CoV2	HPIV1-3/SARS-CoV2	RV-EV/SARS-CoV2	VRS/RV-EV											5
41	RV-EV/SARS-CoV2	RV-EV/SARS-CoV2	RV-EV/SARS-CoV2	HCoVOC43/SARS-CoV2	HPIV1-3/RV-EV											5
42	RV-EV/SARS-CoV2	HCoVE229/RV-EV	VRS/RV-EV	VRS/RV-EV	VRS/RV-EV	HMPV/SARS-CoV2/RV-EV/VRS	RV-EV/SARS-CoV2	RV-EV/SARS-CoV2								8
43	VRS/RV-EV	RV-EV/SARS-CoV2	VRS/RV-EV	HPIV1-3/VRS	RV-EV/HAdV	VRS/RV-EV	HPIV1-3/RV-EV									7
44	VRS/RV-EV	HAdV /VRS	RV-EV/SARS-CoV2													3
46	HBoV/RV-EV	VRS/RV-EV	RV-EV/SARS-CoV2	RV-EV/IA	VRS/RV-EV	VRS/RV-EV										6
47	IA/VRS	HPIV1-3/RV-EV/HBoV/SARS-CoV2	RV-EV/SARS-CoV2	RV-EV/SARS-CoV2	RV-EV/SARS-CoV2											5
48	HAdV /VRS	RV-EV/SARS-CoV2	RV-EV/SARS-CoV2													3
49	HMPV/SARS-CoV2	VRS/RV-EV	HBoV/RV-EV	VRS/RV-EV	HAdV /HBoV	HCoVOC43/SARS-CoV2										6
50	HBoV/IA	IA/VRS	HBoV/SARS-CoV2	SARS-CoV2/VRS	HCoVOC43/IA	IA/SARS-CoV2	RV-EV/HAdV/HCoVOC43	RV-EV/IA	RV-EV/HAdV	VRS/RV-EV						10
51	HMPV/VRS	HCoVOC43/HBoV	IA/SARS-CoV2	RV-EV/IA	HMPV/IA	HCoVOC43/SARS-CoV2	HAdV/RV-EV/HBoV/SARS-CoV2	IA/SARS-CoV2	RV-EV/IA	SARS-CoV2/VRS	HCoVOC43/IA	VRS/RV-EV	RV-EV/IA	RV-EV/HBoV/HCoVOC4	HCoVOC43/IA	15
52	HCoVOC43/IA	VRS/RV-EV	RV-EV/IA	RV-EV/IA												4
1	HCoVOC43/HMPV	RV-EV/HAdV	RV-EV/HCoVOC43	RV-EV/IA	RV-EV/SARS-CoV2/IA	HCoVOC43/IA	IA/SARS-CoV2	VRS/RV-EV/HAdV	SARS-CoV2/HAdV	IA/VRS	HCoVOC43/IA					11
2	HCoVOC43/HMPV	IA/SARS-CoV2	IA/SARS-CoV2	HMPV/IB												4
3	HCoVOC43/SARS-CoV2/RV-EV	IA/VRS	IA/VRS	IA/VRS	SARS-CoV2/VRS/IA											5
4	RV-EV/IA	SARS-CoV2/VRS/IA	IB/SARS-CoV2	SARS-CoV2/ HAdV/IB	RV-EV/SARS-CoV2/IA											5
5	RV-EV/SARS-CoV2	RV-EV/SARS-CoV2	RV-EV/SARS-CoV2	RV-EV/HAdV	HAdV /IA											5
6	HAdV /IB	HCoVOC43/SARS-CoV2	IB/IA	IB/SARS-CoV2	HCoVOC43/IB	HCoVNL63/SARS-CoV2										6
7	HMPV/IB	HPIV1-3/IB														2
8	IB/SARS-CoV2															1
9	HCoVNL63/HMPV	HCoVNL63/IB	SARS-CoV2/ HAdV	RV-EV/IB												4
10	SARS-CoV2/ HAdV	SARS-CoV2/ HAdV	RV-EV/IA	RV-EV/HAdV	RV-EV/HAdV	SARS-CoV2/ HAdV/ IB										6
11	IB/VRS	HCoVHKU1/HAdV	IB/VRS	HCoVNL63/RV-EV	HPIV1-3/HAdV	HCoVNL63/IB	RV-EV/HMPV	HCoVNL63/SARS-CoV2								8
12	SARS-CoV2/ HAdV	RV-EV/HAdV	RV-EV/SARS-CoV2	HPIV1-3/SARS-CoV2/HCoVNL63	HCoVNL63/RV-EV											5
13	HCoVE229/IB/VRS	HCoVNL63/SARS-CoV2	IB/SARS-CoV2													3
15	HMPV/SARS-CoV2	RV-EV/SARS-CoV2														2
Total																144

Appendix 3: Lists of SARS-CoV-2 isolates submitted to GISAID (40/2022-16/2023)

Isolate name	Pangolin clade	Collection date	GISAID_ID
hCoV-19/Switzerland/BE-SNRCI-HUG-39473351/2022	BA.5.2	20221011	EPI_ISL_15528173
hCoV-19/Switzerland/GR-SNRCI-HUG-39462886/2022	BA.5.1	20221011	EPI_ISL_15528314
hCoV-19/Switzerland/GR-SNRCI-HUG-39463038/2022	BA.5.2	20221011	EPI_ISL_15528313
hCoV-19/Switzerland/AG-SNRCI-HUG-39485381/2022	BA.5.1.23	20221012	EPI_ISL_15528172
hCoV-19/Switzerland/VS-SNRCI-HUG-39485817/2022	BA.5.2.20	20221013	EPI_ISL_15528317
hCoV-19/Switzerland/BE-SNRCI-HUG-39531269/2022	BA.5.2.1	20221017	EPI_ISL_15639390
hCoV-19/Switzerland/BE-SNRCI-HUG-39531133/2022	BA.5.2.6	20221017	EPI_ISL_15639387
hCoV-19/Switzerland/TI-SNRCI-HUG-39518414/2022	BF.7	20221017	EPI_ISL_15639454
hCoV-19/Switzerland/ZH-SNRCI-HUG-39518377/2022	BA.5.2	20221017	EPI_ISL_15639459
hCoV-19/Switzerland/NE-SNRCI-HUG-39518159/2022	BA.5.1	20221017	EPI_ISL_15639450
hCoV-19/Switzerland/BE-SNRCI-HUG-39518115/2022	BA.5.1	20221017	EPI_ISL_15639385
hCoV-19/Switzerland/BE-SNRCI-HUG-39541304/2022	BA.5.2.1	20221018	EPI_ISL_15639389
hCoV-19/Switzerland/ZH-SNRCI-HUG-39541146/2022	BA.5.1	20221018	EPI_ISL_15639461
hCoV-19/Switzerland/NE-SNRCI-HUG-39531244/2022	BA.5.1.10	20221018	EPI_ISL_15639452
hCoV-19/Switzerland/BE-SNRCI-HUG-39531212/2022	BF.10	20221018	EPI_ISL_15639388
hCoV-19/Switzerland/NE-SNRCI-HUG-39531118/2022	BA.5.2	20221018	EPI_ISL_15639451
hCoV-19/Switzerland/TI-SNRCI-HUG-39531033/2022	BF.10	20221018	EPI_ISL_15639455
hCoV-19/Switzerland/AG-SNRCI-HUG-39530650/2022	BA.5.1	20221018	EPI_ISL_15639384
hCoV-19/Switzerland/SG-SNRCI-HUG-39530492/2022	BA.5.2	20221018	EPI_ISL_15639453
hCoV-19/Switzerland/FR-SNRCI-HUG-39541456/2022	BA.5.1.21	20221019	EPI_ISL_15639391
hCoV-19/Switzerland/TI-SNRCI-HUG-39541287/2022	BQ.1	20221019	EPI_ISL_15639456
hCoV-19/Switzerland/BE-SNRCI-HUG-39530677/2022	BA.5.2.27	20221019	EPI_ISL_15639386
hCoV-19/Switzerland/ZH-SNRCI-HUG-39562736/2022	BA.5.2.1	20221020	EPI_ISL_15639460
hCoV-19/Switzerland/VS-SNRCI-HUG-39594902/2022	BA.5.2.1	20221024	EPI_ISL_15743303
hCoV-19/Switzerland/BE-SNRCI-HUG-39594780/2022	BA.5.1.5	20221024	EPI_ISL_15743219
hCoV-19/Switzerland/BE-SNRCI-HUG-39594660/2022	BE.1.1.2	20221024	EPI_ISL_15743218
hCoV-19/Switzerland/BE-SNRCI-HUG-39594630/2022	BE.1.1.2	20221024	EPI_ISL_15743217
hCoV-19/Switzerland/GR-SNRCI-HUG-39584456/2022	BF.7	20221024	EPI_ISL_15743285
hCoV-19/Switzerland/NE-SNRCI-HUG-39584355/2022	BE.1.1	20221024	EPI_ISL_15743289
hCoV-19/Switzerland/VD-SNRCI-HUG-39594749/2022	BF.7	20221025	EPI_ISL_15743301
hCoV-19/Switzerland/GR-SNRCI-HUG-39594397/2022	BM.1.1.3	20221025	EPI_ISL_15743286
hCoV-19/Switzerland/ZH-SNRCI-HUG-39624204/2022	BE.1.1.2	20221027	EPI_ISL_15743305
hCoV-19/Switzerland/ZH-SNRCI-HUG-39624188/2022	BE.1.1.2	20221027	EPI_ISL_15743304
hCoV-19/Switzerland/BE-SNRCI-HUG-39614978/2022	BE.1.1	20221027	EPI_ISL_15743220
hCoV-19/Switzerland/TI-SNRCI-HUG-39614807/2022	BA.5.2	20221027	EPI_ISL_15743290
hCoV-19/Switzerland/GR-SNRCI-HUG-39624220/2022	BA.5.2	20221028	EPI_ISL_15743287
hCoV-19/Switzerland/VD-SNRCI-HUG-39623527/2022	BQ.1.1	20221029	EPI_ISL_15743302
hCoV-19/Switzerland/BE-SNRCI-HUG-39633319/2022	BA.5.1.5	20221028	EPI_ISL_15743221
hCoV-19/Switzerland/LU-SNRCI-HUG-39623546/2022	BA.5.2.7	20221029	EPI_ISL_15743288
hCoV-19/Switzerland/BE-SNRCI-HUG-39676448/2022	BQ.1.1	20221103	EPI_ISL_15985546
hCoV-19/Switzerland/ZH-SNRCI-HUG-39676356/2022	BQ.1.18	20221103	EPI_ISL_15985698
hCoV-19/Switzerland/ZH-SNRCI-HUG-39675859/2022	BA.5.1.28	20221102	EPI_ISL_15985697
hCoV-19/Switzerland/LU-SNRCI-HUG-39675715/2022	BA.5.2	20221103	EPI_ISL_15985691
hCoV-19/Switzerland/BE-SNRCI-HUG-39707598/2022	BA.5.2.20	20221105	EPI_ISL_15985547
hCoV-19/Switzerland/ZH-SNRCI-HUG-39719660/2022	BA.5.2	20221107	EPI_ISL_15985700
hCoV-19/Switzerland/BE-SNRCI-HUG-39719539/2022	BA.5.9	20221107	EPI_ISL_15985551

Isolate name	Pangolin clade	Collection date	GISAID_ID
hCoV-19/Switzerland/BE-SNRCI-HUG-39719405/2022	BF.7	20221107	EPI_ISL_15985550
hCoV-19/Switzerland/GR-SNRCI-HUG-39708152/2022	BA.5.2.6	20221107	EPI_ISL_15985690
hCoV-19/Switzerland/BE-SNRCI-HUG-39707789/2022	BA.5.1	20221107	EPI_ISL_15985548
hCoV-19/Switzerland/BE-SNRCI-HUG-39730438/2022	BQ.1.1	20221108	EPI_ISL_15985549
hCoV-19/Switzerland/ZH-SNRCI-HUG-39719929/2022	BA.5.2.1	20221108	EPI_ISL_15985699
hCoV-19/Switzerland/NE-SNRCI-HUG-39719852/2022	BA.5.1.3	20221108	EPI_ISL_15985694
hCoV-19/Switzerland/LU-SNRCI-HUG-39752910/2022	BA.5.2.1	20221110	EPI_ISL_15985692
hCoV-19/Switzerland/AG-SNRCI-HUG-39752936/2022	BF.7.4	20221111	EPI_ISL_15985545
hCoV-19/Switzerland/LU-SNRCI-HUG-39752857/2022	BA.5.9	20221111	EPI_ISL_15985693
hCoV-19/Switzerland/BE-SNRCI-HUG-39786167/2022	BQ.1.1	20221114	EPI_ISL_16064269
hCoV-19/Switzerland/BE-SNRCI-HUG-39785994/2022	BQ.1.1	20221114	EPI_ISL_16064268
hCoV-19/Switzerland/AG-SNRCI-HUG-39785836/2022	BF.26	20221114	EPI_ISL_16064265
hCoV-19/Switzerland/VS-SNRCI-HUG-39773647/2022	BF.7	20221114	EPI_ISL_16064420
hCoV-19/Switzerland/GR-SNRCI-HUG-39773533/2022	BQ.1	20221114	EPI_ISL_16064414
hCoV-19/Switzerland/TI-SNRCI-HUG-39773249/2022	BA.5.2.1	20221114	EPI_ISL_16064416
hCoV-19/Switzerland/BE-SNRCI-HUG-39796208/2022	BA.5.2.6	20221115	EPI_ISL_16064266
hCoV-19/Switzerland/BE-SNRCI-HUG-39785960/2022	BQ.1.2	20221116	EPI_ISL_16064270
hCoV-19/Switzerland/BE-SNRCI-HUG-39796440/2022	BQ.1.1.7	20221116	EPI_ISL_16064267
hCoV-19/Switzerland/LU-SNRCI-HUG-39796394/2022	BF.7	20221116	EPI_ISL_16064415
hCoV-19/Switzerland/GR-SNRCI-HUG-40200479/2022	XBF	20221229	EPI_ISL_16490178
hCoV-19/Switzerland/TG-SNRCI-HUG-40223572/2022	BA.5.1	20221229	EPI_ISL_16583376
hCoV-19/Switzerland/ZH-SNRCI-HUG-40223686/2022	BQ.1.1	20221230	EPI_ISL_16583380
hCoV-19/Switzerland/BE-SNRCI-HUG-40223964/2022	CH.1.1	20221230	EPI_ISL_16583381
hCoV-19/Switzerland/GE-SNRCI-HUG-40245133/2023	CH.1.1	20230104	EPI_ISL_16583379
hCoV-19/Switzerland/ZH-SNCRI-HUG-40245160/2023	BQ.1.2	20230104	EPI_ISL_16583377
hCoV-19/Switzerland/AG-SNRCI-HUG-40245487/2023	BQ.1.1	20230104	EPI_ISL_16583378
hCoV-19/Switzerland/TI-SNRCI-HUG-40393218/2023	BQ.1.1	20230120	EPI_ISL_16760612
hCoV-19/Switzerland/AG-SNRCI-HUG-40424159/2023	BQ.1.21	20230123	EPI_ISL_16941735
hCoV-19/Switzerland/NW-SNRCI-HUG-40490959/2023	XBB.1.5	20230130	EPI_ISL_16941755
hCoV-19/Switzerland/ZH-SNRCI-HUG-40544860/2023	BQ.1.1	20230201	EPI_ISL_16941722
hCoV-19/Switzerland/BE-SNRCI-HUG-40558952/2023	XBB.1.5	20230203	EPI_ISL_16941720
hCoV-19/Switzerland/BE-SNRCI-HUG-40545802/2023	XBB.1.5	20230203	EPI_ISL_16941723
hCoV-19/Switzerland/AG-SNRCI-HUG-40544953/2023	BQ.1.1.18	20230203	EPI_ISL_16941721
hCoV-19/Switzerland/TI-SNRCI-HUG-40571202/2023	BQ.1.1.15	20230207	EPI_ISL_17075286
hCoV-19/Switzerland/AG-SNRCI-HUG-40583019/2023	XBB.1.5	20230208	EPI_ISL_17075287
hCoV-19/Switzerland/AG-SNRCI-HUG-40640049/2023	BQ.1.1.47	20230214	EPI_ISL_17075313
hCoV-19/Switzerland/LU-SNRCI-HUG-40685906/2023	BQ.1.1	20230217	EPI_ISL_17075337
hCoV-19/Switzerland/NE-SNRCI-HUG-40685512/2023	CH.1.1	20230217	EPI_ISL_17075336
hCoV-19/Switzerland/AG-SNRCI-HUG-40684924/2023	BQ.1.10	20230217	EPI_ISL_17075334
hCoV-19/Switzerland/VS-SNRCI-HUG-40709649/2023	XBF.2	20230220	EPI_ISL_17222223
hCoV-19/Switzerland/ZH-SNRCI-HUG-40732620/2023	XBB.1.5	20230223	EPI_ISL_17222225
hCoV-19/Switzerland/SG-SNRCI-HUG-40732337/2023	XBB.1.5	20230223	EPI_ISL_17222222
hCoV-19/Switzerland/ZH-SNRCI-HUG-40732491/2023	XBB.1.5	20230224	EPI_ISL_17222224
hCoV-19/Switzerland/ZH-SNRCI-HUG-40752846/2023	XBB.1.5	20230224	EPI_ISL_17222226
hCoV-19/Switzerland/BE-SNRCI-HUG-40832468/2023	XBB.1.9.2	20230306	EPI_ISL_17222169
hCoV-19/Switzerland/LU-SNRCI-HUG-40832546/2023	XBB.1.5	20230306	EPI_ISL_17222221

Isolate name	Pangolin clade	Collection date	GISAID_ID
hCoV-19/Switzerland/VD-SNRCI-HUG-40843472/2023	XBB.1.5	20230307	EPI_ISL_17347252
hCoV-19/Switzerland/BE-SNRCI-HUG-40867087/2023	XBB.1.5	20230309	EPI_ISL_17347260
hCoV-19/Switzerland/BE-SNRCI-HUG-40887620/2023	XBB.1.9.2	20230310	EPI_ISL_17347266
hCoV-19/Switzerland/AG-SNRCI-HUG-40887484/2023	XBB.1.5	20230310	EPI_ISL_17347267
hCoV-19/Switzerland/TG-SNRCI-HUG-40887349/2023	XBB.1.5	20230310	EPI_ISL_17347268
hCoV-19/Switzerland/FR-SNRCI-HUG-40900466/2023	XBB.1.5	20230313	EPI_ISL_17347276
hCoV-19/Switzerland/TI-SNRCI-HUG-40900125/2023	BN.1.4	20230313	EPI_ISL_17347277
hCoV-19/Switzerland/BL-SNRCI-HUG-40923102/2023	XBB.1.5	20230314	EPI_ISL_17347281
hCoV-19/Switzerland/SG-SNRCI-HUG-40922608/2023	BQ.1.13.1	20230314	EPI_ISL_17347282
hCoV-19/Switzerland/BE-SNRCI-HUG-40911461/2023	XBB.1.9.2	20230314	EPI_ISL_17347284
hCoV-19/Switzerland/VS-SNRCI-HUG-40911422/2023	XBB.1.5	20230314	EPI_ISL_17347283
hCoV-19/Switzerland/GL-SNRCI-HUG-40977471/2023	XBB.1.5.7	20230317	EPI_ISL_17475223
hCoV-19/Switzerland/AG-SNRCI-HUG-40953958/2023	XBB.1.5	20230317	EPI_ISL_17347295
hCoV-19/Switzerland/VD-SNRCI-HUG-40953623/2023	XBB.1.5	20230317	EPI_ISL_17347292
hCoV-19/Switzerland/VS-SNRCI-HUG-40953581/2023	XBB.1.5	20230317	EPI_ISL_17347294
hCoV-19/Switzerland/VS-SNRCI-HUG-40953448/2023	XBB.1.9.2	20230317	EPI_ISL_17347293
hCoV-19/Switzerland/TI-SNRCI-HUG-40977564/2023	XBB.1.9.1	20230320	EPI_ISL_17475226
hCoV-19/Switzerland/NE-SNRCI-HUG-40966206/2023	CH.1.1	20230320	EPI_ISL_17347298
hCoV-19/Switzerland/BE-SNRCI-HUG-40965955/2023	XBB.1.9	20230320	EPI_ISL_17347296
hCoV-19/Switzerland/AG-SNRCI-HUG-40965566/2023	BQ.1.1	20230320	EPI_ISL_17347297
hCoV-19/Switzerland/BE-SNRCI-HUG-40977804/2023	XBB.1.5.12	20230321	EPI_ISL_17475225
hCoV-19/Switzerland/ZH-SNRCI-HUG-40977733/2023	XBB.1.9.1	20230321	EPI_ISL_17475222
hCoV-19/Switzerland/BE-SNRCI-HUG-40977646/2023	XBB.1.9.1	20230321	EPI_ISL_17475221
hCoV-19/Switzerland/SG-SNRCI-HUG-40977515/2023	XBF.7.1	20230321	EPI_ISL_17475224
hCoV-19/Switzerland/SG-SNRCI-HUG-41045603/2023	XBB.1.5	20230327	EPI_ISL_17475244
hCoV-19/Switzerland/BE-SNRCI-HUG-41045475/2023	XBB.1.5	20230327	EPI_ISL_17475243
hCoV-19/Switzerland/ZH-SNRCI-HUG-41032880/2023	XBB.1.5	20230327	EPI_ISL_17475238
hCoV-19/Switzerland/BE-SNRCI-HUG-41057383/2023	XBB.1.5	20230328	EPI_ISL_17475249
hCoV-19/Switzerland/ZH-SNRCI-HUG-41045347/2023	XBB.1.5.7	20230328	EPI_ISL_17475246
hCoV-19/Switzerland/ZH-SNRCI-HUG-41068619/2023	XBB.1.5	20230329	EPI_ISL_17475251
hCoV-19/Switzerland/VS-SNRCI-HUG-41057571/2023	XBB.1.5	20230329	EPI_ISL_17475248
hCoV-19/Switzerland/SG-SNRCI-HUG-41057339/2023	XBB.1.9.1	20230329	EPI_ISL_17475247
hCoV-19/Switzerland/LU-SNRCI-HUG-41045641/2023	EG.1	20230329	EPI_ISL_17475245
hCoV-19/Switzerland/BE-SNRCI-HUG-41068649/2023	XBB.1.9.1	20230330	EPI_ISL_17475252
hCoV-19/Switzerland/ZH-SNRCI-HUG-41057248/2023	XBB.1.5	20230330	EPI_ISL_17475250
hCoV-19/Switzerland/VS-SNRCI-HUG-41089625/2023	XBB.1.5.15	20230331	EPI_ISL_17475260
hCoV-19/Switzerland/TI-SNRCI-HUG-41089545/2023	XBB.1.5	20230331	EPI_ISL_17475259
hCoV-19/Switzerland/ZH-SNRCI-HUG-41089513/2023	XBB.1.5	20230331	EPI_ISL_17475258
hCoV-19/Switzerland/TI-SNRCI-HUG-41113308/2023	BQ.1.1.45	20230404	EPI_ISL_17557550
hCoV-19/Switzerland/BE-SNRCI-HUG-41155554/2023	XBB.1.5	20230405	EPI_ISL_17557498
hCoV-19/Switzerland/BE-SNRCI-HUG-41190513/2023	XBB.1.5	20230411	EPI_ISL_17557499
hCoV-19/Switzerland/VS-SNRCI-HUG-41209567/2023	XBB.1.9.2	20230414	EPI_ISL_17557553
hCoV-19/Switzerland/SG-SNRCI-HUG-41209396/2023	XBB.2.3	20230414	EPI_ISL_17557549
hCoV-19/Switzerland/ZH-SNRCI-HUG-41209135/2023	XBB.1.5	20230414	EPI_ISL_17557555
hCoV-19/Switzerland/ZH-SNRCI-HUG-41209868/2023	XBB.1.9.2	20230417	EPI_ISL_17557554
hCoV-19/Switzerland/ZH-SNRCI-HUG-41253624/2023	XBB.1.9.1	20230419	EPI_ISL_17655849
hCoV-19/Switzerland/BL-SNRCI-HUG-41273221/2023	XBB.1.16	20230421	EPI_ISL_17655854
hCoV-19/Switzerland/VS-SNRCI-HUG-41273127/2023	XBB.1.5.37	20230421	EPI_ISL_17655856

Appendix 4: Antigenic analyses of influenza A(H3N2) viruses (Guinea Pig RBC with 20nM Oseltamivir) 2023-03-24, WIC

Viruses	HA1 substitutions additional to those defining subclades of 3C.2a1b.2a	Passage history Ferret number Genetic group	Collection date	Passage history	Haemagglutination inhibition titre Post-infection ferret antisera										
					A/Cambodia/925256/2020 SIAT F03/21 1a	A/Cambodia/e0826360/2020 Egg F10/21 1a	A/Thuringen/10/22 SIAT F36/22 2b	A/Stockholm/5/21 SIAT F15/22 2a	A/Darwin/9/21 Egg F39/21 2a	A/Norway/24873/21 SIAT F10/22 2a.3	A/Norway/24873/21 Egg F11/22 2a.3	A/Poland/97/22 SIAT F39/22 2a.2	A/Slovenia/8720/22 SIAT F24/22 2a.1	A/Lille/50053/22 SIAT F02/23 2a.1	A/Catalonia/NSVH-2067/22 SIAT F41/22 2a.1b
REFERENCE VIRUSES															
A/Cambodia/925256/2020		1a	2020-09-25	SIAT5	320	160	<40	160	160	<40	<40	80	<40	80	<40
A/Cambodia/e0826360/2020		1a	2020-07-16	E5/E3	160	1280	40	160	320	40	80	80	160	160	<40
A/Thuringen/10/2022	S262N	2b	2022-04-01	P1/SIAT2	160	640	320	320	640	320	160	160	320	640	80
A/Stockholm/5/2021		2a	2021-04-16	SIAT0/SIAT4	80	160	80	640	320	80	160	320	320	320	160
A/Darwin/9/2021	D186N, D225G (egg)	2a	2021-04-17	E3/E4	80	320	160	320	640	160	320	320	640	320	160
A/Norway/24873/2021		2a.3	2021-10-24	SIAT3	40	80	80	160	320	160	160	80	160	160	80
A/Norway/24873/2021	D225G (egg)	2a.3	2021-10-24	E3/E1	40	160	160	320	640	160	640	160	640	320	80
A/Poland/97/2022	P3S, I25V, S145N, R201K	2a.2	2022-05-09	SIAT3	40	80	80	320	640	160	320	640	640	640	160
A/Slovenia/8720/2022		2a.1	2022-02-10	SIAT1/MDCK1/SIAT2	80	160	160	320	640	320	320	640	1280	1280	640
A/Lille/50053/2022	T135A(-cho), T167S, N190S	2a.1	2022-09-06	MDCK1/SIAT5	40	80	40	80	160	40	40	160	320	1280	160
A/Catalonia/NSVH161512067/2022		2a.1b	2022-09-14	SIAT1/SIAT3	40	80	80	160	320	80	160	320	640	1280	640
TEST VIRUSES															
A/England/123/2022		2a.1	2022-06-06	SIAT1/SIAT1	40	40	40	160	160	80	80	160	320	320	160
A/Palencia/210/2022		2a.1	2022-09-20	SIAT2	<40	80	40	80	160	40	40	160	320	640	160
A/Lisboa/629/2022		2a.1	2022-11-02	SIAT1	<40	40	<40	80	160	<40	40	80	160	640	40
A/Switzerland/06948/2022		2a.1b	2022-10-05	MDCK1/SIAT1	80	160	160	320	640	160	320	320	640	1280	640
A/Hessen/6/2023		2a.1b	2023-02-03	P1/SIAT1	<40	40	40	80	160	40	40	80	320	320	80
A/England/139/2022		2a.3	2022-05-04	SIAT1/SIAT1	40	40	40	80	160	160	160	80	80	160	80
A/England/148/2022		2a.3a.1	2022-09-01	SIAT1/SIAT1	40	80	80	160	320	320	320	80	160	160	80
A/England/122/2022		2a.3a.1	2022-09-02	SIAT1/SIAT1	<40	40	80	80	160	80	160	80	160	160	40
A/Soria/220/2022		2a.3a.1	2022-09-26	SIAT3	40	160	160	160	320	320	320	160	320	320	80
A/Bayern/5/2023		2a.3a.1	2023-01-25	P1/SIAT1	40	80	80	80	320	160	320	80	160	160	80
A/Bayern/6/2023		2a.3a.1	2023-01-26	P1/SIAT1	40	80	80	160	320	160	320	80	160	160	80
A/Lisboa/731/2022		2b	2022-12-05	SIAT1	40	160	160	320	160	80	40	40	80	320	<40
A/Lisboa/739/2022		2b	2022-12-06	SIAT1	<40	80	80	80	80	40	80	80	80	160	<40
A/Lisboa/751/2022		2b	2022-12-14	SIAT1	40	80	80	160	80	80	40	40	80	160	<40
A/Baden-Wurttemberg/10/2023		2b	2023-01-26	P1/SIAT1	40	80	160	160	160	80	80	80	160	160	40
A/Baden-Wurttemberg/14/2023		2b	2023-02-10	P1/SIAT1	80	320	160	640	1280	320	320	80	320	640	40
A/Berlin/3/2023		2b	2023-02-14	P1/SIAT1	80	160	160	320	160	160	80	80	160	160	<40
						Vaccine NH 2021-22			Vaccine SH 2022 NH 2022-23 SH 2023 NH 2023-24						

< relates to the lowest dilution of antiserum used
ND = Not Done

Appendix 5: Antigenic analyses of influenza A(H3N2) viruses (Guinea Pig RBC with 20nM Oseltamivir) 2023-01-20, WIC

Viruses	HA1 substitutions additional to those defining subclades of 3C.2a1b.2a	Passage history Ferret number Genetic group	Collection date	Passage history	Haemagglutination inhibition titre Post-infection ferret antisera A/Camb 925256/20 SIAT F03/21 3C.2a1b.2a.1	A/Camb e0826360/20 Egg F10/21 3C.2a1b.2a.1	A/Thuringen 10/22 SIAT F36/22 3C.2a1b.2a.2	A/Stockholm 5/21 SIAT F35/21 3C.2a1b.2a.2	A/Darwin 9/21 Egg F39/21 3C.2a1b.2a.2	A/Norway 24873/21 SIAT F10/22 3C.2a1b.2a.2	A/Norway 24873/21 Egg F11/22 3C.2a1b.2a.2	A/Poland 97/22 SIAT F39/22 3C.2a1b.2a.2	A/Slov 8720/2022 SIAT F24/22 3C.2a1b.2a.2	A/Catal NSVH-2067/22 SIAT F41/22 3C.2a1b.2a.2
REFERENCE VIRUSES														
A/Cambodia/925256/2020		1a	2020-09-25	SIAT5	1280	160	40	320	640	<40	80	80	<40	<40
A/Cambodia/e0826360/2020		1a	2020-07-16	E5/E3	160	1280	80	160	320	40	80	40	160	<40
A/Thuringen/10/2022	S262N	2b	2022-04-01	P1/SIAT2	80	320	320	640	320	160	160	160	320	80
A/Stockholm/5/2021		2a	2021-04-16	SIAT0/SIAT3	80	160	80	640	640	160	320	320	640	160
A/Darwin/9/2021	D186N, D225G (egg)	2a	2021-04-17	E3/E4	80	640	160	640	1280	160	320	320	640	160
A/Norway/24873/2021		2a.3	2021-10-24	SIAT3	80	80	80	320	640	320	320	160	320	160
A/Norway/24873/2021	D225G (egg)	2a.3	2021-10-24	E3/E1	80	320	160	640	640	320	1280	320	640	160
A/Poland/97/2022	P3S, I25V, S145N, R201K	2a.2	2022-05-09	SIAT2	80	160	80	640	640	320	320	640	1280	320
A/Slovenia/8720/2022		2a.1	2022-02-10	SIAT1/MDCK1/SIAT2	80	160	160	640	640	160	320	640	1280	640
A/Catalonia/NSVH161512067/2022		2a.1b	2022-09-14	SIAT1/SIAT3	40	160	80	640	640	80	320	320	640	320
TEST VIRUSES														
A/Dakar/27/2022		3C.2a1b.2a.2	2022-06-28	P1/SIAT1	40	160	160	320	640	160	640	160	320	160
A/Argentina/3155/2022		3C.2a1b.2a.2	2022-08-31	SIAT2	40	160	80	160	320	160	320	160	160	80
A/Argentina/3151/2022		2b	2022-09-05	SIAT1	80	320	320	320	320	160	160	160	320	80
A/Switzerland/24157/2022		2b	2022-12-23	SIAT3/SIAT1	80	160	320	320	320	80	160	80	320	40
A/Switzerland/18284/2022	R33Q, S262N	2b	2022-10-06	SIAT2/SIAT1	80	80	160	160	160	80	80	80	160	40
A/Burgos/257/2022	R33Q, S262N	2b	2022-10-13	SIAT1	80	160	160	160	160	80	80	80	160	40
A/Soria/213/2022	R33Q, S262N	2b	2022-10-13	SIAT1	80	160	320	320	320	80	160	160	320	40
A/Salamanca/198/2022	R33Q, S262N	2b	2022-10-13	SIAT1	80	160	320	320	320	80	160	80	320	80
A/Salamanca/196/2022	R33Q, S262N	2b	2022-10-13	SIAT1	80	160	320	320	320	80	320	80	320	80
A/Switzerland/18694/2022	R33Q, S262N	2b	2022-11-18	MDCK1/SIAT1	80	160	320	320	320	80	160	80	320	40
A/Palencia/118/2022	R33Q, N94S, S262N	2b	2022-10-13	SIAT1	80	160	320	320	320	80	160	80	320	40
A/Switzerland/39985/2022	R33Q, N81D, A163X, S262N	2b	2022-11-21	MDCK1/SIAT1	80	80	320	320	320	80	80	80	320	40
A/Switzerland/07426/2022	T135A(-cho), S262N	2b	2022-11-17	SIAT1/SIAT1	80	160	320	320	320	80	80	80	160	40
A/Ireland/73304/2022	T135A(-cho), S262N	2b	2022-11-23	SIAT1	80	160	320	320	320	80	160	80	160	40
A/Ireland/74535/2022	T128A(-cho), T135A(-cho), S262N	2b	2022-11-28	SIAT2	80	160	160	160	160	80	80	80	160	40
A/Lithuania/48774/2022		2a.1	2022-11-24	SIAT1	40	40	80	320	640	160	160	320	640	320
A/Burgos/82/2022	T135A(-cho), T167S	2a.1	2022-10-13	SIAT1	40	160	40	320	320	80	80	320	640	320
A/Hong Kong/34/2022	N45S(-cho), K276	2a.1	2022-11-26	MDCK1/SIAT1	80	80	80	640	640	160	320	640	640	320
A/Switzerland/54601/2022		2a.1b	2022-11-01	MDCK1/SIAT1	<40	40	40	160	160	40	80	160	320	80
A/Ireland/74250/2022		2a.1b	2022-11-27	SIAT2	40	80	80	320	320	80	160	320	640	320
A/Ireland/74511/2022		2a.1b	2022-11-29	SIAT2	40	80	80	320	320	80	160	320	640	320
A/Switzerland/76550/2022		2a.1b	2022-12-05	SIAT1/SIAT1	40	40	80	320	320	80	160	320	640	160
A/Switzerland/01284/2022		2a.1b	2022-12-05	SIAT1/SIAT1	40	80	80	640	640	160	320	320	1280	320
A/Switzerland/89053/2022		2a.1b	2022-12-06	SIAT1/SIAT1	40	80	80	320	320	80	160	320	640	320
A/Switzerland/12082/2022	R92K	2a.1b	2022-12-08	SIAT1/SIAT1	<40	40	80	160	320	40	80	160	320	160
A/Georgia/2369/2022	N290T	2a.1b	2022-11-24	SIAT1	40	160	80	320	640	80	160	320	640	320
A/Georgia/8/2022	N290T	2a.1b	not known	SIAT1	40	160	80	640	640	160	320	640	640	320
A/Georgia/4/2022	N290T	2a.1b	not known	SIAT1	40	80	160	640	640	80	320	640	1280	320
A/Argentina/3486/2022	N94K, I223	2a.3a	2022-10-01	SIAT1	80	80	80	320	640	320	640	160	320	160
A/Argentina/3498/2022	T135K(-cho), S145N, I223	2a.3a	2022-09-29	SIAT1	40	160	80	160	320	320	320	160	320	160
A/Argentina/3485/2022	T135K(-cho), S145N, I223	2a.3a	2022-10-01	SIAT1	40	160	80	160	320	160	320	160	160	80
A/Hong Kong/17/2022		2a.3	2022-10-24	MDCK1/SIAT1	40	80	80	80	160	80	160	80	80	80
A/Hong Kong/19/2022	L15I	2a.3a.1	2022-11-09	MDCK1/SIAT1	80	80	160	640	640	320	640	160	640	160
A/Hong Kong/22/2022	L15I	2a.3a.1	2022-11-13	MDCK1/SIAT1	80	160	160	640	640	320	640	320	640	160
A/Hong Kong/24/2022	L15I	2a.3a.1	2022-11-15	MDCK1/SIAT1	80	320	320	320	1280	640	1280	320	640	320
A/Hong Kong/28/2022	L15I	2a.3a.1	2022-11-16	MDCK1/SIAT1	80	160	160	320	640	320	640	160	320	80
A/Hong Kong/30/2022	L15I	2a.3a.1	2022-11-20	MDCK1/SIAT1	40	80	160	160	320	160	320	80	160	80
A/Hong Kong/38/2022	L15I	2a.3a.1	2022-12-04	MDCK1/SIAT1	80	80	160	320	320	320	640	160	320	80
A/Hong Kong/26/2022	L15I, R222X	2a.3a.1	2022-11-16	MDCK1/SIAT1	80	160	160	320	640	320	640	160	320	160
A/Switzerland/52849/2022	N91	2a.3a.1	2022-11-11	SIAT1/SIAT1	40	80	80	160	320	160	320	160	160	80
A/Switzerland/86247/2022	N91	2a.3a.1	2022-11-14	MDCK1/SIAT1	40	80	160	320	320	160	320	80	160	80
A/Switzerland/85876/2022	N91, V182X	2a.3a.1	2022-11-14	MDCK1/SIAT1	40	80	80	160	320	160	320	160	320	80
A/Hong Kong/32/2022		2a.3a.1	2022-11-25	MDCK1/SIAT1	40	80	160	320	320	160	320	160	320	80
A/Hong Kong/15/2022		2a.3b	2022-10-04	MDCK1/SIAT1	40	80	80	160	320	160	160	160	160	80

< relates to the lowest dilution of antiserum used
ND = Not Done

Vaccine NH 2021-22

Vaccine SH 2022 NH 2022-23 SH 2023

< 4-fold | 4-fold | 8-fold | > 8-fold | < not recognised by the antiserum | ≥ 160 (when homologous titre ≥ 2560) | ≥ 160 (no homologous titre)

Appendix 6: Antigenic analyses of influenza A(H3N2) viruses (Guinea Pig RBC with 20nM Oseltamivir) 2023-01-27, WIC

Viruses	HA1 substitutions additional to those defining subclades of 3C.2a1b.2a	Passage history Ferret number Genetic group	Collection date	Passage history	Haemagglutination inhibition titre Post-infection ferret antisera A/Camb 925256/20 SIAT F03/21 1a	A/Camb e0826360/20 Egg F10/21 1a	A/Thuringen 10/22 SIAT F36/22 2b	A/Stock 5/21 SIAT F35/21 2a	A/Darwin 9/21 Egg F39/21 2a	A/Norway 24873/21 SIAT F10/22 2a.3	A/Norway 24873/21 Egg F11/22 2a.3	A/Poland 97/22 SIAT F39/22 2a.2	A/Slov 8720/2022 SIAT F24/22 2a.1	A/Catal NSVH-2067/22 SIAT F41/22 2a.1b
REFERENCE VIRUSES														
A/Cambodia/925256/2020		1a	2020-09-25	SIAT5	640	160	<40	160	320	40	40	80	<40	<40
A/Cambodia/e0826360/2020		1a	2020-07-16	E5/E3	80	640	80	160	160	40	80	40	160	<40
A/Thuringen/10/2022	S262N	2b	2022-04-01	P1/SIAT2	80	160	320	320	320	80	160	80	320	40
A/Stockholm/5/2021		2a	2021-04-16	SIAT0/SIAT3	80	80	80	640	640	160	160	320	640	80
A/Darwin/9/2021	D186N, D225G (egg)	2a	2021-04-17	E3/E4	160	640	160	640	1280	160	320	640	1280	160
A/Norway/24873/2021		2a.3	2021-10-24	SIAT3	40	80	80	320	320	320	320	160	160	80
A/Norway/24873/2021	D225G (egg)	2a.3	2021-10-24	E3/E1	80	320	160	320	640	320	640	320	640	160
A/Poland/97/2022	P3S, I25V, S145N, R201K	2a.2	2022-05-09	SIAT2	40	80	80	320	640	160	320	640	640	320
A/Slovenia/8720/2022		2a.1	2022-02-10	SIAT1/MDCK1/SIAT2	80	80	160	640	640	160	320	640	1280	640
A/Catalonia/NSVH161512067/2022		2a.1b	2022-09-14	SIAT1/SIAT3	40	80	80	640	320	80	160	320	640	320
TEST VIRUSES														
A/Croatia/101024/2022	I242M	2b	2022-09-01	MDCKx/SIAT1	80	80	320	320	160	80	160	80	160	40
A/Norway/32641/2022	I224M	2b	2022-10-17	SIAT1	40	80	320	320	160	80	80	80	160	40
A/Castilla La Mancha/4112/2022	R33Q, S262N	2b	2022-10-15	SIAT1	80	160	320	320	320	40	80	80	160	40
A/Castilla La Mancha/4057/2022	R33Q, S262N	2b	2022-10-17	SIAT1	80	80	320	160	160	40	80	40	160	40
A/Castilla La Mancha/4107/2022	R33Q, S262N	2b	2022-10-17	SIAT2	40	80	320	160	160	40	80	80	160	40
A/Norway/33623/2022	R33Q, S262N	2b	2022-10-31	SIAT1	80	160	320	320	320	80	160	80	320	40
A/Norway/33536/2022	R33Q, S262N	2b	2022-11-01	SIAT1	40	80	160	160	160	40	80	40	160	<40
A/Castilla La Mancha/4542/2022	R33Q, S262N	2b	2022-11-24	SIAT1	40	80	160	160	160	80	40	40	80	<40
A/Castilla La Mancha/4541/2022	R33Q, S262N	2b	2022-11-24	SIAT1	40	80	160	160	160	80	80	80	160	40
A/Castilla La Mancha/4547/2022	R33Q, S262N	2b	2022-11-26	SIAT1	80	160	320	320	160	80	80	80	160	40
A/Switzerland/68410/2022	R33Q, S262N	2b	2022-12-13	SIAT1	40	80	160	160	160	40	80	40	160	40
A/Switzerland/56875/2022	R33Q, S262N	2b	2022-12-13	SIAT1	40	80	160	160	160	80	80	80	160	40
A/Switzerland/68971/2022	R33Q, N96K, S262N	2b	2022-12-13	SIAT1	40	160	160	160	160	80	80	80	160	40
A/Galicia/3991/2022	R33Q, S199P, S262N	2b	2022-10-16	SIAT1	40	80	160	160	160	40	80	40	160	<40
A/Hungary/73/2022	R33Q, S262N, A272T	2b	2022-11-28	MDCK1/SIAT1	80	80	160	160	160	80	80	40	160	40
A/Hungary/87/2022	R33Q, E41X, D101E, S262N, D291N	2b	2022-12-07	MDCK1/SIAT1	40	80	160	160	160	80	80	40	160	40
A/Switzerland/12279/2022	T135A(-cho), S262N	2b	2022-12-09	SIAT1	80	160	160	160	160	80	160	80	160	40
A/Switzerland/28719/2022	T135A(-cho), S262N	2b	2022-12-19	SIAT1	80	160	320	160	160	80	160	80	160	40
A/Switzerland/68854/2022	T135A(-cho), S262N	2b	2022-12-23	SIAT1	40	80	160	160	160	80	80	40	80	40
A/Slovenia/11512/2022	T135A(-cho), S144N(+cho), S262N	2b	2022-12-19	MDCKx/SIAT1	40	160	160	160	160	80	80	80	160	40
A/Slovenia/11696/2022	T135A(-cho), S144N(+cho), S262N	2b	2022-12-29	SIATx/SIAT1	40	160	160	320	160	80	80	80	160	<40
A/Slovenia/11516/2022	T10K(-cho), T135A(-cho), S262N	2b	2022-12-19	SIATx/SIAT1	40	160	160	160	160	80	80	80	160	<40
A/Slovenia/11514/2022	T10K(-cho), T135A(-cho), S262N	2b	2022-12-19	SIATx/SIAT1	80	160	160	320	160	80	160	80	160	40
A/Slovenia/11622/2022	T10K(-cho), T135A(-cho), S262N	2b	2022-12-27	MDCKx/SIAT1	40	80	160	160	160	80	80	40	160	<40
A/Slovenia/11517/2022	T10K(-cho), V79I, T135A(-cho), S262N	2b	2022-12-20	MDCKx/SIAT1	80	160	160	160	160	80	80	80	160	40
A/Slovenia/42/2023	T10K(-cho), V79I, T135A(-cho), S262N	2b	2023-01-03	MDCKx/SIAT1	80	160	160	320	320	80	160	80	80	<40
A/Slovenia/11665/2022	T10K(-cho), V79I, T135A(-cho), Q210*, S262N	2b	2022-12-28	SIATx/SIAT1	160	320	320	640	320	80	160	80	320	40

< relates to the lowest dilution of antiserum used
ND = Not Done

Vaccine
NH 2021-22

Vaccine
SH 2022
NH 2022-23
SH 2023

Appendix 7: Antigenic analyses of influenza A(H1N1)pdm09 viruses 2023-01-24, WIC

Viruses	Other information	Passage history	Collection date	Passage history	Haemagglutination inhibition titre: Post-infection ferret antisera									
					A/G-M SWL1536/19 MDCK	A/G-M SWL1536/19 Egg	A/Ghana 1894/21 Egg	A/Lyon 820/21 Egg	A/Denmark 3280/19 MDCK	IVR-215 A/Vic/2570/19 Egg	A/Sydney 5/21 MDCK	A/Sydney 5/21 Egg	A/Norway 25089/22 MDCK	A/Norway/ 31694/2022 Egg
		Ferret number			F09/20	F12/20	F02/22	F06/22	F28/20	F37/21	F46/22	F04/22	F38/22	F48/22
		Genetic group			5a.1	5a.1	5a.1	5a.1	5a.2	5a.2	5a.2a	5a.2a	5a.2a.1	5a.2a.1
REFERENCE VIRUSES														
A/Guangdong-Maonan/SWL1536/2019		5a.1	2019-06-17	C2/MDCK1	2560	2560	1280	320	40	40	<40	40	<40	<40
A/Guangdong-Maonan/SWL1536/2019		5a.1	2019-06-17	E3/E2	1280	1280	640	320	<40	80	<40	40	<40	<40
A/Ghana/1894/2021		5a.1	2021-07-21	E2/E1	1280	2560	1280	320	40	80	40	40	<40	<40
A/Lyon/820/2021		5a.1	2021-11-16	E1/E2	320	320	160	320	40	40	40	40	<40	<40
A/Denmark/3280/2019	K130N, N156K, L161I, V250A, E189Q	5a.2	2019-11-10	MDCK4/MDCK5	160	40	<40	40	2560	2560	1280	2560	1280	320
IVR-215 (A/Victoria/2570/2019)	K130N, N156K, L161I, V250A, E189Q (A195E, Q223R)	5a.2	2018-11-22	E4/D7/E2	80	80	40	80	640	1280	640	640	320	320
A/Sydney/5/2021 clone 3.4.1	K54Q, A186T, E224A, R259K, K308R, D94N, T216A	5a.2a	2021-10-16	MDCK3/MDCK3	40	40	40	40	1280	2560	2560	2560	1280	640
A/Sydney/5/2021 pooled clones 10-10	K54Q, A186T, E224A, R259K, K308R, D94N, T216A (Q223R)	5a.2a	2022-10-31	E3/E2	80	40	40	40	640	1280	1280	1280	640	320
A/Norway/25089/2022	P137S, K142R, D260E, T277A	5a.2a.1	2022-06-15	MDCK3	<40	<40	<40	<40	320	640	640	640	640	320
A/Norway/31694/2022	P137S, K142R, D260E, T277A (Q223R)	5a.2a.1	2022-09-24	E3/E1 10-3	<40	40	<40	<40	320	640	320	320	320	640
TEST VIRUSES														
A/Switzerland/95480/2022		5a.2a	2022-10-13	MDCK1/MDCK1	<40	40	<40	<40	320	640	640	1280	640	320
A/Switzerland/74729/2022		5a.2a	2022-11-23	MDCK1/MDCK1	40	40	<40	40	640	640	640	1280	320	160
A/Switzerland/74639/2022		5a.2a	2022-11-24	MDCK1/MDCK1	40	40	<40	40	640	640	640	640	640	320
A/Switzerland/68182/2022		5a.2a	2022-12-13	MDCK1	40	40	<40	40	1280	1280	1280	1280	1280	320
A/Switzerland/28759/2022		5a.2a	2022-12-19	MDCK1	40	40	<40	40	320	640	640	640	640	320
A/Switzerland/28275/2022		5a.2a	2022-12-19	MDCK1	40	40	<40	<40	320	640	640	640	320	160
A/Switzerland/28469/2022		5a.2a	2022-12-20	MDCK1	<40	40	<40	<40	320	640	640	640	320	160
A/Switzerland/75200/2022		5a.2a	2022-12-23	MDCK1	40	40	<40	40	640	1280	1280	1280	1280	320
A/Ukraine/465/2022		5a.2a.1	2022-11-11	MDCK1	<40	<40	<40	<40	640	640	640	640	640	640
A/Ukraine/464/2022		5a.2a.1	2022-11-14	MDCK1	<40	<40	<40	<40	320	640	320	640	640	320
A/Switzerland/86105/2022		5a.2a.1	2022-11-15	MDCK1/MDCK1	<40	40	<40	40	640	640	640	640	1280	640
A/Hungary/70/2022		5a.2a.1	2022-11-21	MDCK1/MDCK1	<40	<40	<40	<40	320	320	320	320	320	320
A/Hungary/71/2022		5a.2a.1	2022-11-29	MDCK1/MDCK1	<40	<40	<40	<40	320	640	640	640	640	320
A/Ukraine/668/2022		5a.2a.1	2022-12-06	MDCK1	<40	40	<40	<40	640	1280	640	640	1280	640
A/Hungary/86/2022		5a.2a.1	2022-12-07	MDCK1/MDCK1	<40	<40	<40	<40	320	320	320	320	320	160
A/Ukraine/667/2022		5a.2a.1	2022-12-11	MDCK1	<40	<40	<40	<40	320	320	320	320	640	320
A/Ukraine/661/2022		5a.2a.1	2022-12-14	MDCK1	<40	40	<40	<40	640	640	640	640	1280	320
A/Switzerland/69094/2022		5a.2a.1	2022-12-14	MDCK1	<40	<40	<40	<40	320	640	640	320	640	320
A/Ukraine/777/2022		5a.2a.1	2022-12-17	MDCK1	<40	40	<40	<40	320	640	320	640	640	320
A/Ukraine/799/2022		5a.2a.1	2022-12-26	MDCK1	<40	<40	<40	<40	320	640	320	640	640	320

< relates to the lowest dilution of antiserum used

ND = Not Done

Vaccine NH 2020-21

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

Vaccine SH 2023

< 4-fold | 4-fold | 8-fold | > 8-fold | < not recognised by the antiserum | ≥ 160 (when homologous titre ≥ 2560) | ≥ 160 (no homologous titre)

Appendix 8: Antigenic analyses of influenza A(H1N1)pdm09 viruses 2023-01-31, WIC

Viruses	Other information	Passage history	Collection date	Passage history	Haemagglutination inhibition titre									
					Post-infection ferret antisera									
					A/G-M SWL1536/19 MDCK	A/G-M SWL1536/19 Egg	A/Ghana 1894/21 Egg	A/Lyon 820/21 Egg	A/Denmark 3280/19 MDCK	IVR-215 A/Vic/2570/19 Egg	A/Sydney 5/21 MDCK	A/Sydney 5/21 Egg	A/Norway 25089/22 MDCK	A/Norway/ 31694/2022 Egg
		Ferret number			F09/20	F12/20	F02/22	F06/22	F28/20	F37/21	F46/22	F04/22	F38/22	F48/22
		Genetic group			5a.1	5a.1	5a.1	5a.1	5a.2	5a.2	5a.2a	5a.2a	5a.2a.1	5a.2a.1
REFERENCE VIRUSES														
A/Guangdong-Maonan/SWL1536/2019		5a.1	2019-06-17	C2/MDCK1	1280	1280	1280	320	40	40	40	40	40	<40
A/Guangdong-Maonan/SWL1536/2019		5a.1	2019-06-17	E3/E2	1280	2560	1280	320	40	80	40	40	<40	<40
A/Ghana/1894/2021		5a.1	2021-07-21	E2/E1	2560	2560	1280	320	40	80	40	80	40	<40
A/Lyon/820/2021		5a.1	2021-11-16	E1/E2	640	320	320	640	40	80	40	80	40	<40
A/Denmark/3280/2019	K130N, N156K, L161I, V250A, E189Q	5a.2	2019-11-10	MDCK4/MDCK5	80	40	40	80	2560	2560	1280	2560	1280	320
IVR-215 (A/Victoria/2570/2019)	K130N, N156K, L161I, V250A, E189Q (A195E, Q223R)	5a.2	2018-11-22	E4/D7/E2	160	160	80	80	640	1280	640	1280	640	320
A/Sydney/5/2021 clone 3.4.1	K54Q, A186T, E224A, R259K, K308R, D94N, T216A	5a.2a	2021-10-16	MDCK3/MDCK3	80	80	40	80	1280	2560	2560	2560	1280	640
A/Sydney/5/2021 pooled clones 10-10	K54Q, A186T, E224A, R259K, K308R, D94N, T216A (Q223R)	5a.2a	2022-10-31	E3/E2	160	80	40	80	1280	1280	1280	2560	1280	320
A/Norway/25089/2022	P137S, K142R, D260E, T277A	5a.2a.1	2022-06-15	MDCK3	40	40	<40	40	640	1280	1280	1280	1280	640
A/Norway/31694/2022	P137S, K142R, D260E, T277A (Q223R)	5a.2a.1	2022-09-24	E3/E1 10^{-3}	40	40	<40	40	640	640	640	320	640	640
TEST VIRUSES														
A/Croatia/114180/2022		5a.2a	2022-10-22	MDCKx/MDCK1	80	80	40	40	1280	2560	1280	2560	1280	640
A/Norway/33620/2022		5a.2a	2022-10-31	MDCK1	80	80	40	80	1280	2560	2560	2560	2560	640
A/Norway/33584/2022		5a.2a	2022-11-07	MDCK1	40	80	40	40	1280	1280	1280	1280	1280	320
A/Norway/33744/2022		5a.2a	2022-11-09	MDCK1	80	80	40	80	1280	2560	2560	1280	1280	640
A/Belgium/G0292/2022		5a.2a	2022-11-21	C1/MDCK1	80	80	40	40	1280	1280	1280	2560	1280	640
A/Croatia/118556/2022		5a.2a	2022-11-22	MDCKx/MDCK1	80	80	40	40	1280	2560	2560	2560	1280	640
A/Croatia/118699/2022		5a.2a	2022-11-23	MDCKx/MDCK1	40	40	<40	<40	640	640	640	640	640	320
A/Belgium/G0302/2022		5a.2a	2022-11-25	C1/MDCK1	80	80	40	40	1280	2560	1280	1280	1280	640
A/Belgium/S2496/2022		5a.2a	2022-11-28	C1/MDCK1	160	80	40	80	1280	2560	2560	2560	1280	640
A/Belgium/S2710/2022		5a.2a	2022-12-01	C1/MDCK1	40	40	<40	40	640	1280	1280	640	640	320
A/Switzerland/32650/2022		5a.2a	2022-12-09	MDCK2	<40	40	<40	<40	640	640	320	640	640	160
A/Belgium/S2691/2022		5a.2a	2022-12-11	C1/MDCK1	40	40	<40	40	1280	1280	1280	1280	1280	320
A/Catalonia/NSVH101922705/2022		5a.2a.1	2022-10-02	SIAT1/MDCK1	80	40	40	40	1280	2560	1280	2560	2560	2560
A/Catalonia/NSVH171764113/2022		5a.2a.1	2022-10-04	SIAT1/MDCK1	40	40	<40	<40	1280	1280	1280	2560	1280	1280
A/Catalonia/NSVH151195412/2022		5a.2a.1	2022-10-18	SIAT1/MDCK1	<40	<40	<40	<40	640	1280	640	1280	1280	640
A/Croatia/115187/2022		5a.2a.1	2022-10-27	MDCKx/MDCK2	40	40	<40	<40	640	1280	640	640	1280	640
A/Norway/33370/2022		5a.2a.1	2022-10-28	MDCK1	40	80	<40	40	1280	2560	1280	1280	1280	1280
A/Norway/33307/2022		5a.2a.1	2022-11-02	MDCK1	40	80	<40	40	1280	1280	640	1280	1280	640
A/Norway/33583/2022		5a.2a.1	2022-11-07	MDCK1	40	40	<40	80	640	1280	640	1280	1280	640
A/Norway/33662/2022		5a.2a.1	2022-11-09	MDCK1	40	40	<40	40	1280	1280	640	640	1280	640
A/Norway/33760/2022		5a.2a.1	2022-11-11	MDCK1	40	40	<40	40	640	640	640	320	1280	640
A/Croatia/118701/2022		5a.2a.1	2022-11-21	MDCKx/MDCK2	40	40	<40	<40	1280	1280	1280	1280	1280	1280
A/Switzerland/32713/2022		5a.2a.1	2022-12-09	MDCK2	40	160	<40	40	1280	2560	1280	1280	1280	1280

< relates to the lowest dilution of antiserum used

ND = Not Done

Vaccine NH 2020-21

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

Vaccine SH 2023

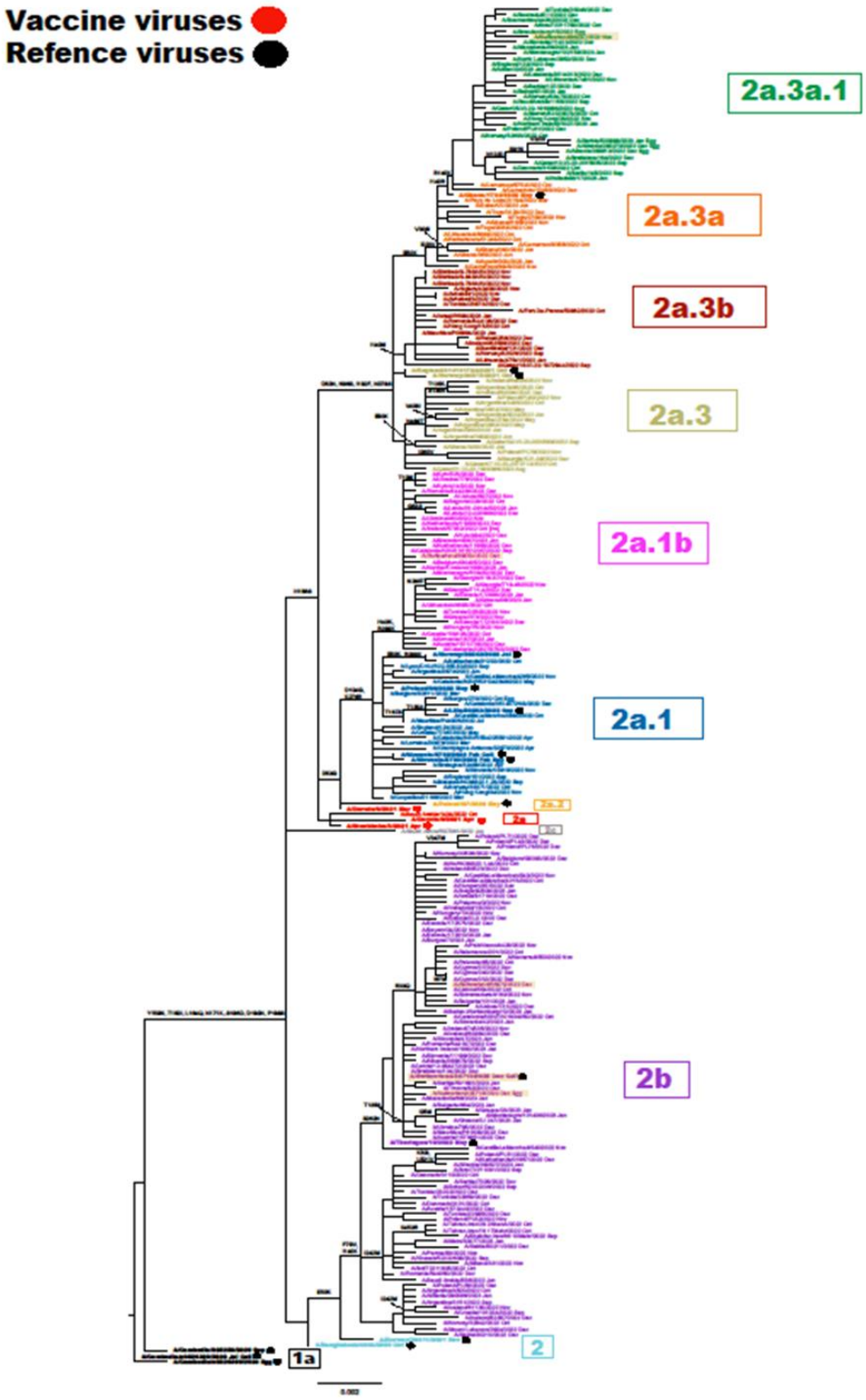
Appendix 9: Antigenic analyses of influenza B viruses (Victoria lineage) 2023-01-24, WIC

Viruses	Other information		Collection date	Passage history	Haemagglutination inhibition titre: Post-infection ferret antiserum								
		Passage history			B/Bris 60/08 Egg	B/Colorado 06/17 Egg	B/Wash'ton 02/19 Egg	B/Neth 11267/22 MDCK	B/Neth 10894/22 Egg	B/Austria 1359417/21 MDCK	B/Austria 1359417/21 Egg G141	B/Austria 1359417/21 Egg G141R	B/Stock 3/22 MDCK
		Ferret number			Sh 539, 540, 543, 544, 570, 571, 574[1]	F44/18	F20/20	F29/22	F37/22	NIB F01/21	F15/21	F44/21	F28/22
		Genetic group			V1A	V1A.1	V1A.3	V1A.3	V1A.3	V1A.3a.2	V1A.3a.2	V1A.3a.2	V1A.3a.2
REFERENCE VIRUSES													
B/Brisbane/60/2008		V1A	2008-08-04	E4/E4	2560	320	80	<10	160	<40	<40	<40	<40
B/Colorado/06/2017		V1A.1	2017-02-05	E5/E2	1280	320	80	<10	160	40	<40	<40	<40
B/Washington/02/2019		V1A.3	2019-01-19	E3/E3	320	160	160	20	80	<40	<40	<40	<40
B/Netherlands/11267/2022	G184R	V1A.3	2022-04-14	MDCK-MIX/MDCK2	<40	10	<10	160	40	<40	<40	<40	<40
B/Netherlands/10894/2022	G184R, T199A (-cho), V318I	V1A.3	2022-04-02	E4(Am1AL3)	320	80	20	40	160	<40	<40	<40	<40
B/Austria/1359417/2021	A127T, P144L, K302R (G141)	V1A.3a.2	2021-01-09	SIAT1/MDCK4	320	40	<10	20	<10	1280	1280	320	640
B/Austria/1359417/2021 Isolate 2	A127T, P144L, K302R (G141)	V1A.3a.2	2021-01-09	E3/E5	640	20	<10	40	10	2560	1280	640	640
B/Austria/1359417/2021 Isolate 2	A127T, P144L, K302R (G141R)	V1A.3a.2	2021-01-09	E3/E5	320	40	<10	40	10	2560	1280	>5120	640
B/Stockholm/3/2022	D197E, D129G, E183K	V1A.3a.2	2022-03-22	SIAT1/MDCK2	320	40	<10	20	<10	1280	640	320	640
TEST VIRUSES													
B/Bishkek/013/2022		V1A.3a.2	2022-10-08	MDCK1/MDCK1	640	40	<10	20	<10	1280	640	320	640
B/Bishkek/014/2022		V1A.3a.2	2022-10-14	MDCK1/MDCK1	640	40	<10	20	<10	1280	1280	320	1280
B/Bishkek/015/2022		V1A.3a.2	2022-10-22	MDCK1/MDCK1	640	40	<10	20	<10	1280	1280	320	640
B/Bishkek/016/2022		V1A.3a.2	2022-10-23	MDCK1/MDCK1	640	40	<10	20	<10	2560	1280	640	640
B/Hungary/72/2022		V1A.3a.2	2022-11-22	MDCK1/MDCK1	320	40	<10	40	<10	1280	1280	640	640
B/Switzerland/19297/2022		V1A.3a.2	2022-11-28	MDCK1	640	80	<10	20	<10	1280	1280	320	640
B/Switzerland/12216/2022		V1A.3a.2	2022-12-09	MDCK1/MDCK1	640	80	<10	20	<10	1280	1280	320	640
B/Switzerland/69064/2022		V1A.3a.2	2022-12-13	MDCK1	640	80	<10	20	<10	1280	1280	320	640
B/Switzerland/28512/2022		V1A.3a.2	2022-12-19	MDCK1	640	80	<10	20	<10	1280	1280	640	640
							Vaccine NH 2021-22				Vaccine SH 2022 NH 2022-23 SH 2023		

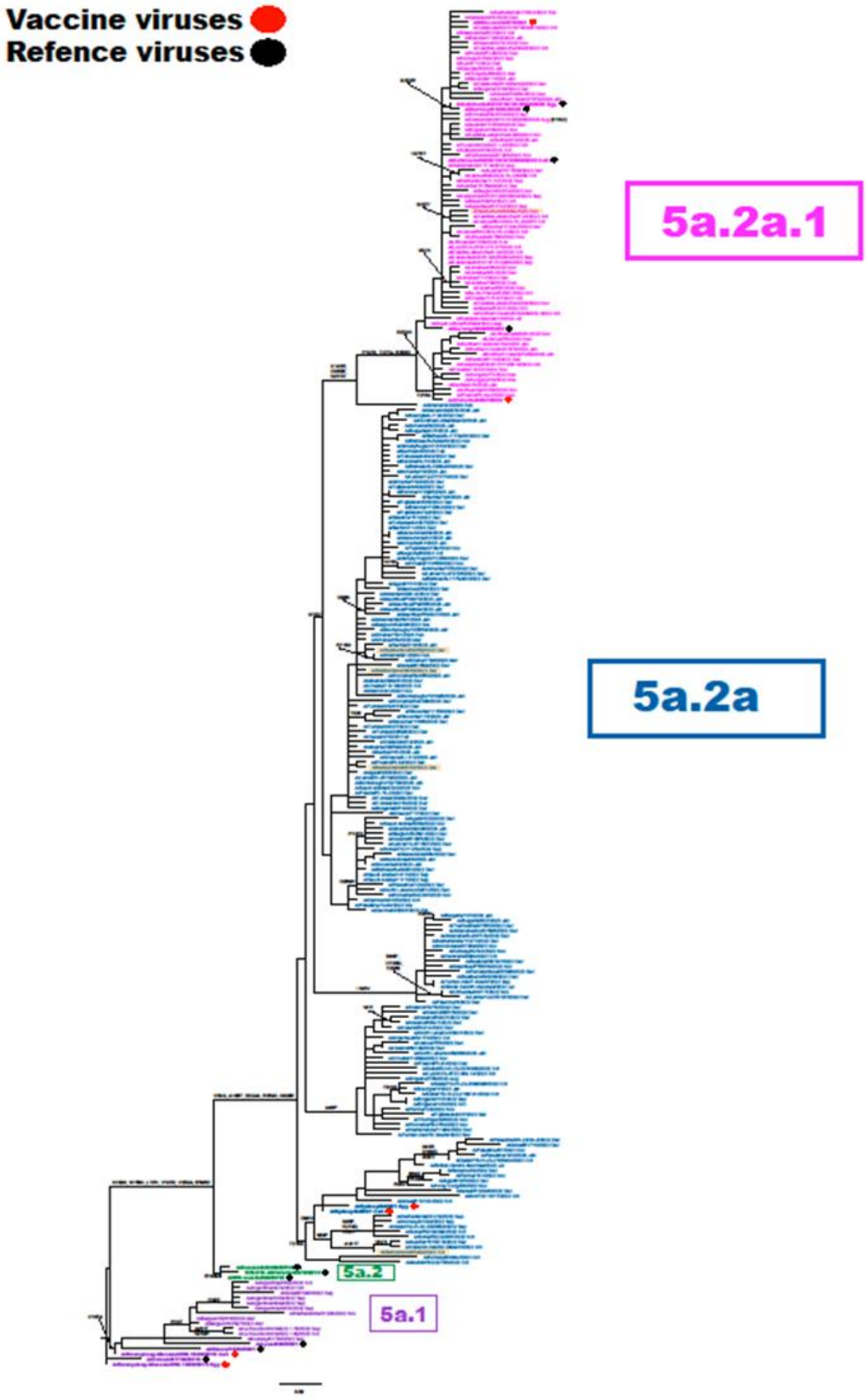
< relates to the lowest dilution of antiserum used

[1] hyperimmune sheep serum; ND = Not Done

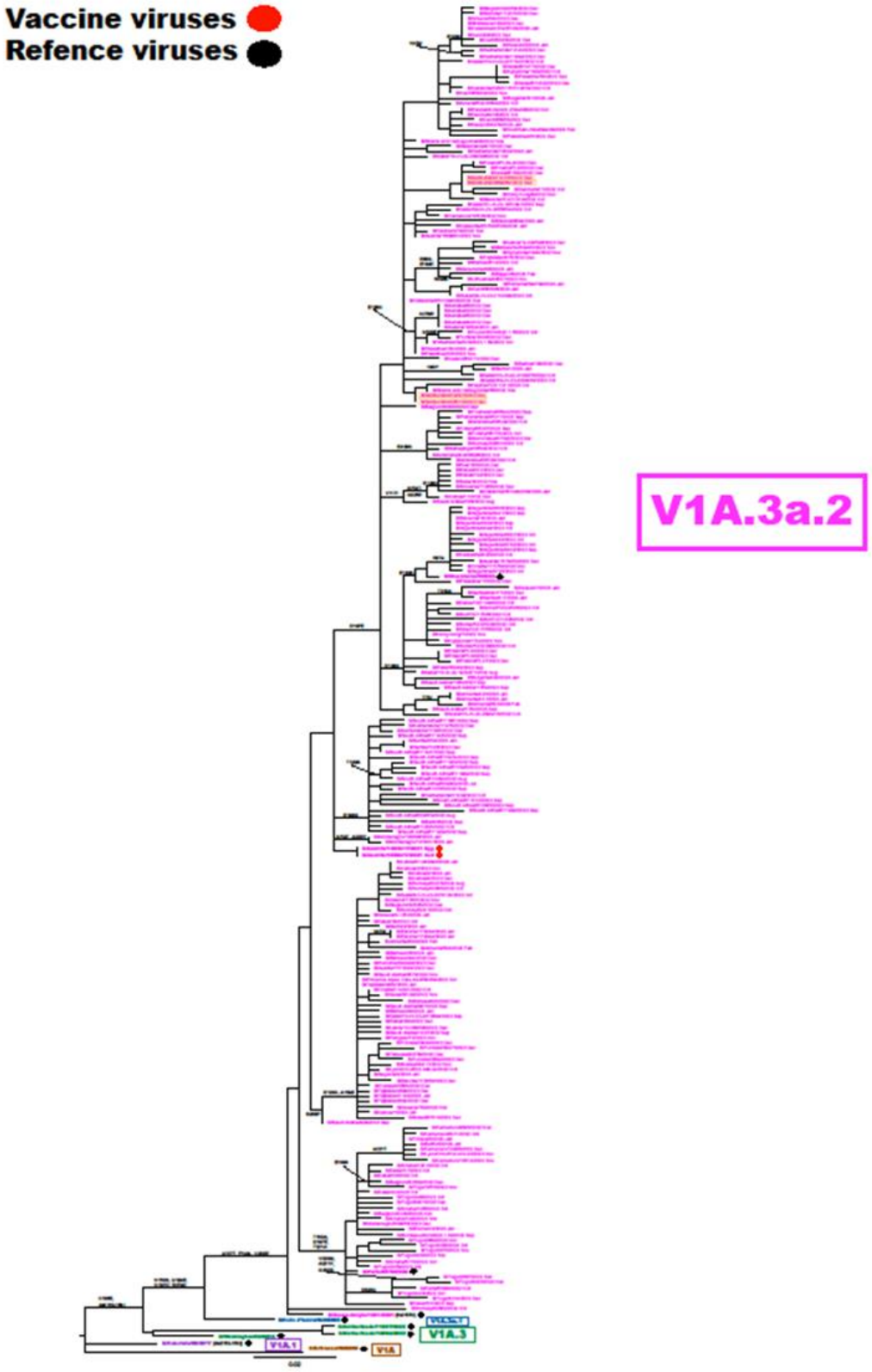
Appendix 10: Phylogenetic analysis of influenza A(H3N2), HA gene sequence, WIC



Appendix 11: Phylogenetic analysis of influenza A(H1N1)pdm09, HA gene sequences, WIC



Appendix 12: Phylogenetic analysis of influenza B-Victoria, HA gene sequences, WIC



Appendix 13: List of Influenza isolates submitted to GISAID (2022/2023)

Collection date	Isolate-ID	Isolate name
2022-Oct-06	EPI_ISL_16681929	A/Switzerland/18284/2022
2022-Oct-13	EPI_ISL_16681930	A/Switzerland/95480/2022
2022-Oct-28	EPI_ISL_16681931	A/Switzerland/24156/2022
2022-Nov-11	EPI_ISL_16681932	A/Switzerland/52849/2022
2022-Nov-14	EPI_ISL_16681933	A/Switzerland/85876/2022
2022-Nov-14	EPI_ISL_16681935	A/Switzerland/86247/2022
2022-Nov-15	EPI_ISL_16681934	A/Switzerland/86105/2022
2022-Nov-17	EPI_ISL_16681936	A/Switzerland/07426/2022
2022-Nov-18	EPI_ISL_16681937	A/Switzerland/18694/2022
2022-Nov-22	EPI_ISL_16681938	A/Switzerland/64237/2022
2022-Nov-23	EPI_ISL_16681940	A/Switzerland/74729/2022
2022-Nov-23	EPI_ISL_16681941	A/Switzerland/63991/2022
2022-Nov-24	EPI_ISL_16681939	A/Switzerland/74639/2022
2022-Nov-27	EPI_ISL_16681942	A/Switzerland/07258/2022
2022-Nov-28	EPI_ISL_16681943	A/Switzerland/07346/2022
2022-Nov-30	EPI_ISL_16681944	A/Switzerland/30827/2022
2022-Dec-01	EPI_ISL_16681945	A/Switzerland/42438/2022
2022-Dec-05	EPI_ISL_16681946	A/Switzerland/76550/2022
2022-Dec-05	EPI_ISL_16681948	A/Switzerland/01284/2022
2022-Dec-05	EPI_ISL_16681952	A/Switzerland/76179/2022
2022-Dec-05	EPI_ISL_16681953	A/Switzerland/76352/2022
2022-Dec-05	EPI_ISL_16681955	A/Switzerland/02187/2022
2022-Dec-06	EPI_ISL_16681947	A/Switzerland/89053/2022
2022-Dec-06	EPI_ISL_16681954	A/Switzerland/89582/2022
2022-Dec-07	EPI_ISL_16681956	A/Switzerland/32689/2022
2022-Dec-08	EPI_ISL_16681949	A/Switzerland/12082/2022
2022-Dec-09	EPI_ISL_16681950	A/Switzerland/12279/2022
2022-Dec-09	EPI_ISL_16681951	A/Switzerland/32650/2022
2022-Dec-09	EPI_ISL_16681957	A/Switzerland/45105/2022
2022-Dec-09	EPI_ISL_16681958	A/Switzerland/56875/2022
2022-Dec-09	EPI_ISL_16682006	B/Switzerland/28512/2022
2022-Dec-12	EPI_ISL_16681966	A/Switzerland/45359/2022
2022-Dec-12	EPI_ISL_16681967	A/Switzerland/45513/2022
2022-Dec-13	EPI_ISL_16681959	A/Switzerland/68182/2022
2022-Dec-13	EPI_ISL_16681960	A/Switzerland/68410/2022
2022-Dec-13	EPI_ISL_16681961	A/Switzerland/68546/2022
2022-Dec-13	EPI_ISL_16681962	A/Switzerland/68912/2022
2022-Dec-13	EPI_ISL_16681964	A/Switzerland/69094/2022
2022-Dec-13	EPI_ISL_16681968	A/Switzerland/56761/2022
2022-Dec-13	EPI_ISL_16681969	A/Switzerland/69128/2022

Collection date	Isolate-ID	Isolate name
2022-Dec-13	EPI_ISL_16682007	B/Switzerland/83674/2022
2022-Dec-14	EPI_ISL_16681963	A/Switzerland/68971/2022
2022-Dec-14	EPI_ISL_16681965	A/Switzerland/45307/2022
2022-Dec-14	EPI_ISL_16681970	A/Switzerland/69171/2022
2022-Dec-14	EPI_ISL_16681971	A/Switzerland/80564/2022
2022-Dec-14	EPI_ISL_16681972	A/Switzerland/80698/2022
2022-Dec-14	EPI_ISL_16681973	A/Switzerland/80856/2022
2022-Dec-15	EPI_ISL_16681974	A/Switzerland/81065/2022
2022-Dec-15	EPI_ISL_16681975	A/Switzerland/02426/2022
2022-Dec-15	EPI_ISL_16681976	A/Switzerland/02650/2022
2022-Dec-15	EPI_ISL_16681977	A/Switzerland/02725/2022
2022-Dec-15	EPI_ISL_16681978	A/Switzerland/03330/2022
2022-Dec-15	EPI_ISL_16681979	A/Switzerland/03494/2022
2022-Dec-15	EPI_ISL_16681980	A/Switzerland/28275/2022
2022-Dec-19	EPI_ISL_16681981	A/Switzerland/28394/2022
2022-Dec-19	EPI_ISL_16681982	A/Switzerland/28469/2022
2022-Dec-19	EPI_ISL_16681984	A/Switzerland/28719/2022
2022-Dec-19	EPI_ISL_16681985	A/Switzerland/28759/2022
2022-Dec-19	EPI_ISL_16681986	A/Switzerland/02383/2022
2022-Dec-19	EPI_ISL_16681987	A/Switzerland/16056/2022
2022-Dec-19	EPI_ISL_16681988	A/Switzerland/16443/2022
2022-Dec-19	EPI_ISL_16681989	A/Switzerland/16667/2022
2022-Dec-19	EPI_ISL_16681990	A/Switzerland/27816/2022
2022-Dec-19	EPI_ISL_16681992	A/Switzerland/28039/2022
2022-Dec-19	EPI_ISL_16682008	B/Switzerland/23703/2022
2022-Dec-20	EPI_ISL_16681983	A/Switzerland/28577/2022
2022-Dec-20	EPI_ISL_16681991	A/Switzerland/27921/2022
2022-Dec-20	EPI_ISL_16681994	A/Switzerland/83684/2022
2022-Dec-21	EPI_ISL_16681993	A/Switzerland/49943/2022
2022-Dec-22	EPI_ISL_16681995	A/Switzerland/92032/2022
2022-Dec-27	EPI_ISL_16681996	A/Switzerland/00505/2022
2022-Dec-27	EPI_ISL_16681997	A/Switzerland/00569/2022
2022-Dec-28	EPI_ISL_16682005	B/Switzerland/69064/2022
2022-Dec-29	EPI_ISL_16681998	A/Switzerland/23906/2022
2022-Dec-29	EPI_ISL_16681999	A/Switzerland/34487/2023
2022-Dec-29	EPI_ISL_16682000	A/Switzerland/34560/2023
2023-Jan-02	EPI_ISL_16682002	A/Switzerland/34738/2023
2023-Jan-03	EPI_ISL_16682001	A/Switzerland/34603/2023
2023-Jan-03	EPI_ISL_16682003	B/Switzerland/19297/2022
2023-Jan-03	EPI_ISL_16682004	B/Switzerland/12216/2022

Appendix 14: Map of influenza A and B viruses, 2022-09 to 2023-05, MicroReact

https://microreact.org/