NIPH
Norwegian Institute of Public Health

REPORT

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NORWAY:

Interim Influenza Virological and Epidemiological season report prepared for the WHO Consultation on the Composition of Influenza Virus Vaccines for the Northern Hemisphere 2023/2024

February 2023

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prepared for the WHO Consultation on the Composition of Influenza Virus Vaccines for the Northern Hemisphere 2023/2024,

February 2023

Division of Infection Control

Department of Virology

Section for Influenza and other respiratory viruses

and

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The 2022-2023 influenza season, Norway

Summary

- The preceding 2021-2022-influenza season developed unusually late, only after the distancing measures against COVID-19 were lifted in February, and at a time when the Omicron-variant driven main pandemic wave was on its decline. The influenza outbreak peaked around week 15, was of low-to medium magnitude, and influenza A(H3N2) viruses predominated.
- Seroprevalence against A/Victoria/2570/2019(H1N1) was at a moderate level in sera collected in August 2022. However, there was significantly less antibodies against the A/Norway/25089/2022 strain, which has been a prominent subvariant during the H1 outbreak seen in early winter. Seroprevalence against recent B/Victoria-lineage virus was at a low level, especially in the younger age groups, suggesting a high degree of susceptibility.
- The current season started early with outbreak threshold of 10 % positives in week 48 (sentinel)/week 49 (comprehensive) and had a sharp first peak in weeks 51-52/2022, before falling markedly in the first weeks after New Year, then stabilising at about 15% influenza positivity rate among all tested and about 24% among sentinel specimens for the last few weeks (week 4).
- Influenza A viruses have been in great majority until recently, but the proportion and numbers of influenza B detections are rising steadily and was at 15% in week 4. Among the type A viruses, the majority have been subtype H1, but the proportion of H3 are increasing. All circulating influenza B viruses that have been tested for lineage have belonged to the B/Victoria/2/1987 lineage.
- The age group representing school-age children has had the highest proportion of influenza positives throughout the period and has shown rising numbers earlier than the other age groups. The proportion of influenza-like illness (ILI) consultations in primary health care gradually increased from week 48/2022. After a peak in week 52/2022, the proportion decreased to a low level of intensity in week 2/2023, has continued to decline until week 3/2023, and has levelled off since.
- The numbers of hospitalisations and ICU admissions with influenza began to increase around week 46-2022, reaching a peak in week 52-2022. As of week 4-2023, 3653 hospital admissions and 126 ICU admissions have been reported, clearly exceeding numbers reported for the entire preceding season 2021-2022. The weekly number of influenza-associated deaths peaked during weeks 52-2022 – 2-2023, coinciding with the highest rate of all-cause mortality in Norway since 2017.
- Near 16% of all samples received for surveillance have been whole genome sequenced. Both the H1N1 A/Sydney/5/2021 6B.1A.5a.2 lineage and the A/Norway25089/2022 6B.1A.5a.2.1 with the HA P137S substitution have been circulating, but in the last weeks the A/Sydney-lineage are predominating with several separate clusters . The H3N2 viruses are all categorized as 3C.2a.1b.2a.2 belonging to the A/Slovenia/8720/2022 group of viruses with the R299K substitution. All influenza B viruses sequenced were B/Victoria lineage, belonging to the B/Austria/1359417/2021 clade, but several subgroups were detected with several mutation differences.

- Vaccination coverage among risk groups younger than 65 years and health care workers decreased compared to the 2021/2022 season. The coverage rate for individuals above 65 years was 63 %, which is at the same level as last season. The number of distributed doses decreased by 9 % compared to the 2021/22 season. 1.2 million doses intended for use in risk groups and health care workers were distributed.
- Highly pathogenic avian influenza viruses (H5N1, H5N5) belonging to clade 2.3.4.4b continued to be detected in wild birds in Norway. During autumn 2022 there were two outbreaks of H5N1 in commercial poultry flocks. No human cases were detected, and the risk of human infection was assessed as very low.

Influensasesongen 2022-2023 i Norge (Norwegian)

Hovedbudskap

- Influensautbruddet i den foregående 2021-2022-sesongen kom uvanlig sent. Utbruddet begynte å vokse seg stort først i mars, etter at smittverntiltakene mot covid-19 ble hevet i midten av februar. Det store covid-omikronutbruddet var også i sterk nedgang på denne tiden. Influensatoppen ble nådd rundt uke 15 og var av lavt til middels omfang. Influensavirus A(H3N2) dominerte.
- Seroprevalensen mot influensa A/Victoria/2570/2019(H1N1)-virus var moderat i et panel av serumprøver innsamlet i august 2022. Det var imidlertid signifikant færre som hadde beskyttende antistoff mot den nyere undervarianten A/Norway/25089/2022(H1N1), som har utgjort en stor andel av vinterens influensautbrudd. Andelen med beskyttende antistoff mot nyere influensa B/Victoria-virus var lav, særlig blant de yngste, noe som kan indikere lav befolkningsimmunitet.
- Inneværende influensasesong startet tidlig. Terskelen for utbrudd (10 % av de testede influensapositive) ble nådd i uke 48 basert på fyrtårnprøver og uke 49 basert på alle testede i landets laboratorier. Det økte deretter raskt mot en skarp topp i uke 51/52, med et påfølgende raskt fall over nyttår. Etter dette har det stabilisert seg med en andel influensa-positive på rundt 14-15 % i den totale testingen og rundt 24 % blant fyrtårnprøvene.
- Fram til nå har influensavirus A vært i klart flertall, men det har vært en jevn økning av influensavirus B som utgjorde 15 % i uke 4. Blant type A-virusene har det vært mest subtype H1, men her er andelen med subtype H3 økende. Alle de influensavirus B som har blitt testet for genotype har tilhørt B/Victoria/2/1987 slektslinjen.
- Gjennom hele sesongen til nå har aldersgruppen med høyest andel influensapositive av de testede vært barn i skolealder (5–14 år). Denne gruppen har også hatt tidligere økning enn de øvrige aldersgruppene.
- Andelen legekonsultasjoner for influensa økte gradvis fra uke 48/2022 til andelen nådde en terskel for medium influensaaktivitet i uke 51/2022. Etter en topp i uke 52/2022, sank andelen til et lavt nivå igjen i uke 2/2023 og har fortsatt å synke frem mot uke 3/2023 og deretter flatet ut.
- Antallet sykehusinnleggelser og intensivinnleggelser med influensa begynte å øke rundt uke 46-2022, og nådde en topp i uke 52-2022. Frem t.o.m. uke 4-2023 har det foreløpig blitt rapportert om 3653 innleggelser i sykehus og 126 innleggelser i intensivavdeling. Disse tallene er betydelig høyere enn antallet rapporterte innleggelser under hele sesongen 2021-2022. Ukentlige antall influensa-assosierte dødsfall toppet seg i perioden uke 52-2022 til 2-2023, og sammenfalt med den høyeste raten av dødsfall uavhengig av årsak i Norge siden 2017.
- Nærmere 16 % av overvåkingsprøvene innkommet til FHI har blitt helgenomsekvensert. Blant A(H1N1) virus har både A/Sydney/5/2021 (subclade 6B.1A.5a.2) og A/Norway25089/2022 (subclade 6B.1A.5a.2.1 med HA-substitusjonen P137S) sirkulert, men de siste ukene har det vært mest av A/Sydney-gruppen. Influensa A(H3N2)-virusene har alle blitt kategorisert som 3C.2a.1b.2a.2 tilhørende A/Slovenia/8720/2022 gruppen som har HA-substitusjonen R299K. Alle sekvenserte influensavirus B tilhører B/Victoria slektslinjen og den nyere genetiske gruppen representert av

B/Austria/1359417/2021. Blant de sekvenserte virusene er det imidlertid flere undergrupper med ytterligere mutasjoner.

- Vaksinasjonsdekningen i risikogrupper og blant helsepersonell gikk ned sammenlignet med fjorårssesongen, selv om dekningen blant personer over 65 år holdt seg på omtrent samme nivå som i fjor på samme tid. Vaksinasjonsdekningen blant personer over 65 år var 63 % på landsbasis. Antallet distribuerte doser gikk ned med 9 % fra sesongen 2021/22. Forbruket i programmet var omtrent 1,2 millioner doser.
- Høypatogene fugleinfluensavirus (H5N1 og H5N5) tilhørende undergruppen 2.3.4.4b fortsatte å bli påvist hos ville fugler i Norge. Høsten 2022 var det to utbrudd av H5N1 i kommersielle fjørfebesetninger. Det ble ikke påvist smitte til mennesker og risiko for smitte til mennesker ble vurdert som svært lav.

A look back at the preceding 2021/2022 season

The 2021/22 season in Norway saw the return of influenza after its almost total absence during the preceding 2020/21 winter. The outbreak was, however, unusually late, peaking only in April.

It is likely that public health and social measures against COVID-19 were holding influenza back, with most measures being lifted in February 2022 and influenza indicators rising from early March.

The proportion of influenza-like illness (ILI) increased from mid-March and only reached low-level intensity at its peak in week 15, with 5 weeks above the outbreak threshold. Similarly, the frequency of influenza virus detections in non-sentinel and sentinel specimens peaked in week 14.

The trends of influenza hospitalisations and ICU admissions reflected the trends in influenza detections well, with a late peak around week 14-16 in 2022. Between week 2021-40 and 2022-39, a total of 2737 patients were admitted to hospital with influenza, and 64 patients were admitted to ICU, indicating a low-to moderate severity level of the epidemic compared to previous seasons. The weekly number of influenza-associated deaths also peaked during weeks 14-19 in 2022, with a total of 143 influenza-associated deaths being reported between week 40-2021 and 39-2022.

Influenza A(H3N2) viruses predominated. Out of more than 600 000 specimens tested for influenza, 14 706 type A and 140 type B viruses were detected. 95% of subtyped A viruses were H3and 5% were H1pdm09. All lineage typed influenza B viruses belonged to the B/Victoria/2/1987 lineage.

The influenza A(H3N2) viruses driving the 2021/22 influenza outbreak were characterized as A/Bangladesh/4005/2020-like viruses, i.e., belonging to the genetic group 3C.2a1b.2a.2. The majority of the viruses possessed the antigen drift substitution H156*S* in the HA protein. These viruses corresponded well to the H3 vaccine component for the Northern hemisphere 2022/23 season, A/Darwin/6/2021.

Highly pathogenic avian influenza viruses (HPAIVs) belonging to H5 clade 2.3.4.4b were detected in wild birds all across Norway, including Spitzbergen and Jan Mayen. A/H5N1 and A/H5N5 predominated. During summer 2022, H5N1 was detected in a large number of sick or dead seabirds found along the Norwegian coast, and in a few wild red foxes that probably fed on such birds. This was the first detection of the virus in mammals in Norway. In November 2021, Norway experienced the first ever outbreak of HPAI in a commercial poultry, when HPAI H5N1 was detected in two flocks. No cases of avian influenza were detected in humans and the risk of human infection was assessed as very low.

The 2022/2023 season

The components of the surveillance system are briefly described in Appendices.

Influenza-like illness (ILI) in primary health care

The proportion ILI consultations began to rise gradually from week 48/2023 and crossed the epidemic threshold in week 49. Influenza activity of medium intensity has been present from week 51/2022, with a peak in week 52/2022, until week 2/2023 when the rates declined to a low intensity according to the present-season MEM intensity thresholds. The decline has continued after that and has been relatively stable since week 3/2023. (Figure 1).

The ILI-indicator seems to not fully reflect the influenza situation in Norway this season. This may be caused by changed coding practices for influenza due to the covid-19 pandemic. Comparing ILI to proportion positive laboratory tests, it seems that the ILI reflects the trend, and also the beginning of the outbreak. However, the top week at medium intensity seems too low compared to both proportion positive tests and the number of influenza hospitalizations.

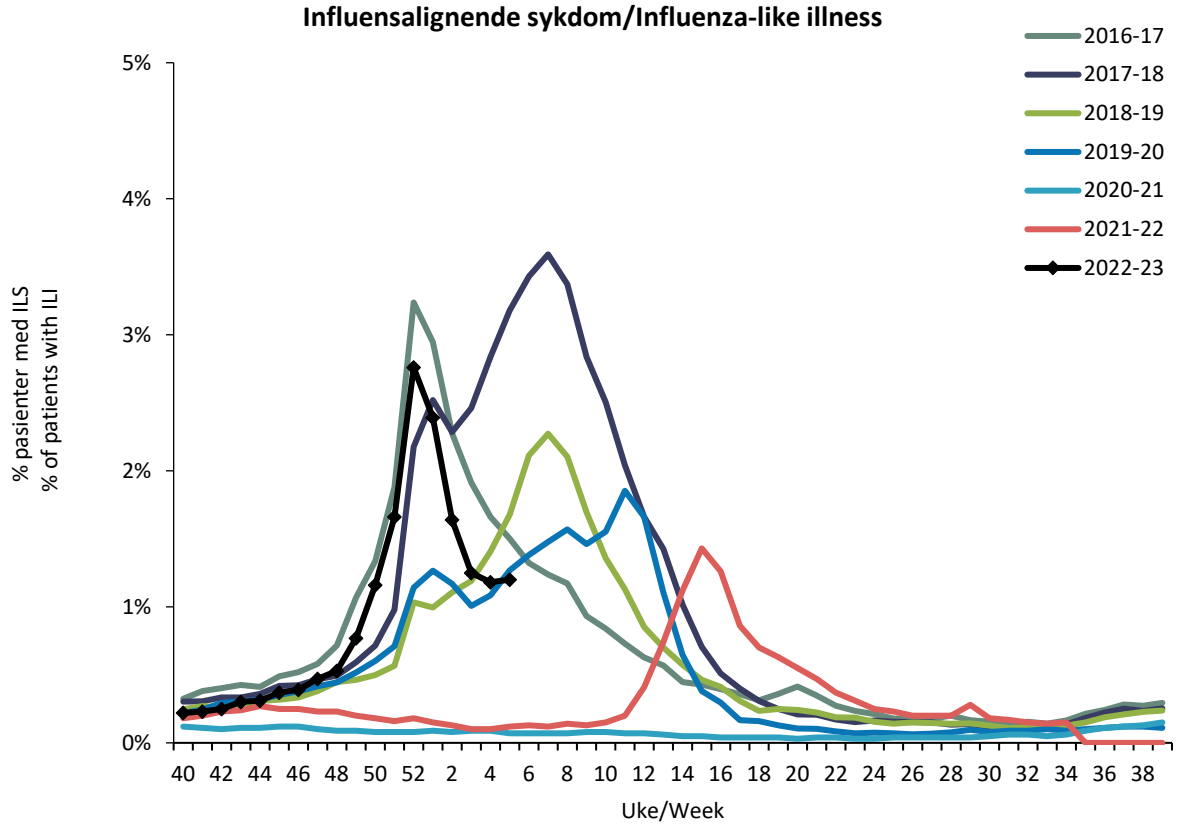


Figure 1. Weekly proportion of consultations for ILI, Norway 2022-2023 season (black dotted line). The graph shows the proportion of patients in general practice and emergency clinics diagnosed with ILI, by calendar week. The six previous seasons are also shown. Source: Sykdomspulsen with data from KUHR, NIPH.

Influenza hospitalisations based on registry data

Between week 40-2022 and 4-2023, 3653 (67.3 per 100 000 inhabitants) new hospital admissions with influenza have been reported, with a peak of 861 new admissions in week 2022-52 (figure 2). The median age of the patients is 68 years, and 49 % (1775) of the admissions were among females. The admission rates were highest in the age groups 65-79 and 80+ years, followed by children aged 0-4 years (table 1). Fifty percent of the hospitalised patients were vaccinated ≥14 days before testing positive for influenza virus.

In comparison, in season 2021/2022 the influenza epidemic started late, with hospital admission peaking in week 15 (424 new admissions). The number of admissions reported in the current season has already exceeded the number of new admissions reported between weeks 2021-40 and 2022-39 (2737).

While registry data on influenza-positive PCR tests have been available only since the start of the COVID-19 pandemic, registry data based on hospital discharge codes alone suggest that prior to the COVID-19 pandemic, an average of ca. 5000 patients were hospitalised with influenza per season. In comparison the previous 5 seasons for which data are available, the weekly number of hospitalisations in week 2022-52 (n=908) was significantly higher than during the top weeks in the other seasons (n=280-625). Furthermore, in the current season, the hospitalisation rate has been higher among the 0-4- and 5-14-year-olds than during any of the previous seasons (figure 3). For the 0-4-year-olds also the second-highest peak (the 2018/19 season) was an A(H1N1) outbreak.

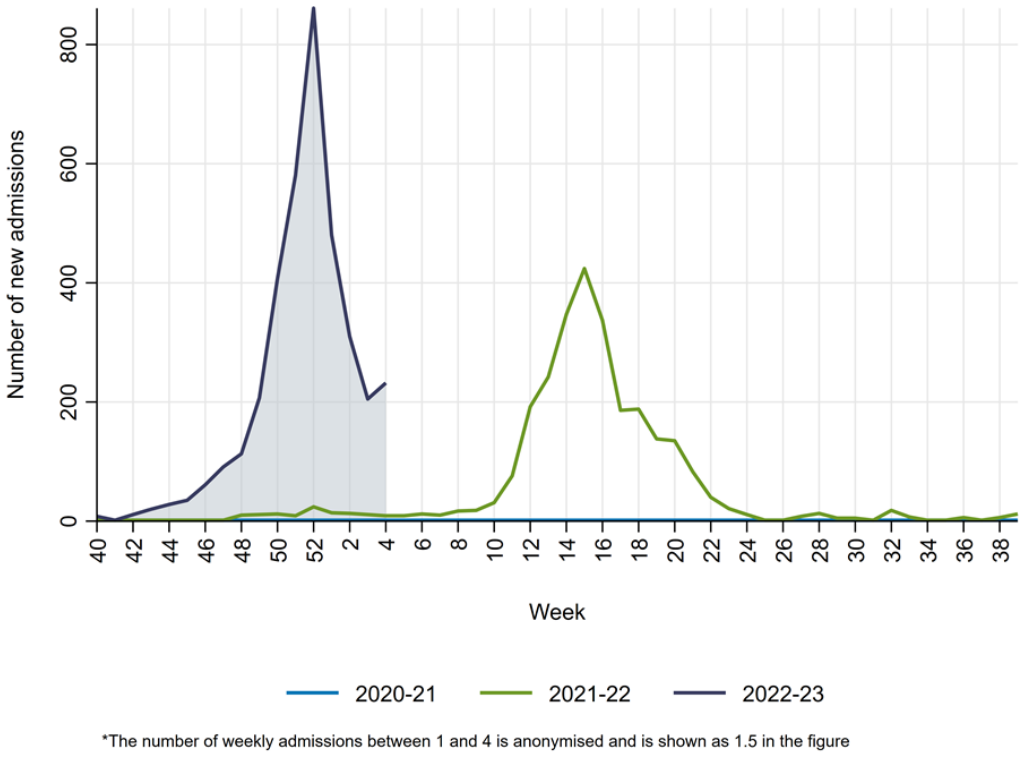


Figure 2. Weekly number of new hospital admissions with influenza by week and season, Norway, 28 September 2020 – 29 January 2023. Source: The Norwegian Emergency Preparedness Registry (Beredt C19) with data from the Norwegian Surveillance System form Communicable Diseases laboratory database and the Norwegian Patient Registry.

Table 1. Number of new hospital admissions with influenza by age group, Norway, 2 October 2022 – 29 January 2023. Source: The Norwegian Emergency Preparedness Registry (Beredt C19) with data from the Norwegian Surveillance System for Communicable Diseases laboratory database and the Norwegian Patient Registry.

	Weeks 40-2022 to 4-2023		
		Admissions per	
Age group	Admissions	100 000	Proportion (%)
0-4 years	274	97.8	7.5
5-14 years	166	26.1	4.5
15-29 years	188	18.4	5.1
30-64 years	997	39.9	27.3
65-79 years	1218	162.6	33.3
80+ years	810	337.1	22.2
Total	3653	67.3	100.0

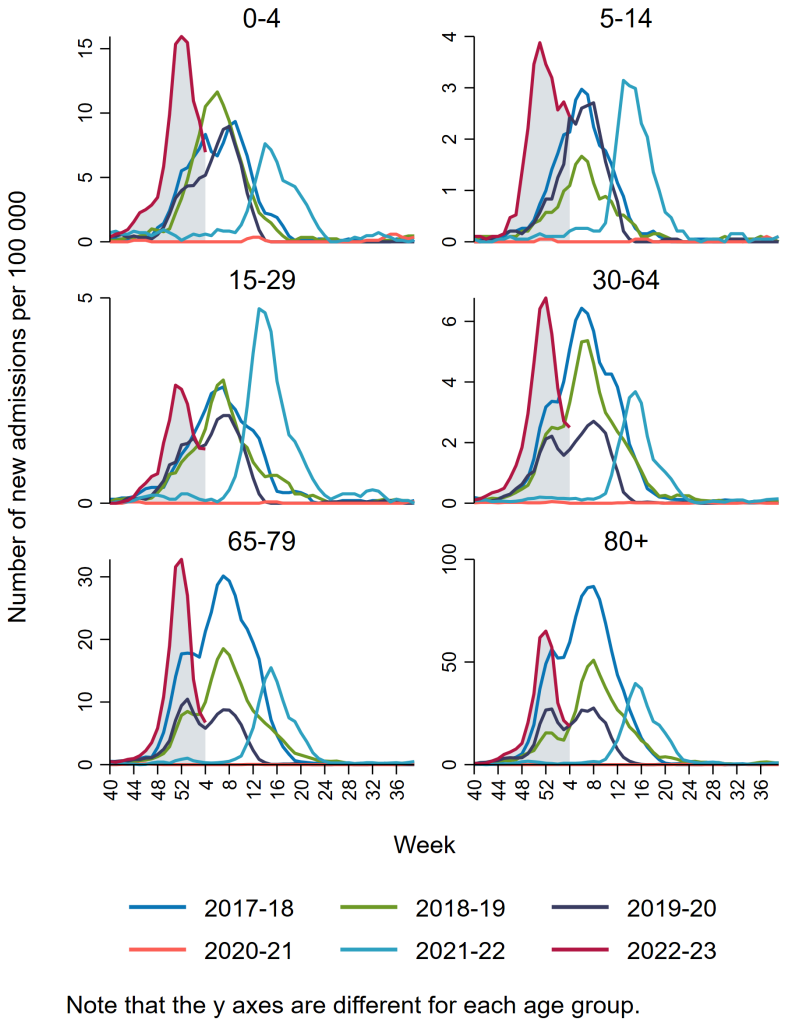


Figure 3. Weekly number of new hospital admissions with influenza by week and season, Norway, 28 September 2020 – 29 January 2023. Source: The Norwegian Emergency Preparedness Registry (Beredt C19) with data from the Norwegian Patient Registry.

Influenza patients in intensive care units

Between week 40-2022 and 4-2023, a total of 126 patients (2.3 per 100 000 inhabitants) have been admitted to ICU with confirmed influenza, with a peak of 36 patients admitted in week 52. The median age of the patients is 64 years, and 49 % (62) are female.

In comparison, 64 patients were admitted to ICU with influenza in Norway between weeks 40 and 24 in 2021-2022.

Influenza-associated deaths

Between week 40-2022 and 4-2023 there were 158 recorded influenza-associated deaths (ICD-10 diagnosis codes J09-J11 stated as one of the causes of death on the death certificate) in Norway, compared to 6 (2021/22), <5 (2020/21), 39 (2019/20), 35 (2018/19), 119 (2017/18) and 178 (2016/17) for the same time period in the preceding seasons. The highest weekly rates of influenza-associated deaths occurred during weeks 52, 1, and 2. This coincided with the highest weekly rate of all-cause death in Norway (during week 52-2022) since week 2-2017. The total number deaths caused by influenza is most likely underestimated here, since the influenza-specific ICD-codes are generally used when concurrent laboratory test results are also available, while testing for influenza in e.g. nursing homes is not comprehensive.

Laboratory confirmed influenza: Virological surveillance

Altogether, 122,137 patients in Norway were tested for influenza during weeks 40/2022-5/2023, resulting in 13,905 recorded detections of influenza A virus and 606 influenza B virus (Figure 4, Table 2).

Of these, 1,407 influenza A and 208 influenza B positive specimens have been referred to the NIC for further identification and characterisation. Among these 1,403 type A viruses were subtyped (1015 H1(72 %) and 389 H3 (28%). Three type A virus specimens were too weak for successful subtyping. All 200 lineage-typed influenza B viruses belonged to the B/Victoria/2/1987 lineage and 8 influenza B positive specimens contained too little viral RNA for lineage determination.

In addition to this, primary testing laboratories have identified 1,529 type A viruses as H1 and 28 as H3. This testing is biased by several laboratories testing for H1pdm09 but not H3.

The number of detections started to rise in early November and increased more and more rapidly until reaching a peak in weeks 51-52/2022, when approx. 25 % of samples in the comprehensive surveillance and 46 % (week 52) in the sentinel surveillance tested positive for influenza. There was a marked drop after New Year, which soon levelled out at a positivity rate around 13-15 % in comprehensive and 22-25% in the sentinel surveillance (Figure 4, 6). This pattern at the national level may be seen as a composite of regions in the country where the influenza detections still are dropping after a very early peak, and other regions where numbers are on the rise. Furthermore, the drop in detections after New Year was all in influenza A, whereas influenza B detections have continued to rise steadily, by week 4 comprising 15 % of influenza detections. It remains to be seen how these trends in the different parts of the country will develop as we progress toward spring.

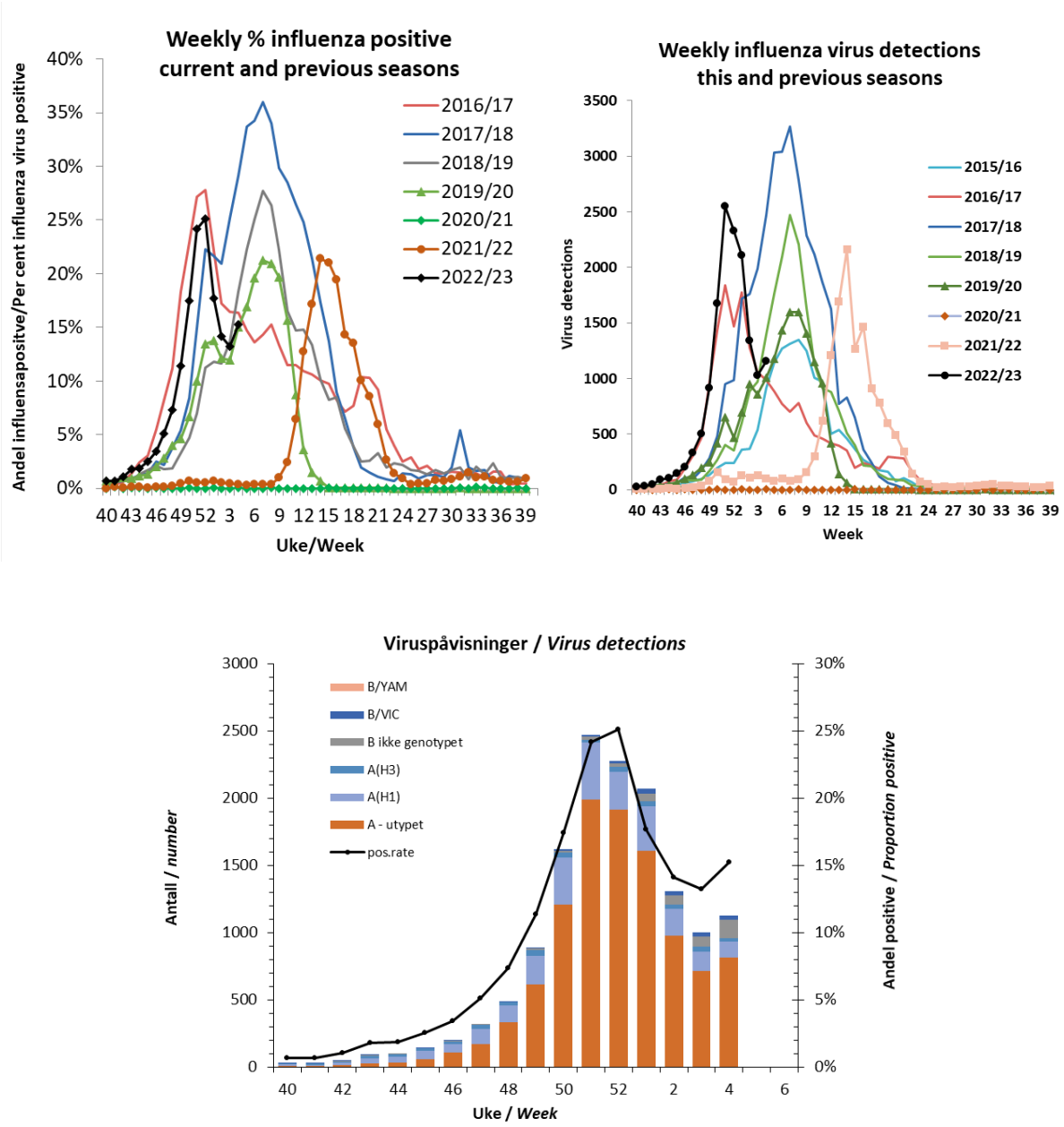


Figure 4. Laboratory detections, Norway 2022-2023. Upper left-hand panel: Weekly proportion of influenza virus positive specimens, with previous season proportions shown for comparison. Upper right-hand panel: Weekly number of influenza virus detections, with previous season numbers shown for comparison. Seasons impacted by Covid-19 are marked with symbols.
Lower panel: Weekly number of the different influenza viruses, displayed as stacked bars.

This far influenza A viruses have been strongly predominant, but with a steady trend of increasing type B since New Year; type B viruses comprised 85% of influenza detections in week 4. Among type A viruses, subtype H1 has been in clear majority during the active part of the season, with a trend recently toward more equal proportions (Figure 5). There is some regional heterogeneity in the proportions of the different influenza types and subtypes. The subtype

analysis is limited to viruses that have been tested for both H1 and H3, since many laboratories test only for H1 and not H3, thus producing a strong subtype bias.

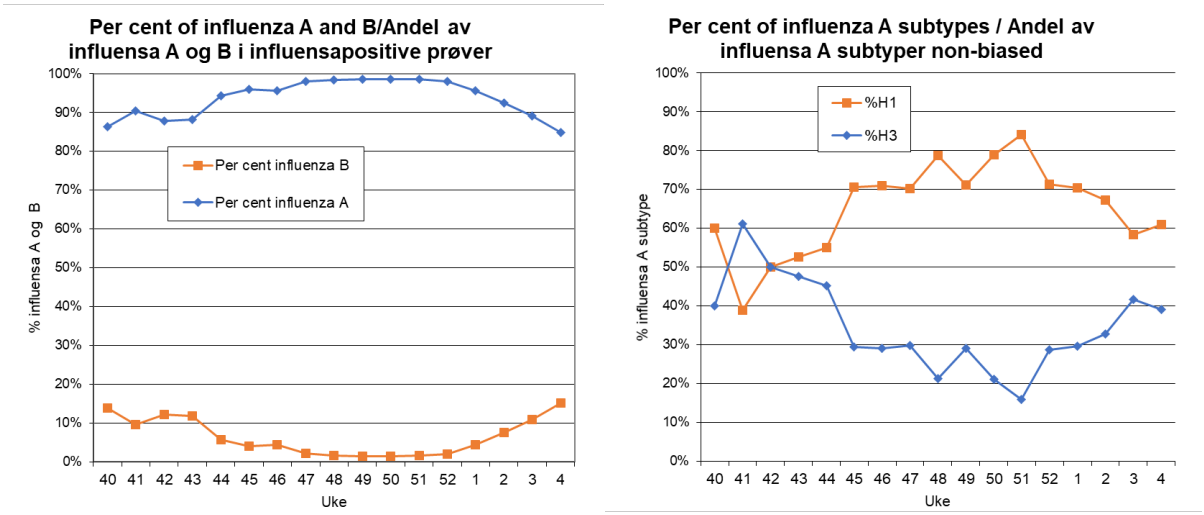


Figure 5. Influenza virus detections since week 40/2022, proportions per type A and B (left panel) and influenza A subtypes H1 and H3 (right panel). Only viruses tested for both subtypes are counted in the subtype analysis.

False positives due to vaccine contaminating sampling workstations?

Similar to earlier seasons, in a few instances in the autumn trace amounts of virus RNA representing three or four different subtypes/lineages were detected in the same sample; this has been interpreted as likely contamination with tetravalent influenza vaccine and they have not been counted as infections in the surveillance. In one case there was sufficient virus to obtain partial sequence, and the genetic profile was indicating the genetic backbone of live attenuated vaccine strains. However, the use of LAIV in Norway has been extremely low, and in most cases the source is believed to be environmental contamination with inactivated vaccine in settings where administration of vaccine and respiratory specimen collection is done at the same workstation.

Sentinel-based surveillance

From week 40/2022 through week 4/2023, 2028 sentinel specimens have been tested, with 366 detections of influenza virus A (260 subtype H1, 90 subtype H3, and 16 not yet subtyped), and 17 influenza virus B (of which 15 were Victoria-lineage and 2 were not (yet) lineage identified). In addition, 291 SARS-CoV-2, 136 RSV, 280 rhinovirus, 41 human metapneumovirus(hMpV), 102 parainfluenza virus and 64 other human coronaviruses were detected (Fig 6). Influenza detections increased and peaked simultaneously to the detections in the non-sentinel virological surveillance.

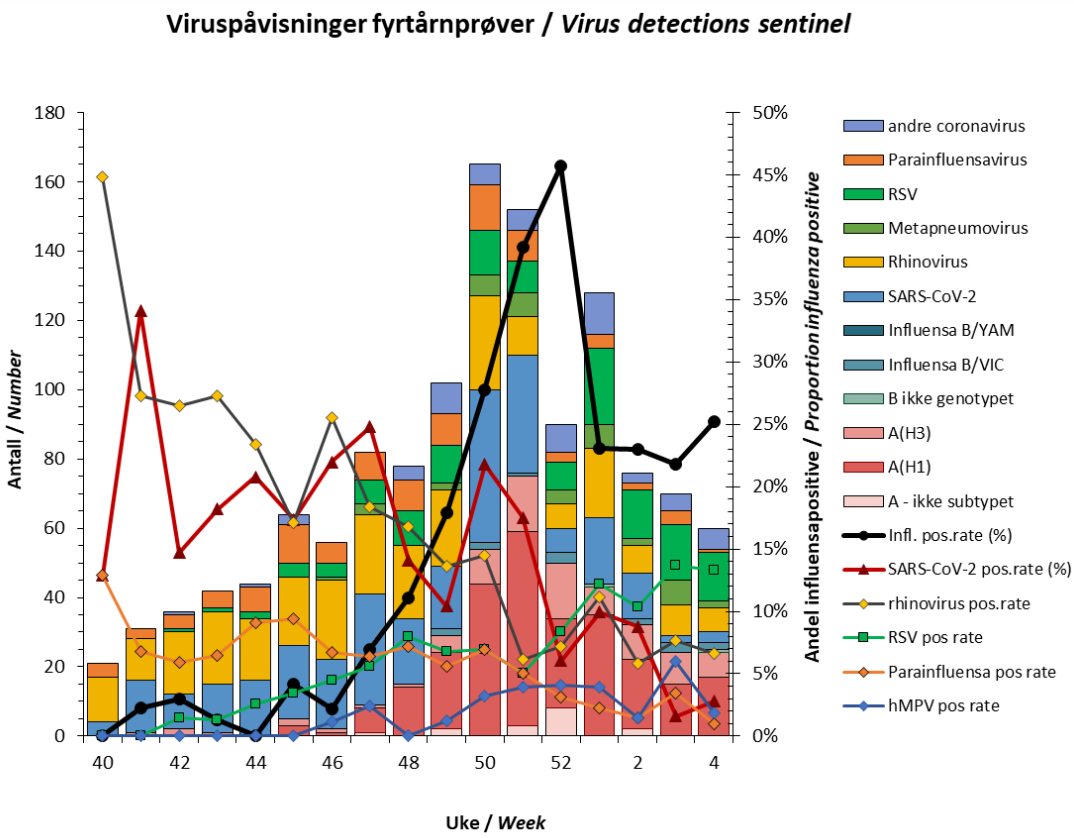


Figure 6. Weekly numbers of detections and per cent positives of respiratory viruses in the respiratory sentinel surveillance.

Table 2. Weekly total number of specimens tested for influenza, proportion of specimens positive for influenza virus, and influenza virus detections per type/subtype/lineage (all are non-sentinel), in Norway from week 40/2021 through week 4/2022.

UKE/ *week*	Viruspåvisninger/*Virus detections*							
	Prøver/ *Specimens*	% positive	A(utypet) *not subtyped*	A(H1)	A(H3)	B ikke genotypet *not lineage typed*	B/ Victoria lineage	B/ Yamagata lineage
40	4385	0,7 %	7	12	6	2	2	0
41	4487	0,7 %	8	9	11	2	1	0
42	4623	1,1 %	15	18	10	5	1	0
43	5176	1,8 %	27	36	19	5	6	0
44	5549	1,9 %	33	42	23	6	0	0
45	5884	2,5 %	55	67	20	4	2	0
46	5880	3,4 %	107	67	18	7	2	0
47	6512	5,1 %	174	117	33	7	0	0
48	6863	7,3 %	330	143	22	5	3	0
49	8058	11,4 %	615	236	51	7	7	0
50	9601	17,4 %	1210	393	46	14	11	0
51	10549	24,1 %	1993	482	32	23	17	0
52	9272	25,1 %	1924	306	50	29	20	0
1	11940	17,7 %	1608	365	46	58	35	0
2	9478	14,1 %	977	221	40	69	33	0
3	7808	13,2 %	714	157	48	77	35	0
4	7571	15,3 %	814	133	32	143	33	0
Total	123636		10611	2804	507	463	208	0
UKE/ *week*	Prøver/ *Specimens*	% positive	A(utypet) *not subtyped*	A(H1)	A(H3)	B ikke genotypet *not lineage typed*	B/ Victoria lineage	B/ Yamagata lineage
		Type A: 13922			Type B: 671			

Genetic characterization of Influenza viruses in Norway

So far this season NIPH has received 2,856 influenza viruses for analysis and 15.8 % of these has been characterized further with whole genome sequencing. This season 47 clinical isolates have so far been shared with the WHO collaborating laboratory Crick and 504 HA gene sequences have been submitted to GISAID.

H1N1-viruses

So far, all characterized H1N1 viruses are classified as 6B.1A.5a.2, as shown in Figure 7 and Table 3. During the summer and fall of the previous season 2021-22, new strains of H1N1 virus emerged and constituted a larger proportion of the H1 viruses. These H1 viruses are this season defined by the WHO as A/Norway/25089/2022-like viruses, NextClade classified as 6B.1.A.5a.2.1 and are being closely monitored due to the emergence of immune evasion mutations. At the beginning of the 2022/23 influenza season, these viruses made up about half of all detections in Norway together with the A/Sydney/5/2021 viruses. The A/Norway-like viruses (circulating in Norway) carry haemagglutinin mutations P137S, K142R and T277A. Two clusters of the H1 A/Sydney/5/2021 lineage are defined by the N129D and T185I mutation and are related to the earlier A/Victoria/2570/2019 line, both clusters continue to grow as seen in Figure 8A and Figure 9. One more cluster of A/Sydney/5/2021 like viruses was characterized by the T185V and A186T mutations, however the last detection of a representative in this cluster was week 50, 2022. it is unclear if they are still in circulation. Although A/Norway/25089/2022-like viruses dominated at the beginning of the season, A/Sydney/5/2021 viruses have been dominant since the end of December. For the neuraminidase no reassortment between the clades have been observed as seen in Figure 9.

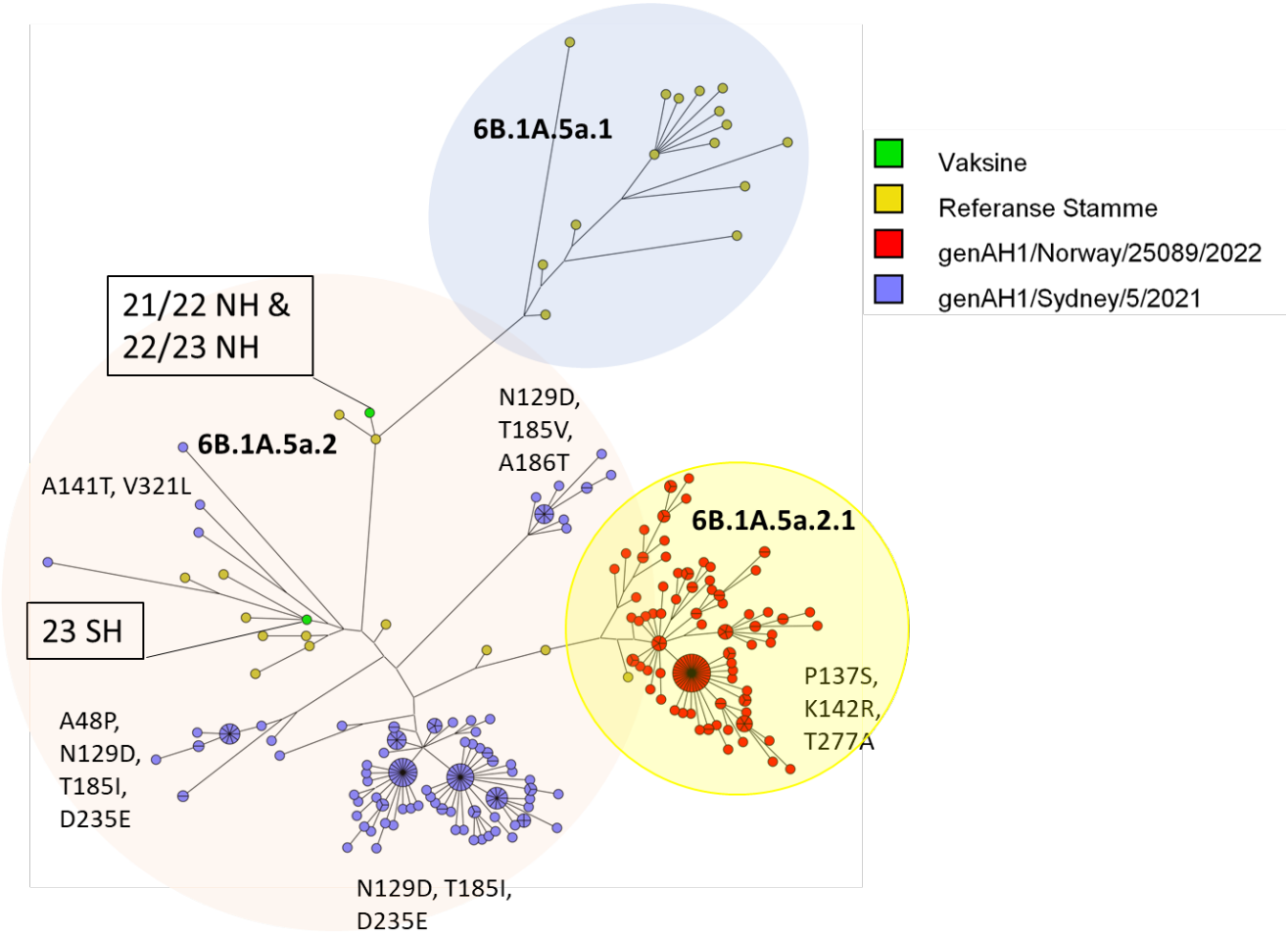


Figure 7 H1N1 Maximum Parsimony tree: The figure shows how the haemagglutinin sequences of H1N1 influenza genomes from viruses in Norway group genetically with reference viruses and vaccine strains from the northern and southern hemispheres, colour coded by ECDC/EuroFlu reporting category.

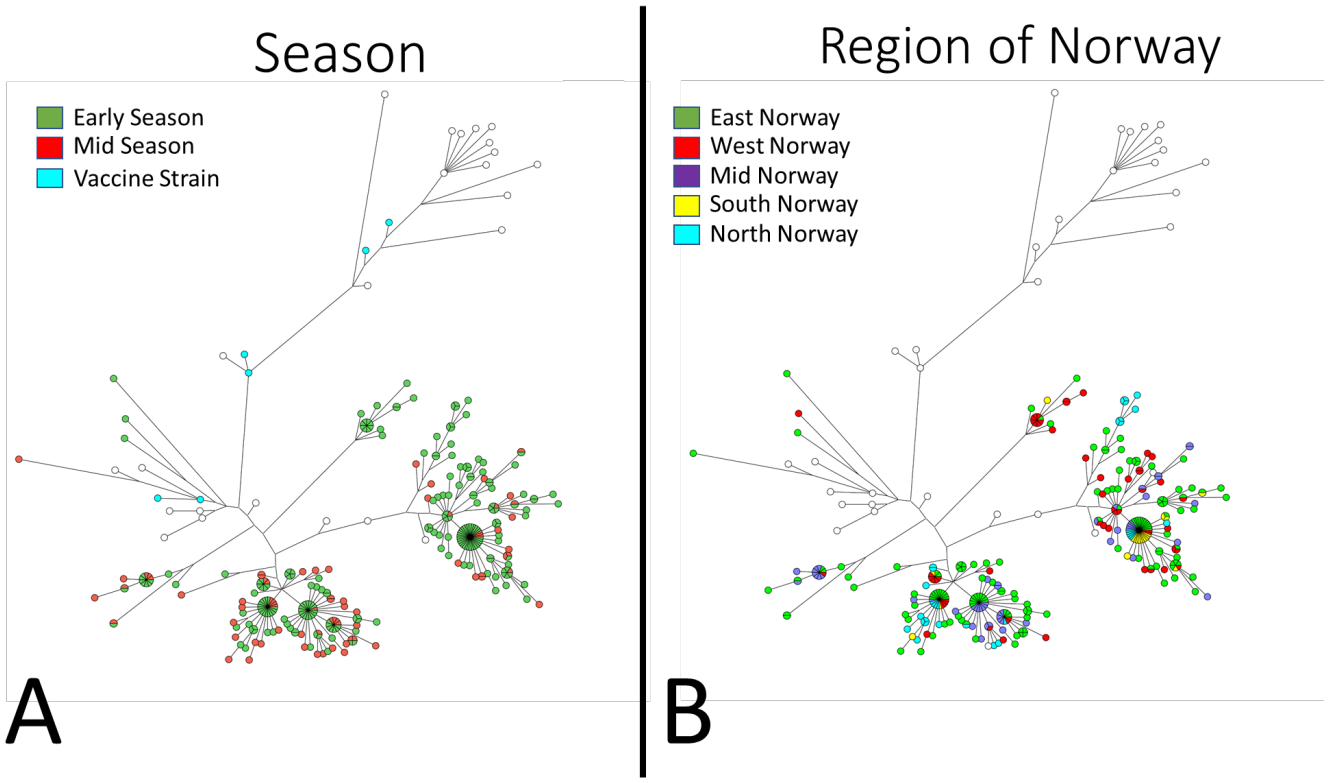
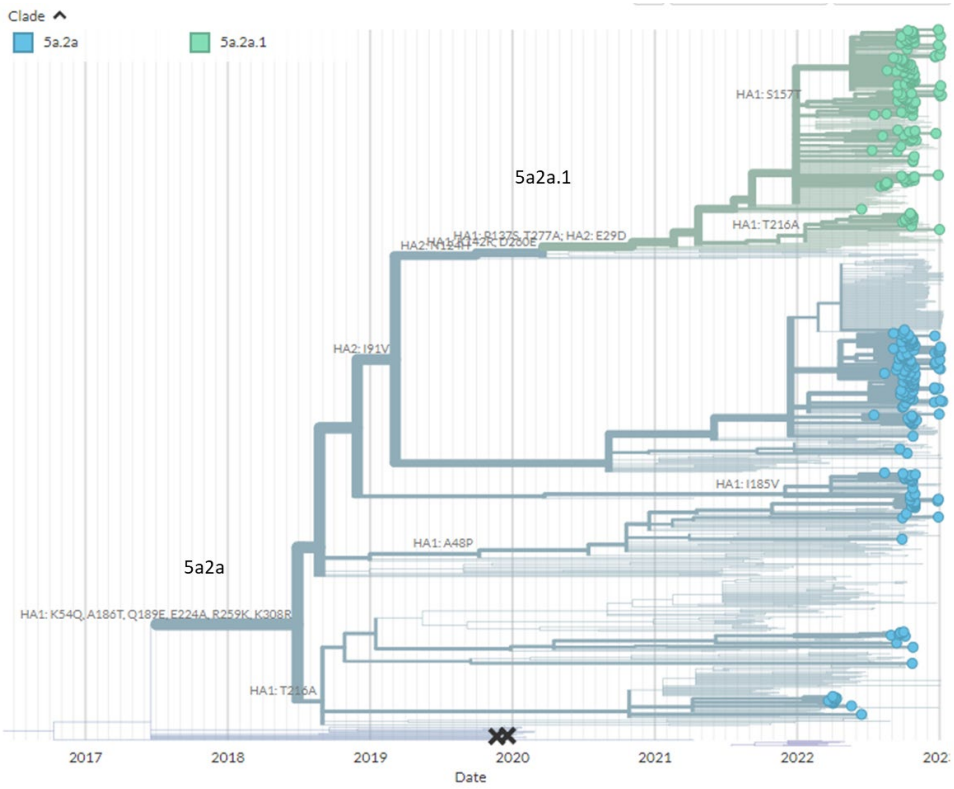


Figure 8 H1N1 Maximum Parsimony tree: The figure shows how the haemagglutinin sequences of H1N1 influenza genomes from viruses in Norway group genetically with reference viruses and vaccine strains from the northern and southern hemispheres, colour-coded by Season of detection (A) or Region of detection (B). Early Season defines the period between week 40 and week 50 in 2022 while Mid-Season is between week 50 2022 and week 12 2023)



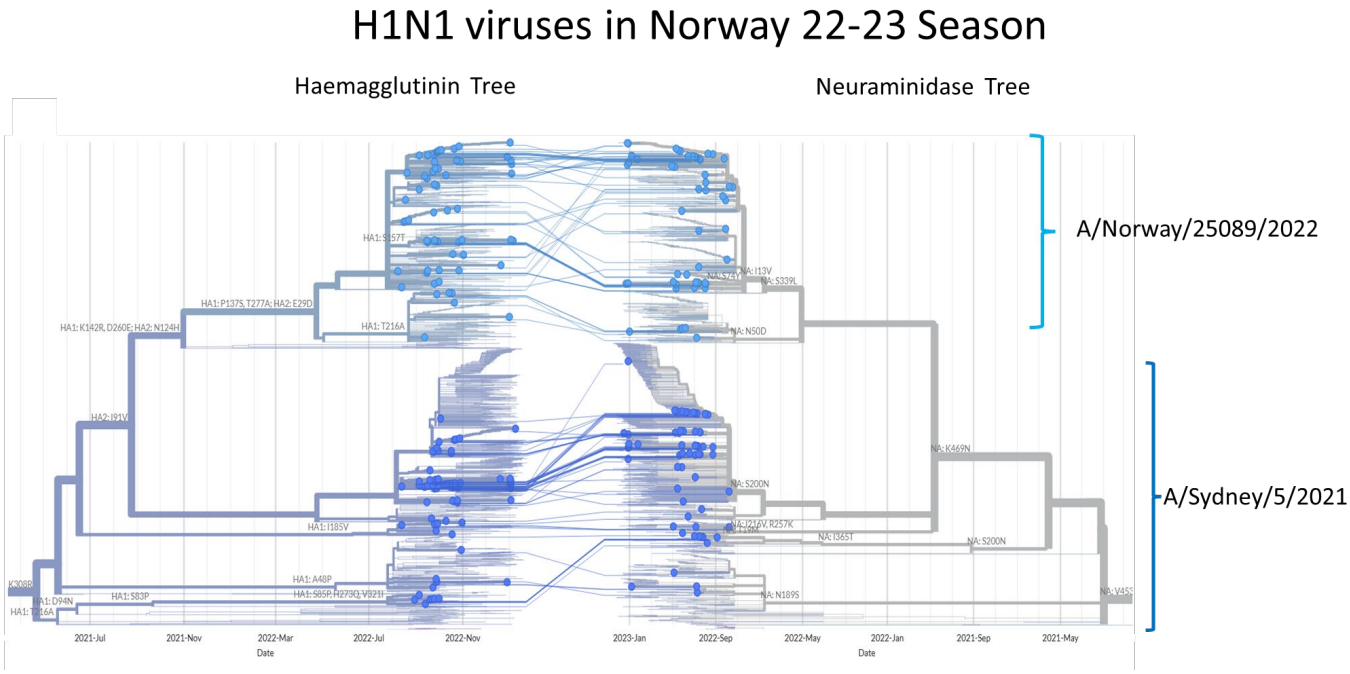


Figure 9. H1N1 Phylogenetic tree: Top: NextClade phylogenetic tree of H1 from Norway compared with other international strains. Clade defining amino acids indicated on key nodes. Lower: The figure compares the branching order of haemagglutinin and neuraminidase sequences of H1N1 influenza genomes from viruses in Norway in the 22-23 influenza season. Key mutations are indicated on the nodes, colours represent the genetic classifications.

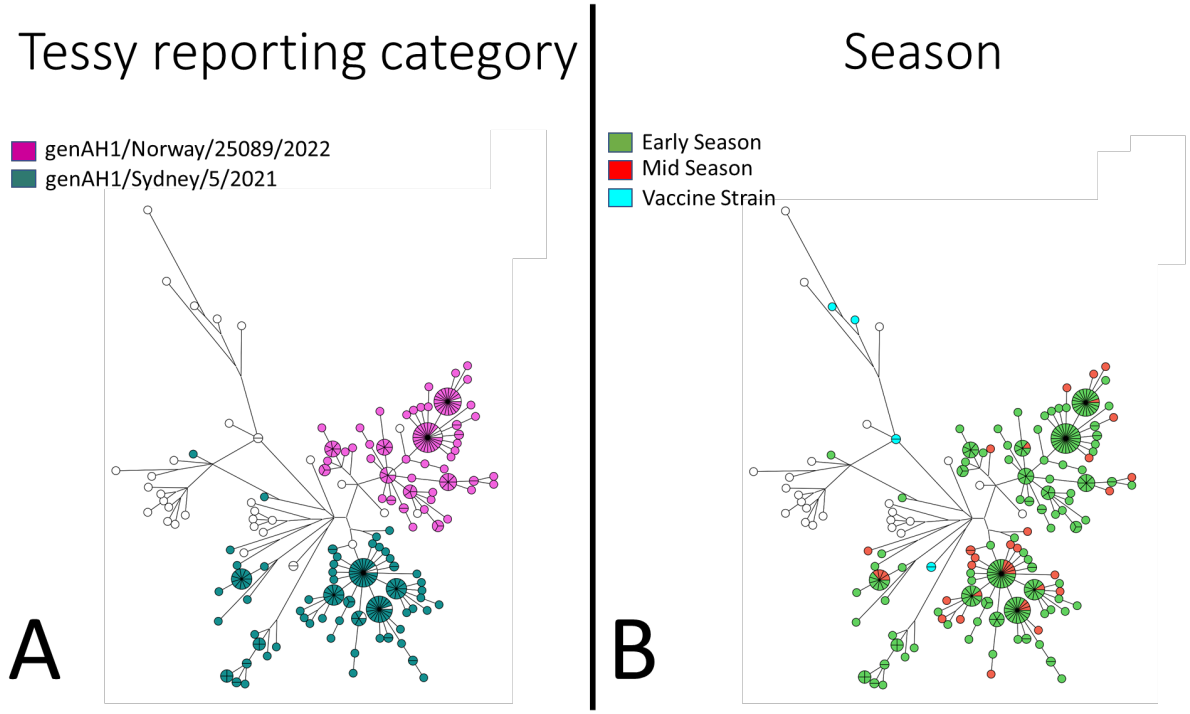


Figure 10. H1N1 Maximum Parsimony tree: The figure shows how the neuraminidase sequences of H1N1 influenza genomes from viruses in Norway group genetically with reference viruses and vaccine strains from the northern and southern hemispheres, color-coded by ECDC/EuroFlu reporting category based on the HA Sequence (A) or Season of detection (B). Early Season defines the period between week 40 and week 50 in 2022 while Mid-Season is between 50 2022 and week 12 2023)

H3N2 viruses

So far, the H3N2 viruses have been classified as belonging to the 3C.2a.1b.2a.2 group of H3 viruses, as shown in Figure 11 and Table 3. Most of the viruses belonged to the A/Slovenia/8720/2022 group of viruses and carry mutations R33Q, E50K, I203T, S262N and R299K in HA. Other viruses were characterized as A/Bangladesh/4005/2020-like (R33Q, E50K, F79V, I140K, I203T, I242M, and S262N) and A/Darwin/9/2021 group of viruses defined by D53N and I223V mutations are also detected. All subvariants appear to be genetically well covered by the vaccine. All genetic clusters had detections since week 51 2022 and are continuing to grow although slower than the H1N1 lineages (Figure 12A, Table 3). Interestingly, the NA gene shows many reassortment events between the A/Bangladesh/4005/2020-like and the A/Slovenia/8720/2022 like viruses. While the A/Darwin/9/2021-like NA genes mainly cluster like the HA based clusters (Figure 13A).

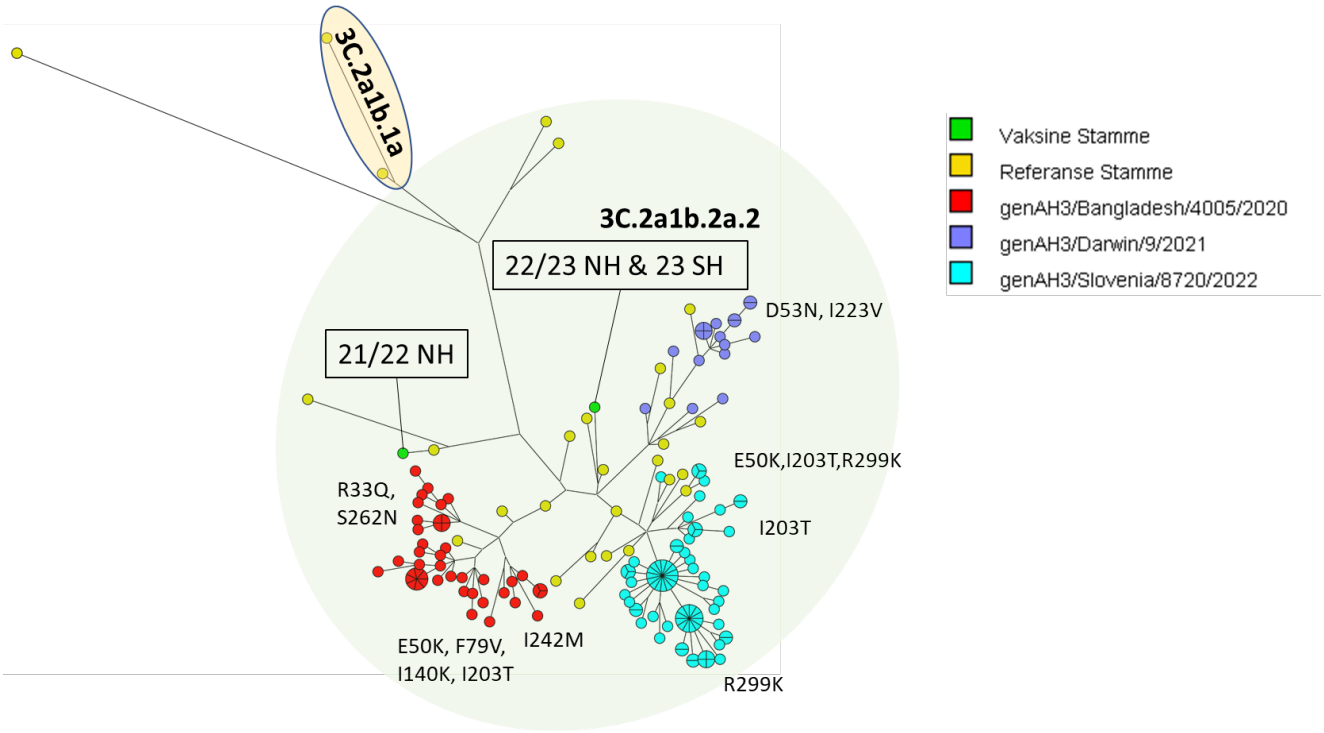


Figure 11. The H3N2 Maximum Parsimony Tree: The figure shows how the hemagglutinin sequence of the H3N2 viruses from Norway genetically groups with reference Viruses and vaccine strains from the northern and southern hemisphere, color-coded by ECDC/EuroFlu reporting category.

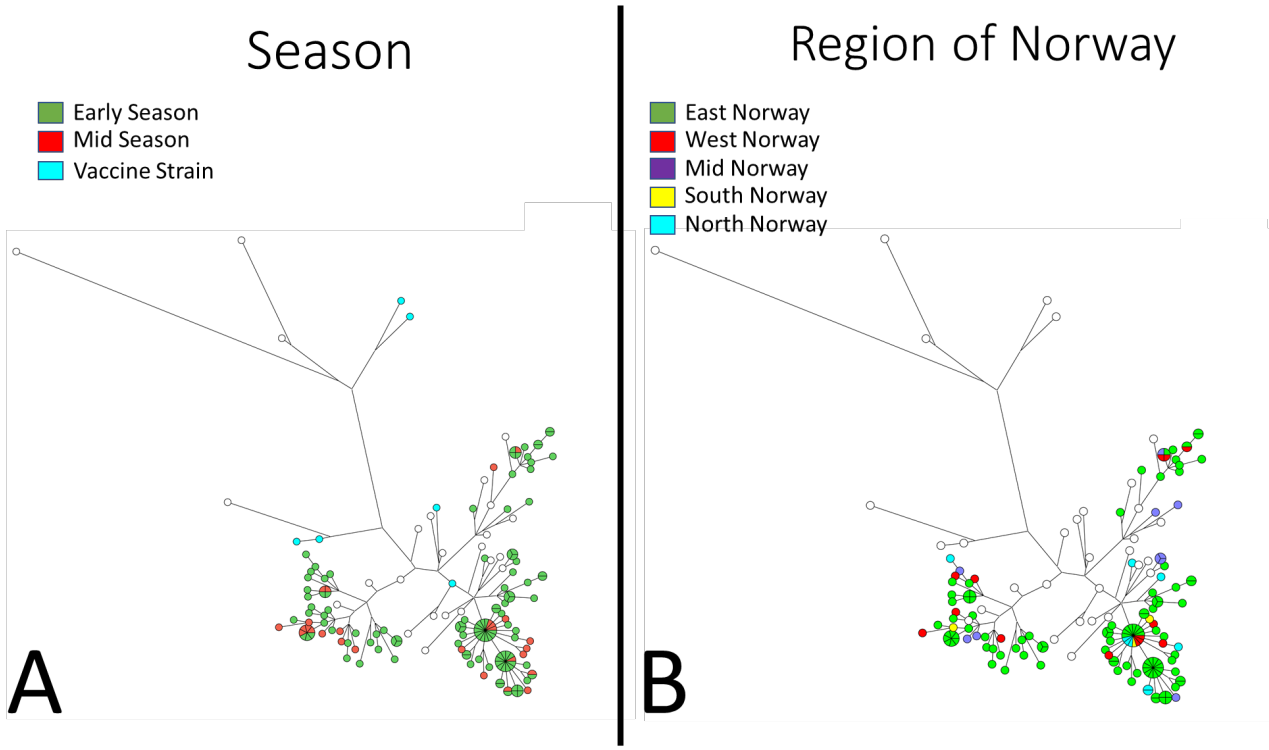


Figure 12. H3N2 Maximum Parsimony tree: The figure shows how the hemagglutinin sequences of H3N2 influenza genomes from viruses in Norway group genetically with reference viruses and vaccine strains from the northern and southern hemispheres, color-coded by Season of detection (A) or Region of detection (B)

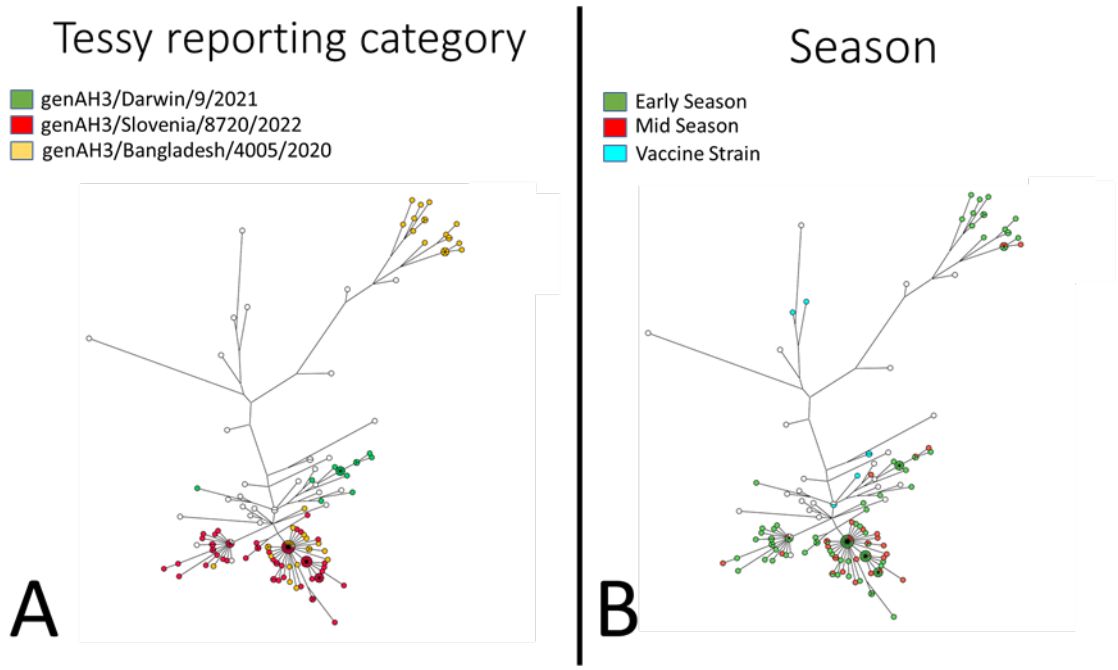


Figure 13. H3N2 Maximum Parsimony tree: The figure shows how the neuraminidase sequences of H3N2 influenza genomes from viruses in Norway group genetically with reference viruses and vaccine strains from the northern and southern hemispheres, color-coded by ECDC/EuroFlu reporting category based on the HA Sequence (A) or Season of detection (B). Early Season defines the period between week 40 and week 50 in 2022 while Mid-Season is between 50 2022 and week 12 2023)

B/Victoria-lineage viruses

The B/Victoria virus sequences fall under the B/Austria/1359417/2021-like virus group (Figure 14). Viruses with a number of additional mutations have also been detected, such as viruses with A127T, N129D, N197E, Y586C/R and S208P. Although over the whole season only 42 B/Victoria strains have been sequenced the frequency is increasing in the early weeks of 2023. However, all variants appear to be genetically well covered by the vaccine.

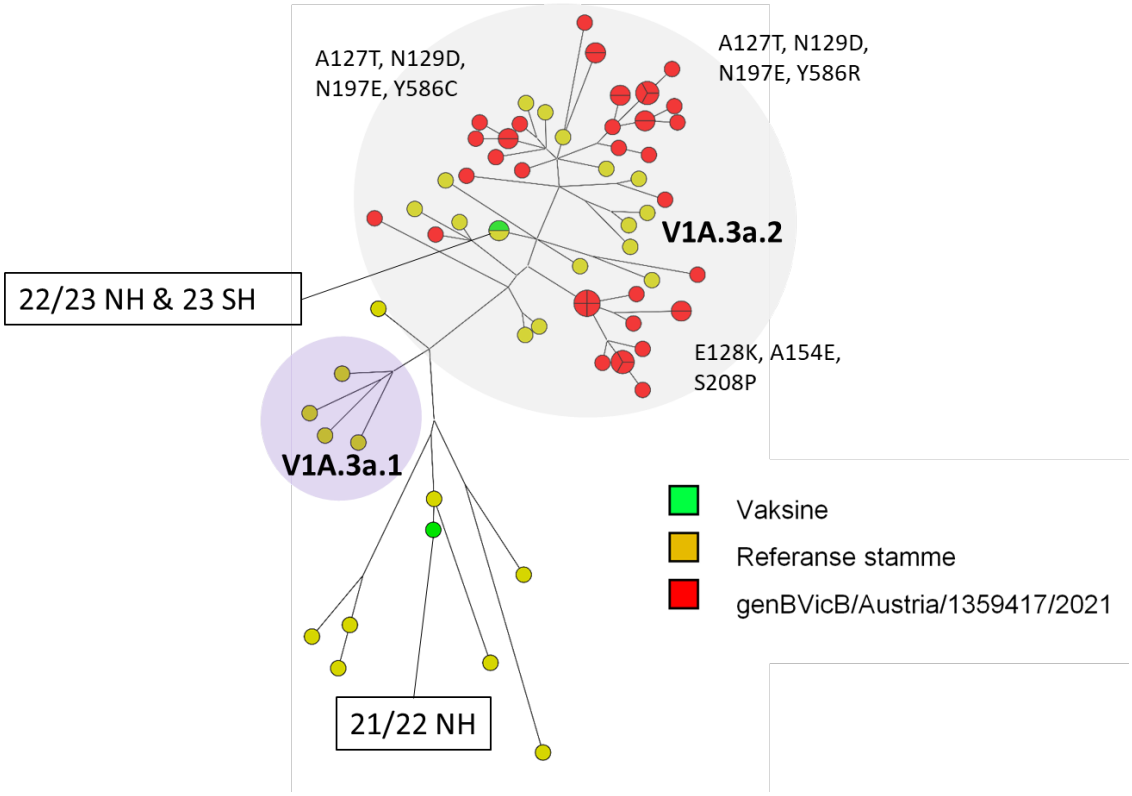


Figure 14. B/Victoria Maximum Parsimony tree: The figure shows how the hemagglutinin sequence of B/Victoria influenza genome sequences from viruses in Norway genetically groups with reference viruses and vaccine strains from the northern and southern hemispheres, color-coded according to the ECDC reporting category.

Table 3. Genetic characterization results for influenza viruses detected in Norway in the past four weeks and in total. Source: National Influenza Centre at FHI.

Strain	40	41	42	43	44	45	46	47	48	49	50	51	52	1	2	3	4	Total
6B.1A.5a.2.1	3	0	6	6	11	17	7	12	11	27	14	3	5	9	4	2	0	137
genAH1/Norway/25089/2022	3	0	6	6	11	17	7	12	11	27	14	3	5	9	4	2	0	137
6B.1A.5a.2	3	2	4	6	7	14	11	20	15	26	7	8	7	11	19	4	2	166
genAH1/Sydney/5/2021	3	2	4	6	7	14	11	20	15	26	7	8	7	11	19	4	2	166
3C.2a1b.2a.2	3	8	6	9	10	16	10	13	6	25	7	2	3	11	13	8	0	150
genAH3/Bangladesh/4005/2020	1	3	3	1	3	5	4	2	1	4	5	2	0	5	5	3	0	47
genAH3/Slovenia/8720/2022	1	4	1	6	4	11	6	8	5	18	1	0	3	5	7	4	0	84
genAH3/Darwin/9/2021	1	1	2	2	3	0	0	3	0	3	1	0	0	1	1	1	0	19
V1A.3a.2	1	1	0	3	0	0	2	0	0	2	3	2	6	9	10	3	0	42
genBVicB/Austria/1359417/2021	1	1	0	3	0	0	2	0	0	2	3	2	6	9	10	3	0	42
genBYamB	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	10	11	16	24	28	47	30	45	32	80	31	15	21	40	46	17	2	495

Surveillance of antiviral resistance in Influenza viruses

For Influenza infections, especially for people belonging to risk groups, the attending physician should consider the need for use of antivirals. This applies to both vaccinated and unvaccinated individuals. Treatment should be initiated as early as possible in the course of the infection. Patients who are so sick that they are admitted to the hospital should always be assessed for antiviral drugs, even later in the course of the disease. Preventive treatment may be appropriate in nursing homes with outbreaks.

So far this season, 496 Influenza viruses have been tested for resistance (150 H3N2, 303 H1N1, 43 B-Victoria) to neuraminidase inhibitors such as oseltamivir and polymerase inhibitor Baloxavir. No resistance mutations have been detected and all viruses tested are sensitive to treatment with Tamiflu® and XOFLUZA®.

Population immunity against recent influenza viruses, August 2022

In August each year, the National Influenza Seroepidemiology Programme solicits approximately 2000 anonymised residual sera from clinical/microbiological laboratories across Norway. The sera, aimed to be representative of the Norwegian population geographically and by age composition, are tested by the haemagglutination-inhibition assay (HAI) to determine the antibody immunity against relevant circulating influenza viruses. Due to continued increased workload related to COVID-19, A subset of ca. 1200 sera collected in August 2022 were analysed. The main findings are shown in figure 15, table 4, and summarised as follows:

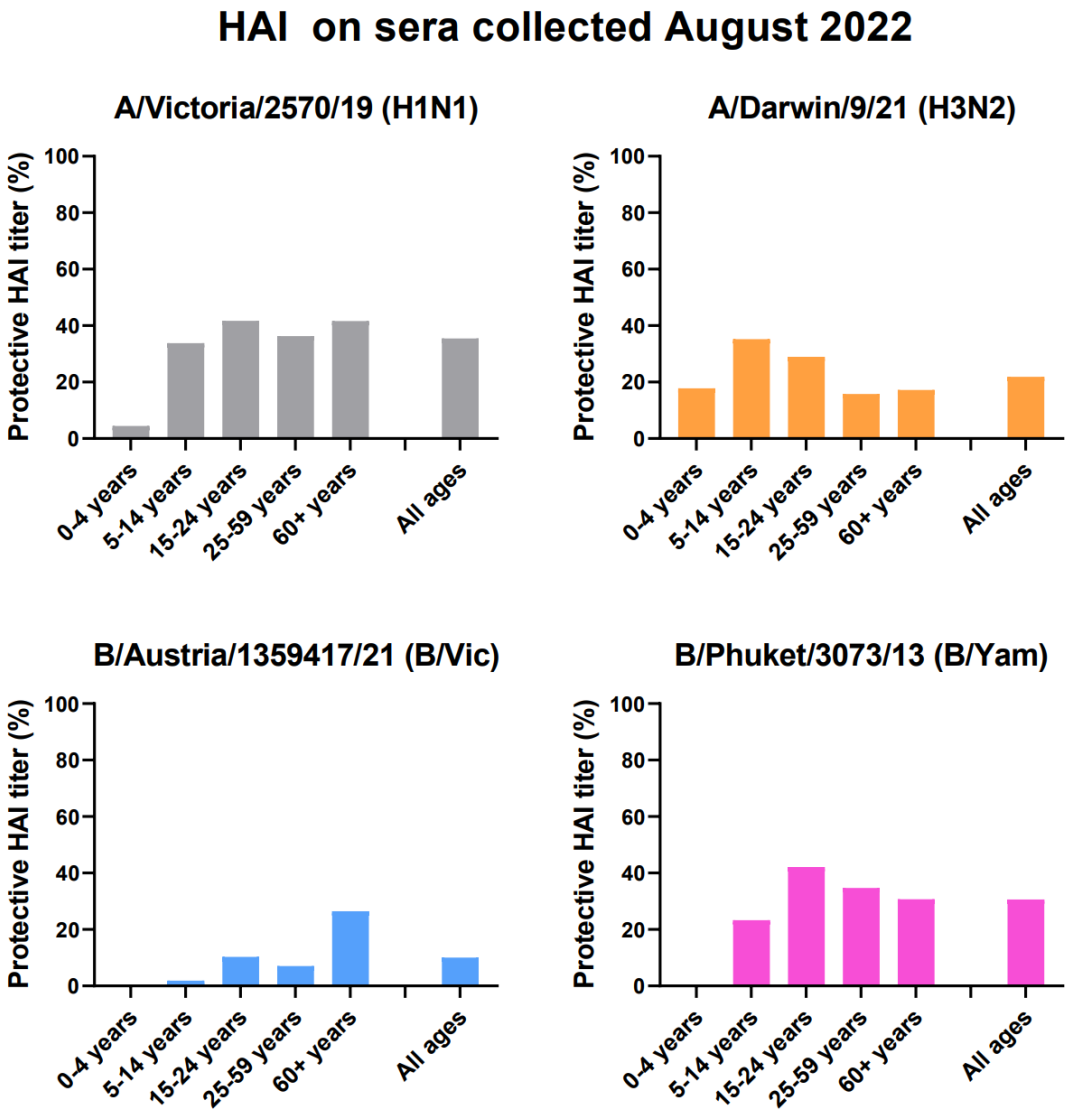


Figure 15. Seroprevalence in August 2022 against current influenza A and B strains for 'All ages' and in various age groups. HAI was performed against A/Victoria/2570/2019 (H1N1, clade 6B.1A.5a.2), A/Darwin/9/2021 (H3N2, 3C.2a1b.2a.2), B/Austria/1359417/2021 (Victoria lineage, V1A.3a.2) and B/Phuket/3073/2013 (Yamagata lineage). Protective HAI titres were defined as ≥40 for influenza A and ≥80 for ether treated influenza B.

For A/Victoria/2570/2019 (H1N1), the seroprevalence was approx. 30-40 % for all age groups, with the exception of the 0-4 age group which had a seroprevalence of 4.4 %. The A/Victoria/2570/2019 strain was included in the 2021/22 influenza vaccine for the Northern Hemisphere, which may have contributed to the seroprevalence seen in the serum samples collected in August 2022.

For A/Darwin/9/2021 (H3N2), the seroprevalence was 35 % for the age groups 5-14 years, ca. 30 % for the age group 15-24 years and just above 15 % for the remaining age groups. The higher seroprevalence seen in the younger age groups may reflect the H3N2 outbreak seen in March/April 2022. Vaccination has had a lesser contribution to H3 seroprevalence, as the A/Darwin/9/2021 strain was first included in the 2022/2023 vaccine administered after collection of sera.

The seroprevalence against contemporary B/Austria/1359417/2021 was generally low; only 10% of the serum samples had a protective HAI titre. The seroprevalence was highest in the 60+ age group (ca 25%), and very low in the youngest age groups.

For the B/Phuket/3073/2013 strain which has been included in the tetravalent influenza vaccine since the 2015/16 season, there was a ca. 30% seroprevalence in the sera from August 2022. The prevalence varied from 23% in 5–14-year age group up to 42% in the 15-24 years age group, with the exception of 0–4-year-olds for whom the seroprevalence was zero.

The 2022/2023 influenza season in Norway has up until the end of January 2023 been dominated by H1N1 virus belonging to the A/Sydney/5/2021 and A/Norway/25089/2022 lineages. Both lineages belong to the 6B.1A.5a.2 clade, which also contains the A/Victoria/2570/2019 vaccine strain. However, the A/Norway/25089/2022 lineage of viruses have acquired a several additional HA1 mutations that are thought to mediate escape from existing antibody responses, including P137S, K142R and T277A. To evaluate if sera collected in August 2022 had reduced protection against the Norway-linage of viruses, 75 sera with HAI titers of ≥160 against A/Victoria/2570/2019 were evaluated against A/Norway/25089/2022. We observed a significant reduction in HAI titers towards the Norway-lineage with geometric mean titers dropping from 187 towards A/Victoria/2570/2019 to 50 against A/Norway/25089/2022 (Fig. 16). When dividing the serum samples into different age groups there was a significant reduction in HAI titers in the older age groups (25-59 and 60+ years). There was also a reduction in HAI titer in the 5-24 years age group, but the difference was not significant.

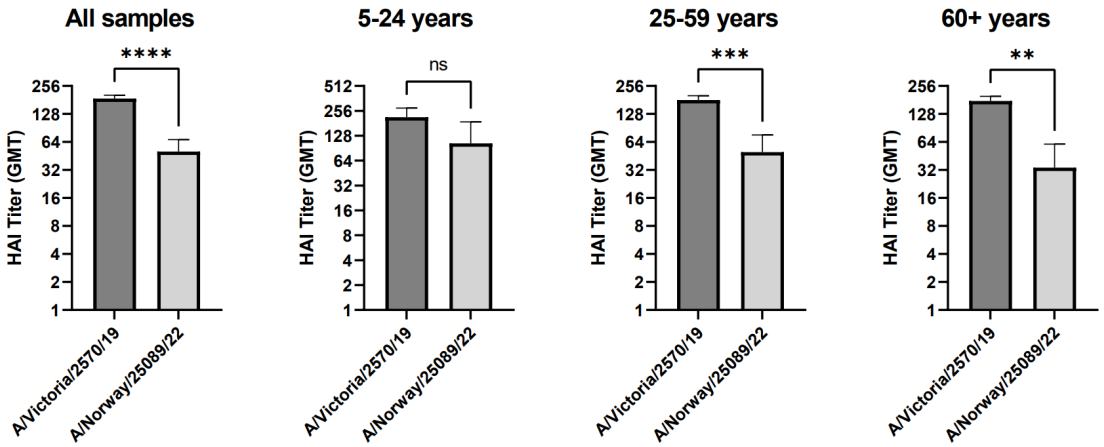


Figure 16: Reduction in HAI titre against A/Norway/25089/22, relative to A/Victoria/2570/2019. Residual serum samples from August 2022 with HAI titre of ≥160 against A/Victoria/2570/19 were evaluated in an HAI assay against A/Norway/25089/22. Data presented is geometric mean titre (GMT) with error bars representing 95% confidence interval. Significance was determined using a Wilcoxon matched-paired signed rank test, and ** = p < 0.01, ** = p<0.001 and **** = p < 0.0001.

Table 4. Influenza seroepidemiology results in August 2022 – Seroprevalence* in age groups.

For comparison data from studies performed for the preceding years 2017-2021 are also included. Due to the covid-19 pandemic, no HAI assays were performed in 2020.

	Age groups						
Influenza strains (Year$)	**0-4**	**5-14**	**15-24**	**0-24**	**25-59**	**60+**	**All ages**
H1 X-179A/A(H1N1)pdm09 (2017)	25	79	77	67	52	46	57
H1 Michigan/45/15 (2017)	26	79	79	68	50	42	56
H1 Michigan/45/15 (2018)	17	67	71	58	48	41	51
H1 Michigan/45/15 (2019)	38	68	75	64	46	41	53
H1 Brisbane/2/18 (2019)	34	62	58	54	37	32	44
H1 Victoria/2570/19 (2021)**	8	37	47	36	22	20	27
H1 Victoria/2570/19 (2022)*	***4***	***34***	***42***	***32***	***36***	***42***	***35***
H3 Hong Kong/5738/14 (2017)	28	78	59	60	30	43	45
H3 Norway/3806/16 (2017)	28	77	68	63	36	45	49
H3 Hong Kong/5738/14 (2018)	25	78	72	63	36	43	50
H3 Sing/INFIMH-16-19/2016 (2018)	19	70	54	52	23	32	38
H3 Switzerland/8060/17(2018)	25	71	47	51	29	34	40
H3 Sing/INFIMH-16-19/2016 (2019)	22	72	53	53	27	34	40
H3 Kansas/14/17 (2019)	6	15	13	12	7	8	10
H3 Cambodia/e0826360/20 (2021)	13	61	61	52	51	32	48
H3 Darwin/9/21 (2021)**	20	39	18	28	18	20	23
H3 Darwin/9/21 (2022)*	***18***	***35***	***29***	***30***	***16***	***17***	***22***
B/Vic Brisbane/60/08 (2017)	11	27	27	23	13	26	20
B/Vic Brisbane/60/08 (2018)	3	23	31	22	15	21	19
B/VicΔ2 Norway/2409/17 (2018)	1	4	15	7	18	23	14
B/Vic Brisbane/60/08 (2019)	7	24	36	24	15	25	21
B/VicΔ2 Norway/2409/17 (2019)	4	6	18	10	15	22	14
B/VicΔ3B Wash/02/19 (2019)	6	10	20	13	15	19	15
B/Wash/02/19 (Vic-Δ3B) (2021)	6	4	5	5	12	13	10
B/Cote d'Ivoire/948/20 (Vic-Δ3B) (2021)	8	3	7	6	8	23	10
B/Austria/1359417/21 (Vic-Δ3B) (2022)*	***6***	***4***	***5***	***5***	***12***	***13***	***10***
B/Yam Phuket/3073/13 (2017)**	4	28	33	25	23	19	23
B/Yam Phuket/3073/13 (2018)**	17	37	50	38	30	24	32
B/Yam Phuket/3073/13 (2019)**	17	48	46	39	36	25	35
B/Yam Phuket/3073/13 (2021)**	0	20	27	19	28	18	22
B/Yam Phuket/3073/13 (2022)*	***0***	***23***	***42***	***27***	***35***	***31***	***31***
Sera analysed (n): 2016 Aug	188	351	333	874	745	411	2028
Sera analysed (n): 2017 Aug	189	318	353	860	797	436	2093
Sera analysed (n): 2018 Aug	155	251	236	642	501	275	1418
Sera analysed (n): 2019 Aug	113	187	171	471	375	208	1054
Sera analysed (n): 2021 Aug	48	107	114	269	250	137	656
Sera analysed (n): 2022 Aug	***90***	***210***	***204***	***504***	***455***	***238***	***1197***

$Year of serum collection and HI analysis.

*All entries are per cent of sera having HI titres ≥ 40 for the A strains and ≥ 80 for the ether-treated B strains.

**(Corresponding to) components of the Northern hemisphere influenza vaccine (trivalent/quadrivalent) for the season 2022-2023.

B/Yam: B/Yamagata/16/1988 lineage; **B/Vic**: B/Victoria/2/1987 lineage

Vaccine distribution and coverage

A total of 1.64 million influenza vaccine doses have been distributed in the 2022/23 season; 1.2 million of these were distributed from the NIPH specifically intended for persons in medical risk groups and health care workers (HCW) involved in direct patient care. The number of distributed doses decreased by 9 % compared to the 2021/22 season. This is probably largely due to a withdrawal of funding for vaccination of risk groups this season, in combination with vaccine fatigue in the population and specifically among HCWs. (Figure 17).

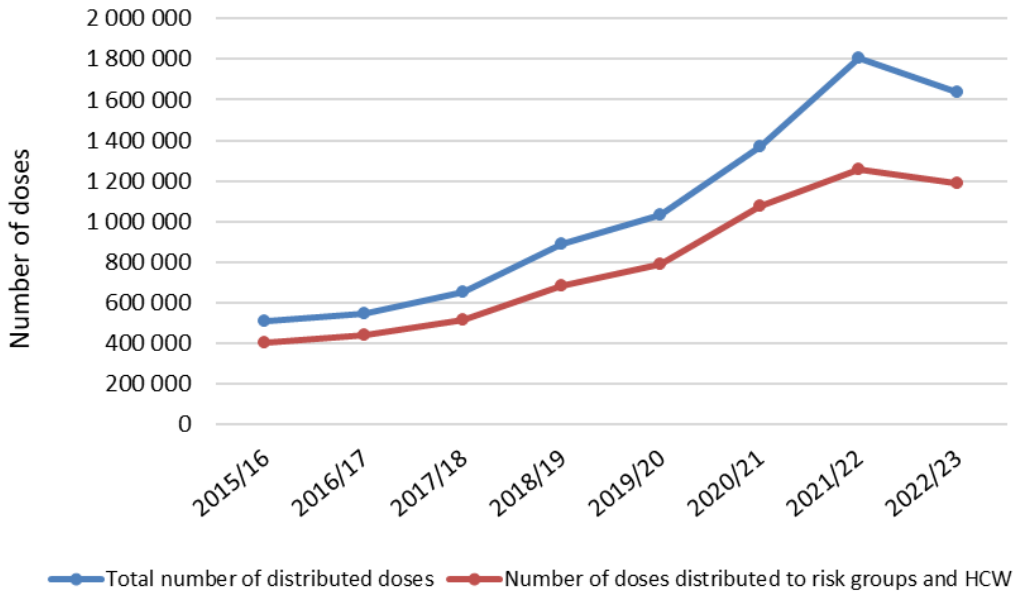


Figure 17. Influenza vaccine doses distributed in Norway, September 2015 through January 2023. HCW = Health Care Workers.

According to the Norwegian Immunization Registry SYSVAK (SYSVAK), at least 63% of the population above 65 years of age received an influenza vaccine this season (Figure 18).

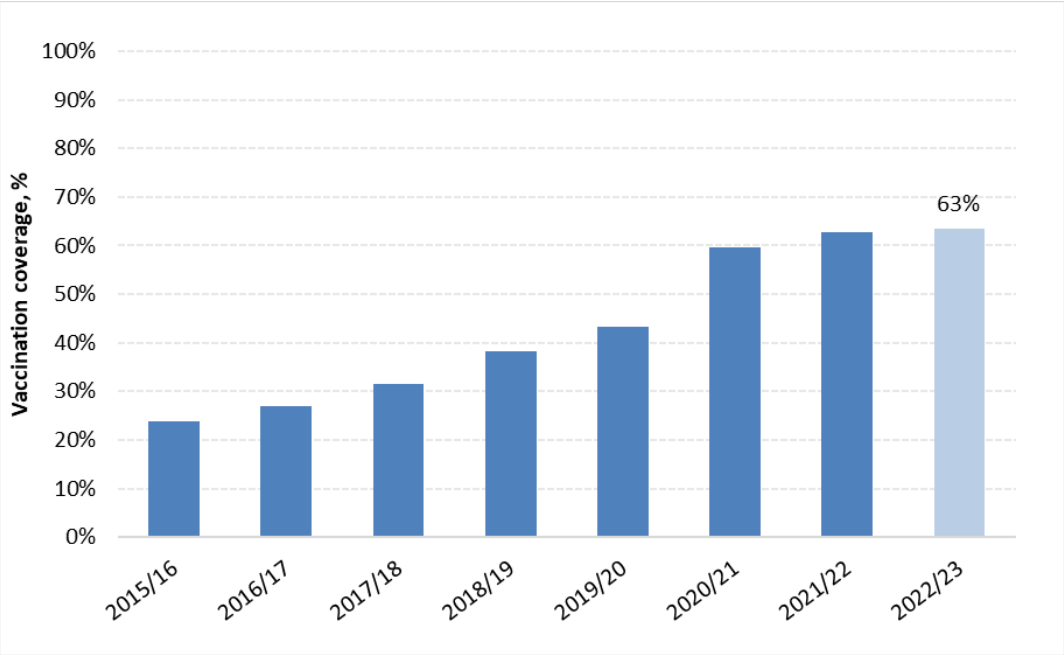


Figure 18. Vaccination coverage among residents above 65 years in Norway, 2015/16 season through to 2022/23 season as of January 2023.

According to the Emergency preparedness register for COVID-19 (Beredt C19), vaccination coverage in risk groups 18-64 years and 0-17 years per 29th of January 2023 was 34% and 7%, respectively. Vaccination coverage among HCWs was 53% in the specialist health care services (mainly hospitals) and 31% in primary healthcare. Coverage decreased in these groups compared to the previous season, from 38%, 8% 59% and 38%, respectively. Approximately 80% of the distributed doses are registered in SYSVAK, due to underreporting and technical issues. Vaccination coverage is therefore also estimated by survey data from Statistics Norway for the various risk groups and HCWs. However, these estimates will not be available until October 2023.

Animal influenza

A panzootic of highly pathogenic avian influenza (HPAI) A(H5N1) virus clade 2.3.4.4.b is ongoing in birds in Europe, Africa, Asia and the Americas. Since 2021, there have been four outbreaks of HPAIV A(H5N1) in commercial poultry flocks in Norway, of which two occurred in October-November 2022 (1). During autumn 2022 and early winter 2023, H5N1 has predominated in wild birds, and the Norwegian Veterinary Institute has reported several detections in anseriform species (swans, ducks), gulls and raptors (2). No cases have been detected in humans in Norway. The Norwegian Institute of Public Health has assessed the risk for human infection as very low (3), but increased awareness and precautionary infection control measures are recommended to prevent zoonotic infection.

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Previous **Norwegian reports prepared for the WHO vaccine consultation meeting:**

WHO-rapporter - FHI (https://www.fhi.no/sv/influensa/influensaovervaking/who-rapporter/)

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National Influenza Centre/Section of Influenza and other respiratory viruses

Section for Respiratory, Blood-borne and Sexually transmitted infections

Division for Infection Control

Norwegian Institute of Public Health,

Oslo, Norway

14 February 2023

Appendices

Description of the surveillance and monitoring components

Influenza-like illness

Norwegian ILI surveillance data is provided by Sykdomspulsen (sKUHR data). Sykdomspulsen receives data from the KUHR-system hosted by the Norwegian Directorate of Health, which daily provides anonymised data on influenza diagnosed in primary health care consultations. The information is admitted to KUHR through doctors' reimbursement claims to the health authorities. Sykdomspulsen has been receiving KUHR data since 2014 and is supported by retrospective data from the 2006-07 season and onwards.

Virological surveillance.

Sentinel virological surveillance: Historically, a network of volunteer sentinel physicians throughout the country has been collecting specimens from patients with ILI for analysis at the National Influenza Centre. It was not possible to continue this sentinel surveillance during the first two years of the COVID-19 pandemic, because community respiratory illness testing was redirected away from primary care practices to dedicated SARS-CoV-2 testing infrastructures. However, with the return of patients to general practices the sentinel system was reactivated and strengthened by including more GPs and engaging sentinel laboratories for some of the primary testing. At the same time, the scope of the surveillance was expanded to comprise several non-influenza respiratory viruses and the testing case definition expanded from ILI to ARI. For sentinel specimens first tested in another laboratory, all data and all influenza/SARS-CoV-2 positive specimens are sent to the NIC.

Comprehensive virus surveillance: In addition, medical microbiology laboratories that perform influenza diagnostics report testing data. Since 2020, all testing outcomes are reported in real-time to the national MSIS laboratory database. Surveillance statistics for laboratory confirmed influenza have been harvested from this database. These laboratories also contribute influenza positive specimens to the NIC for further characterisation. Even though most of these laboratories are affiliated to hospitals, a large proportion of specimens tested for influenza virus are from outpatients visiting general practitioners, and, during the COVID-19 pandemic, SARS-CoV-2 testing stations.

Virus characterisation: As many as possible of influenza virus positive sentinel specimens, and a selection of positive specimens from the comprehensive surveillance are subjected to whole genome sequencing (WGS). Viruses are then selected for shipment to a WHO Collaborating Centre and/or isolated in the NIC, in order to ensure that all significant genetic variants are characterised antigenically. Viruses are also analysed with respect to antiviral resistance and other characteristics.

All the virological surveillance data are shared internationally with ECDC and WHO Global Influenza Surveillance and Response System (GISRS).

Registry-based surveillance of influenza hospitalisations

In 2020-2021, a temporary registry-based system for surveillance of influenza hospitalisations was established in order to strengthen the influenza surveillance during the COVID-19 pandemic. In the beginning, individual-level data originating from the Norwegian Patient

Registry (NPR) was used. Influenza hospitalisations were defined as inpatient hospital admissions combined with ICD-10 codes for influenza (J09-J11). To enhance the specificity of the registry-based surveillance, the data on hospital discharge codes from NPR is now linked to data on PCR tests positive for influenza, which is obtained from the Norwegian Surveillance System for Communicable Diseases (MSIS) laboratory database. Case-based data on PCR-positive influenza tests is available from season 2020-2021 onward. A hospital admission with influenza is defined as an overnight stay where the patient tested positive for influenza with a PCR test within 14 days before or up to 2 days after hospital admission, and where an ICD-10 code for influenza was registered, or where the patient hasn't received any diagnosis code yet. The inclusion of influenza-positive patients without any diagnosis codes yet increases the timeliness of the data, but it means also that the numbers presented in this report may change as data become more complete.

Influenza patients in intensive care units

In the 2016-17 and 2017-18 seasons, the Norwegian Intensive Care Registry (NICR) and NIPH carried out a pilot study to see whether national surveillance of influenza patients in intensive care units is feasible. As part of the pilot, NICR asked all ICUs from week 46/2017 to report weekly numbers of patients in ICUs with laboratory-confirmed influenza, the number of patients in ICUs with clinically suspected influenza and the number of deaths among patients with confirmed or suspected influenza admitted to ICUs. Almost all ICUs in Norway reported data to NICR. Since the 2018-19 season, an electronic form has been used. Up to the 2020-2021 season, only anonymised data were reported from NICR to the NIPH. In the season 2021-2022 the NIPH has begun to receive case-based data on a weekly basis.

Influenza-associated deaths

Influenza-associated deaths were based on data from the Norwegian Cause of Death Registry, and were defined as deaths where J09, J10 or J11 (ICD-10) were recorded as an underlying or contributing cause of death on the death certificate.

Influenza seroepidemiology

The National Influenza Seroepidemiology Programme annually in August solicits about 2000 serum samples collected during the weeks 31-35 from clinical/microbiological laboratories covering the 19 counties of Norway. These anonymised convenience sera are aimed to be representative of the Norwegian population geographically and by age composition. In normal times these sera are tested by the haemagglutination-inhibition (HI) test to determine the antibody immunity to relevant circulating influenza viruses. However, due to capacity limitations imposed by the response to COVID-19 and subsequent austerity measures, the sera collected in 2020 were only tested for antibody against SARS-CoV-2 and not against influenza, and only a subset of the 2021 and 2022 collections was tested against influenza.

Vaccine distribution and coverage

Distribution data are reported by Department of Infection Control and Vaccine at NIPH and by IQVIA Solutions (distribution from other wholesalers). Vaccination coverage data are from the Norwegian immunisation registry SYSVAK. This electronic immunisation registry supplies national coverage estimates based on every individual's vaccination status. It is mandatory to register all influenza vaccinations. However, in recent years the rate of registration has been

around 75-80 % of the doses distributed (adjusted for the number of discarded doses). Coverage estimates from SYSVAK are therefore considered minimum estimates.

For individuals under 65 years of age, information on vaccination status is cross-referenced with information on medical risk for severe influenza from the emergency preparedness register for COVID-19 (Beredt C19) in order to produce coverage estimates for younger individuals in the risk groups. Coverage estimates for HCWs are also captured from Beredt C19. Beredt C19 includes information that has already been collected in the healthcare services, national health registries and medical quality registers, as well as other administrative registers with information about the Norwegian population.

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