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IInfluenza Virological and Epidemiological Information prepared for the WHO Consultation on the Composition of Influenza Virus Vaccines for the Southern Hemisphere 2021

Geneva, September 2020

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Division of Infection Control and Environmental Health;

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Influenza Virological and Epidemiological Information prepared for the WHO Consultation on the Composition of Influenza Virus Vaccines for the Southern Hemisphere 2021

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Content

The 2019-2020 influenza season, Norway

Summary

- Pre-season seroepidemiology data from August 2019 indicated that immunity in Norway against circulating influenza A(H1N1) was quite strong, with considerable immunity also against clade 3C.2a A(H3N2) viruses but with much poorer antibody levels against clade 3C.3a viruses. There was also some immunity against currently circulating B/Yamagata lineage viruses, but much less against B/Victoria-lineage viruses.
- Added to this came the immunity due to the subsequent influenza vaccination campaign in the autumn. Vaccination rates were raised compared to the 2018/19 season.
- The seasonal influenza outbreak began in week 52. It peaked in week 8, and never exceeded low intensity level. The COVID-19 epidemic resulted in an abnormal increase in health care seeking for respiratory symptoms, resulting in a new ILI peak in week 11, exceeding the influenza peak seen in week 8.
- The number of hospitalisations was at a low level comparable to the five preceding seasons. Overall, the highest hospitalisation rates were found in the elderly (60 years or older) and young children (0-4 years). The same pattern was seen for influenza A, but for influenza B the highest hospitalisation rates were found in children (0-4 and 5-14 years).
- The number of influenza patients treated in ICU was also low compared with the three previous seasons.
- Excess all-cause mortality mainly remained within expected levels.
- There was no clearly predominant virus. Influenza A(H3N2) virus was the most numerous, constituting approximately 50% of detections. Second-most numerous was influenza B of the Victoria lineage, making up 28%, followed by influenza A(H1N1) (19%) and with only 4% of the B/Yamagata lineage.
- The majority of the A(H3N2) viruses belonged to the 3C.2a1b subgroup of viruses, carrying the T131K substitution in HA1 and more similar to the vaccine candidate for the Southern hemisphere than the Northern.
- Most of the recent H3 viruses have been in the Q197R+K207R 3C2a.1b group
- The majority of the H1 viruses fell in the 6B.1A A/Norway/3433/2018 6B.1A5A subgroup of viruses.
- All the characterised influenza B-Victoria viruses were triple-deletion variants similar to B/Washington/02/2019. The B-Yamagata viruses characterised were all clade 3 viruses with very few amino acid differences.

A look back at the preceding 2018/2019 season

The 2018/19 influenza outbreak began in week 52. It reached medium intensity in week 6, a level at which it remained for three weeks. The outbreak peaked in week 7, lasted 13 weeks and ended by week 13. Measured by consultations for ILI, the outbreak of 2018/19 was of lesser magnitude than average.

Influenza A(H1N1) virus predominated, constituting approximately 60% of detections. The remainder was mainly A(H3N2) virus, with unusually few (1%) influenza B viruses. Nevertheless, among the elderly, A(H3N2) infection was more likely than A(H1N1).

Among the few influenza B viruses, the B/Victoria-lineage was slightly more frequent than the B/Yamagata-lineage. Only B/Victoria-lineage viruses were observed from week 23 and onwards. The majority of the H1N1 viruses were characterised as subclade 6B.1A5 viruses, but during the summer months a new subgroup under 6B.1A5 emerged possessing a number of substitutions in HA (K130N;K160M;T216K;E235D;H296N and V321I).

A number of different subgroups of H3N2 viruses circulated, but the main group was subclade 3C.2a1b. During the summer, viruses in this group carrying the Q197R together with K207R became more prominent.

All influenza B/Yamagata-lineage viruses were HA clade 3, and most of them closely resembled B/Phuket/3073/2013. Two of them, however, carried a large number of amino acid substitutions in both HA and NA.

Among the B/Victoria-lineage viruses, the “African” triple deletion variant (clade 1A(Δ3)B) was the most prevalent.

In 2018/19, there was a lower level of hospitalisations and fewer influenza patients requiring intensive care unit (ICU) admission when compared to the two preceding seasons. There were also few weeks with excess all-cause mortality in the population. The highest influenza-associated hospitalisation rates were found in the elderly (60 years or older) and in young children (0-4 years). Fewer elderly people were hospitalised. However, in young children, the hospitalisation rate was relatively high.

The 2019/20 season

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

Influenza-like illness (ILI) in primary health care

The proportion of influenza-like illness (ILI) exceeded the epidemic threshold (as defined by national, present-season MEM-levels) in week 52. There was a small peak in the proportion of ILI in week 1. After a trough in week 3, the activity increased again the following week. The outbreak peaked in week 8, never exceeding low intensity level. Measured by number of consultations for ILI, the outbreak appeared to be even milder than the previous season's outbreak, which was below average. However, the COVID-19 epidemic resulted in an abnormal increase in the seeking of healthcare for respiratory symptoms after week 9 in spite of decreasing incidence of influenza and other respiratory viruses. This resulted in a new peak in week 11 which exceeded the influenza peak seen in week 8.

Video consultations have been scarce in the past, but became numerous in week 11 and outnumbered consultations by physical attendance in week 12. For this reason, video consultations have now been included in the ILI graphs (Figure 1 and 2), but alas not in the data basis for calculation of MEM thresholds. This might add inaccuracy, in addition to the fact that the recorded ILI cases from the latter part of the outbreak to a larger degree than usual represent other things than influenza. With these biases in mind, the ILI outbreak ended in week 14 and lasted for 14 weeks, two weeks longer than average.

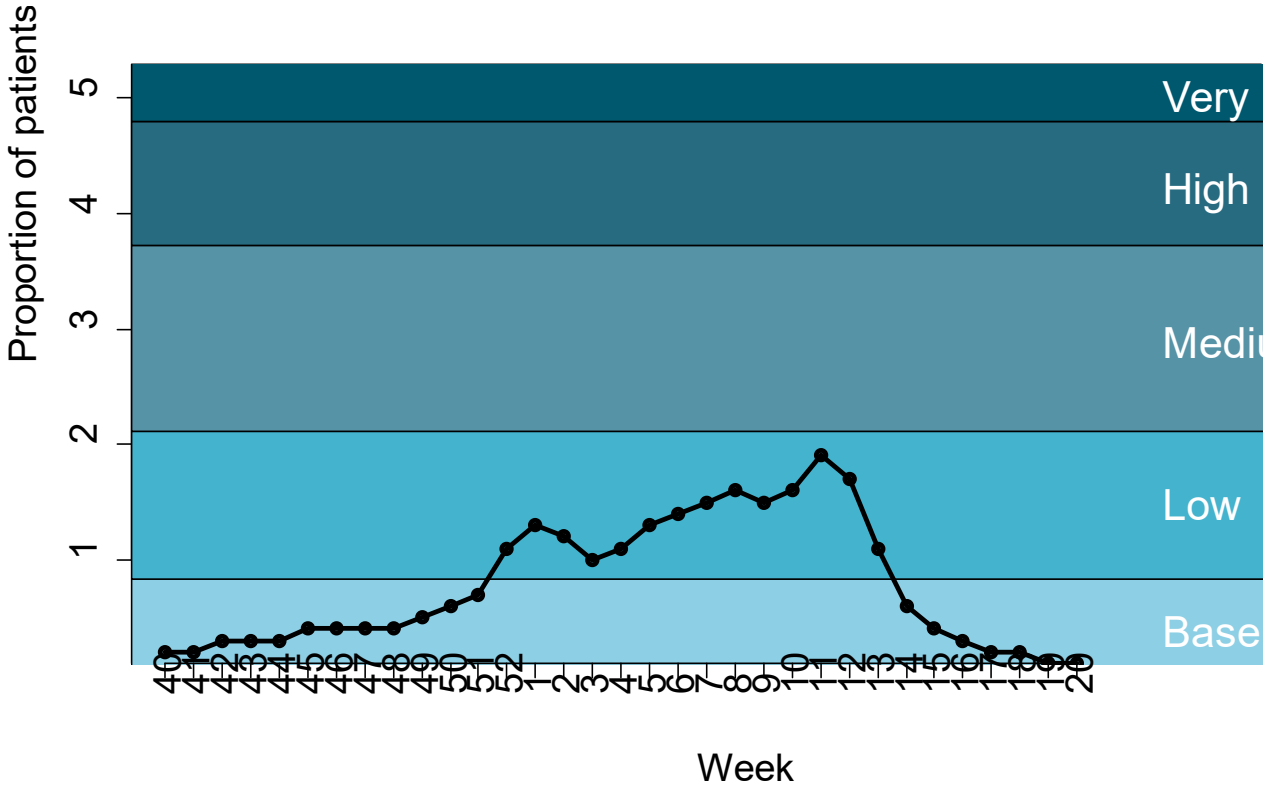


Figure 1: Level of influenza intensity depicted as weekly proportion of consultations in general practice and emergency clinics diagnosed with ILI, Norway 2019-2020 season. Please note that the proportions include consultations by video, whereas these data are not included in the data basis for calculation of MEM thresholds.

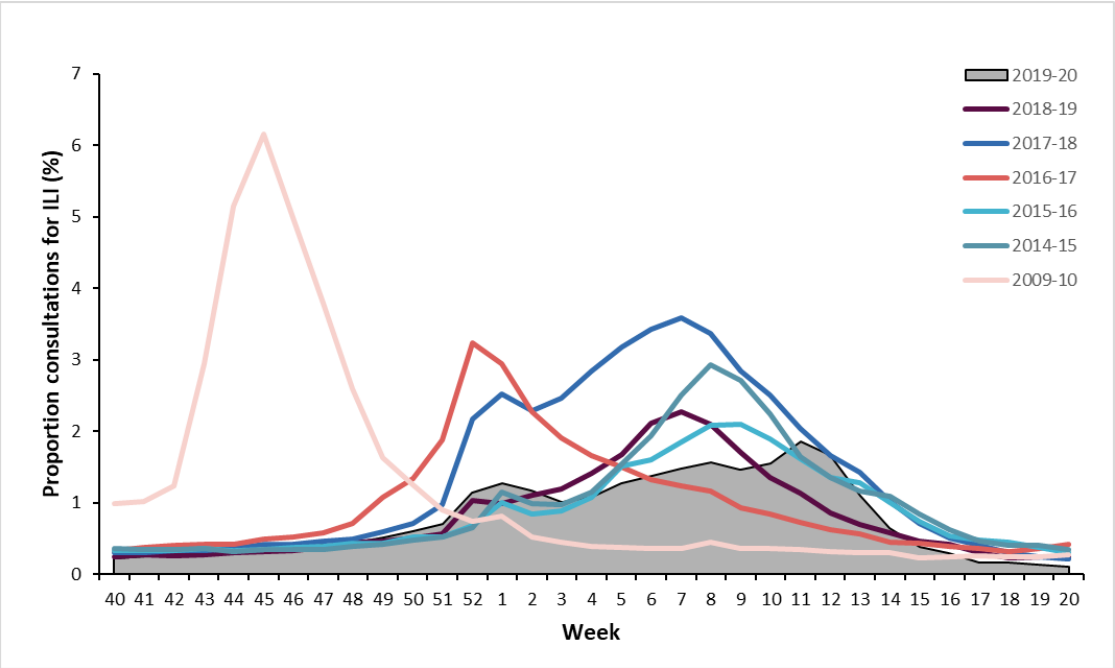


Figure 2: Weekly incidence of ILI, Norway 2019-2020 season (grey). The graph shows the proportion of patients in general practice and emergency clinics presenting with ILI, by calendar week. The five previous seasons are also shown.

Severe influenza: laboratory confirmed hospitalised cases

The number of laboratory-confirmed influenza cases among hospitalised patients began to increase in week 46, reached a temporary peak in week 1 and started to increase again from week 4 to a peak in week 8 (Figure 3). A large drop in the number of cases was seen from week 11 to week 12, and almost no influenza hospitalisations were reported after week 14, despite continued testing activity. This was probably caused by decreased influenza activity due to infection control measures against SARS-CoV-2. Changes in reporting activity may also have contributed to this observation. A total number of 3 000 influenza-associated hospitalisations was estimated for the 2019/20 season in Norway, which is lower than average. The cumulative number of hospitalised patients per 100 000 population was at a low level compared to the five previous seasons (Figure 4). In total for the season, 78% of the detections in hospitalised patients was influenza A and 22% was influenza B. The highest weekly and cumulative incidence rates were found in the elderly (60 years or older) and in young children (0-4 years) (Figure 5). For influenza A, the hospitalisation rate was highest among the elderly and young children. Whereas for influenza B, the hospitalisation rate was highest among children (age groups 0-4 and 5-14 years).

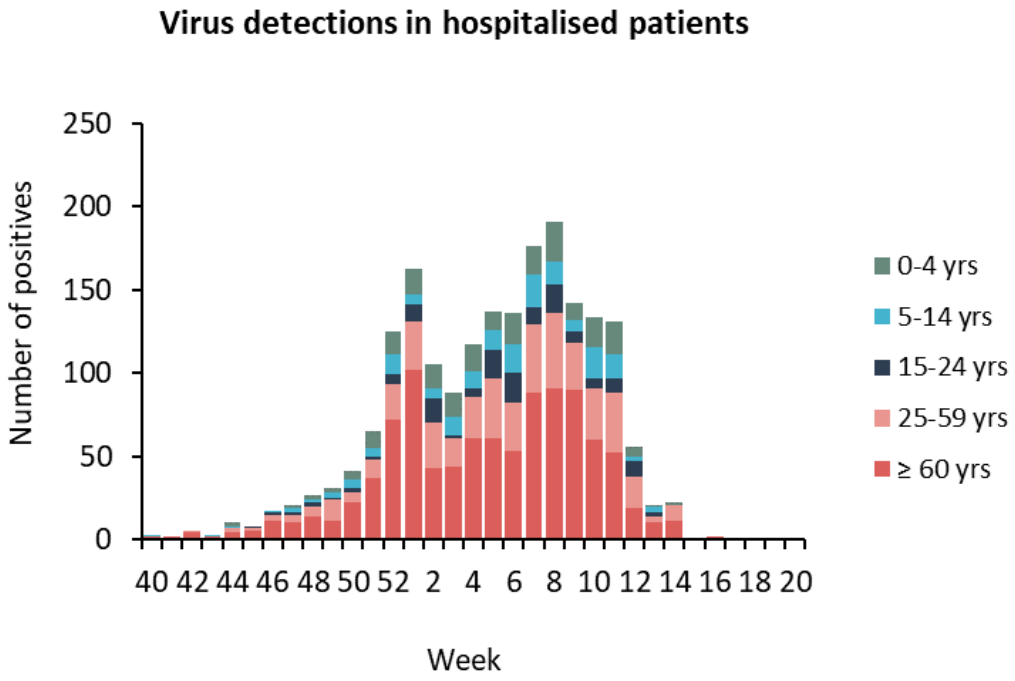


Figure 3: Virus detections in hospitalised patients during the 2019/2020 influenza season, stratified on age groups, based on reports from nine sentinel medical microbiology laboratories.

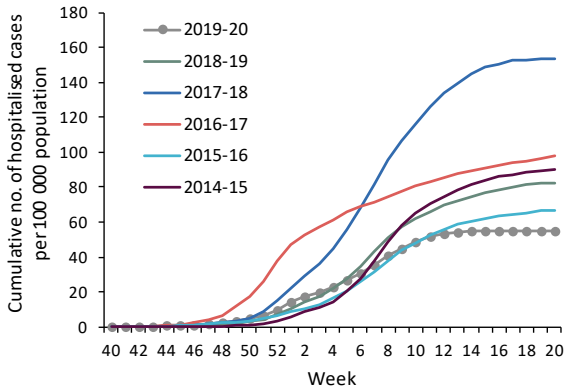


Figure 4: Estimated cumulative incidence of hospitalised patients with confirmed influenza per week compared to the previous five influenza seasons.

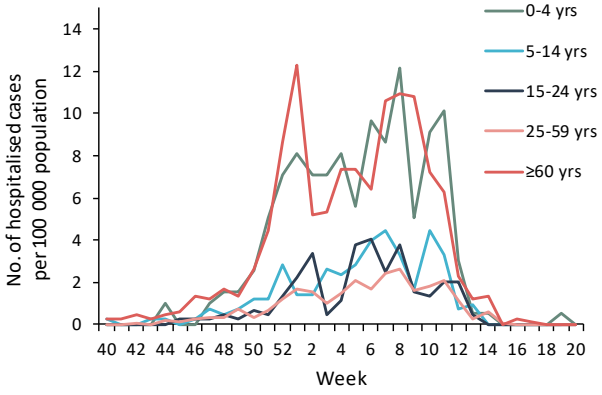


Figure 5: The estimated incidence rate of hospitalised patients per week stratified on age groups, during the 2019/2020 influenza season. The estimation is based on reports from nine sentinel medical microbiology laboratories.

Influenza patients in intensive care units

The number of patients with laboratory-confirmed influenza admitted to ICUs (n =88) was considerably lower than in the previous three seasons (Figure 6), with no confirmed cases after week 12.

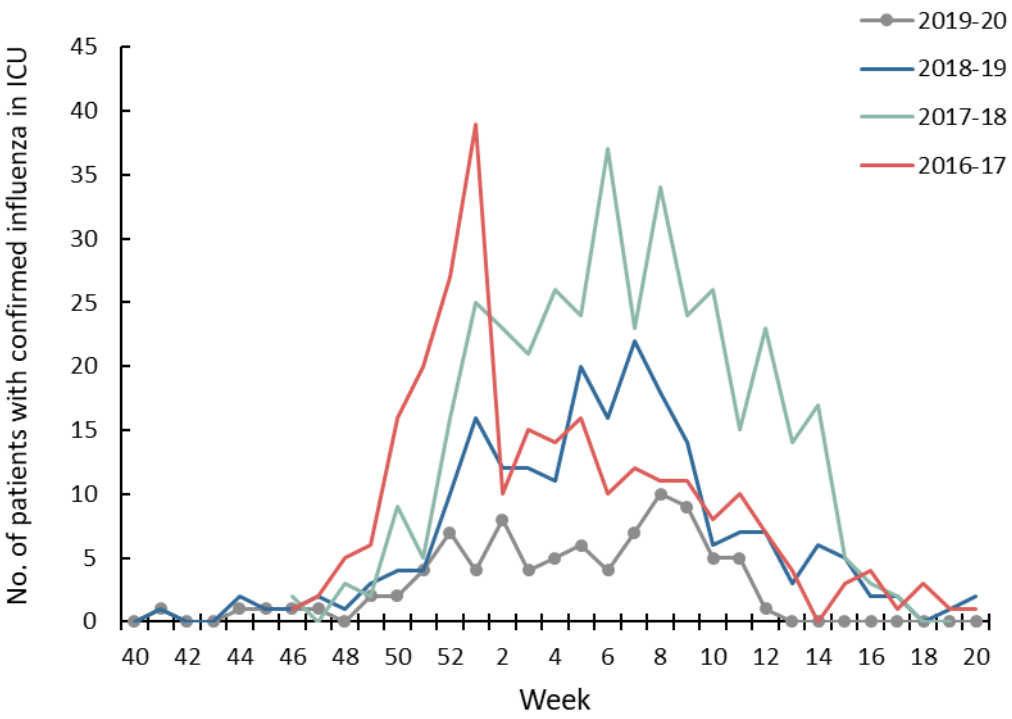


Figure 6. The number of patients admitted to intensive care units (ICUs) with laboratory-confirmed influenza per week during the current and previous three influenza seasons in Norway. Data source: The Norwegian Intensive Care Registry (NICR).

Excess all-cause mortality

From week 40 2019 to week 20 2020, the all-cause mortality was mainly within expected levels. There were a few exceptions. A low level of excess all-cause mortality was estimated for week 2, in total for Norway, and for older adults (65 years and older). In addition, there was also a slightly higher number of deaths than expected in children (5 to 14 years) in week 1. In week 20, there were fewer deaths than expected. Influenza-attributable mortality has not yet been estimated for the 2019/2020 season.

Laboratory confirmed influenza: Virological surveillance

Altogether, 251,505 patients in Norway were tested for influenza during weeks 40/2019-35/2020, resulting in 9,705 detections of influenza A and 6,205 detections of influenza B (Table 1). There was a gradual increase in the detections of influenza viruses from the beginning of October, with a more marked increase in weeks 50 – 52/2019. As in many previous seasons, there was some stagnation during the first weeks of January, after which the increase resumed in week 4/2019 and peaked in weeks 7-8. There was a quite steep decline in detections after the peak, particularly from the time when distancing measures were introduced to limit the spread of COVID-19 in mid-March (Figure 7). Since many laboratories included SARS-CoV-2 testing in their respiratory virus package, many specimens tested for the novel coronavirus were also tested for influenza. Thus the drop in detections was not due to reduced testing.

From that point, the emergence of COVID-19 has substantially influenced both testing practices, the utilisation of health services, as well as behaviour including social distancing in the population.

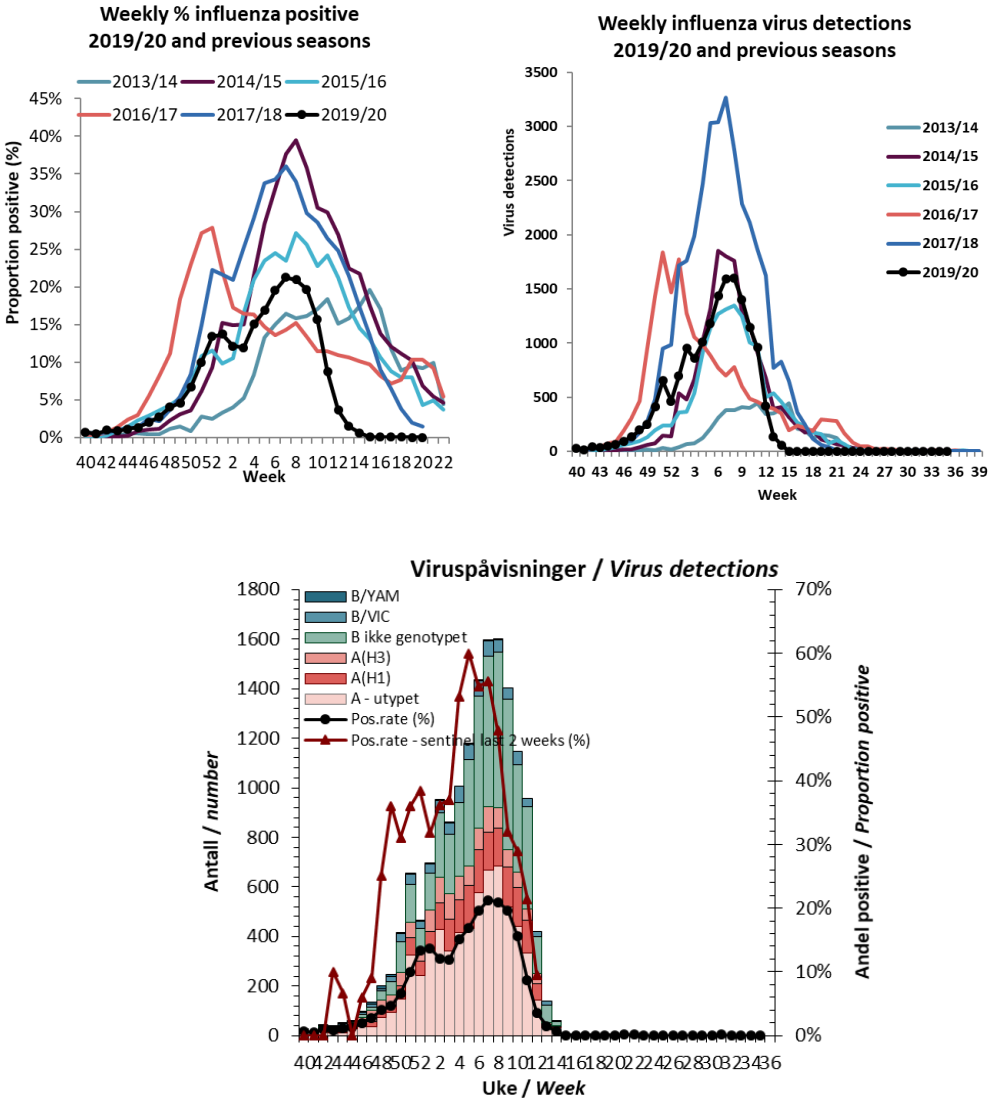


Figure 7: Laboratory detections, Norway 2019-2020. Upper left-hand panel: Weekly proportion of influenza virus positive specimens, with previous season proportions shown for comparison. Upper right-hand panel: Weekly number of influenza virus detections, with previous season numbers shown for comparison. Lower panel: Weekly number of the different influenza viruses is displayed as stacked bars, while influenza virus positivity rates of sentinel specimens (2-wk average) and all lab testing, respectively, are shown as line graphs.

The proportions of the different influenza viruses in the all-laboratories data and from the sentinel specimens are in good agreement (Figure 8).

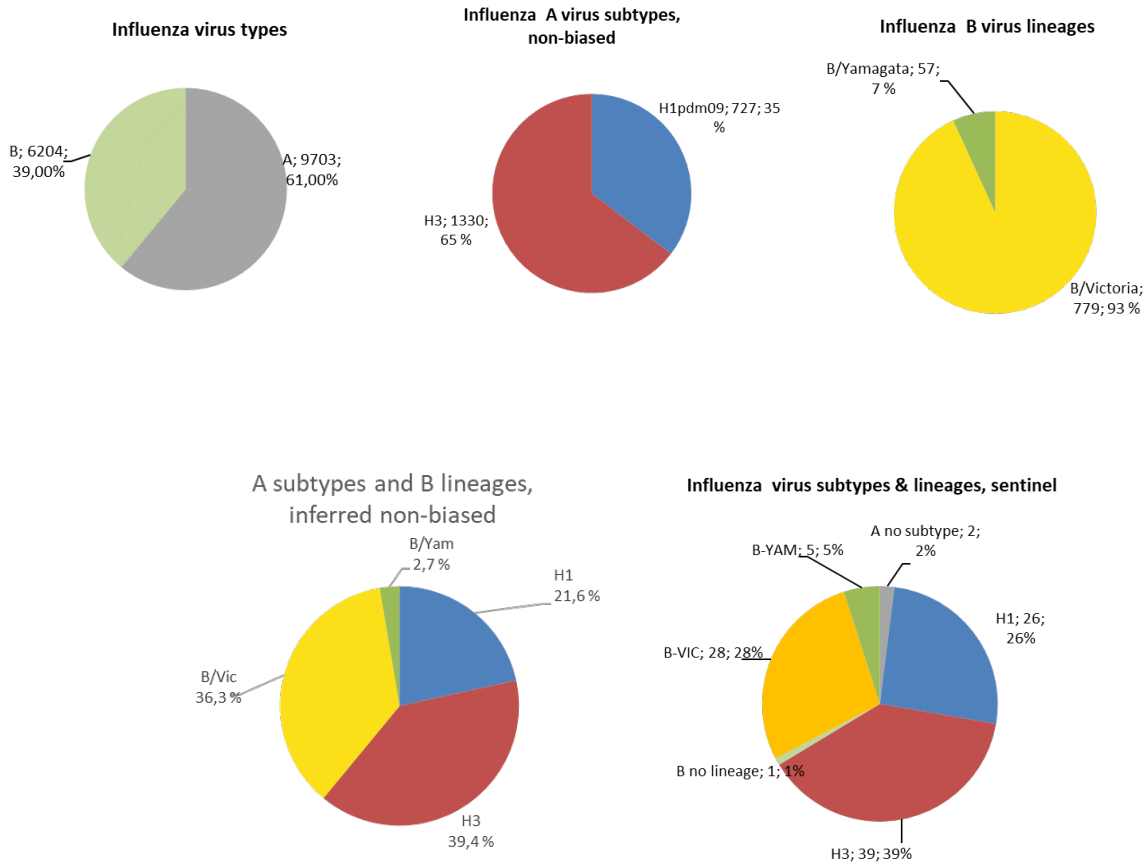


Figure 8. Proportions of 2019/20 season influenza virus subtypes and lineages among viruses analysed in Norway, by week 35, 2020. All-laboratories proportions of A/B type, A subtypes and B lineages are shown in the first three upper diagrams. The subtype and lineage frequencies are superimposed on type distributions in the lower left panel, for comparison with the distribution among sentinel specimen data (lower right panel).

To limit the subtype testing bias in the all-laboratories data (nearly three times more viruses have been tested for H1 than for H3), only H1 positives that have also been tested for H3 are counted in the top-middle diagram. The sentinel data are not subtype biased in this way but the numbers are smaller.

Among the influenza A viruses, subtype A(H3N2) predominance over A(H1N1) was maintained through the season (Figure 9). Among influenza B viruses, the B/Victoria/2/87 lineage was predominating over B/Yamagata/16/88 lineage viruses, except in weeks 46-48 when an early local outbreak with B/Yamagata-lineage viruses lifted the B/Yamagata proportion to levels even with B/Victoria.

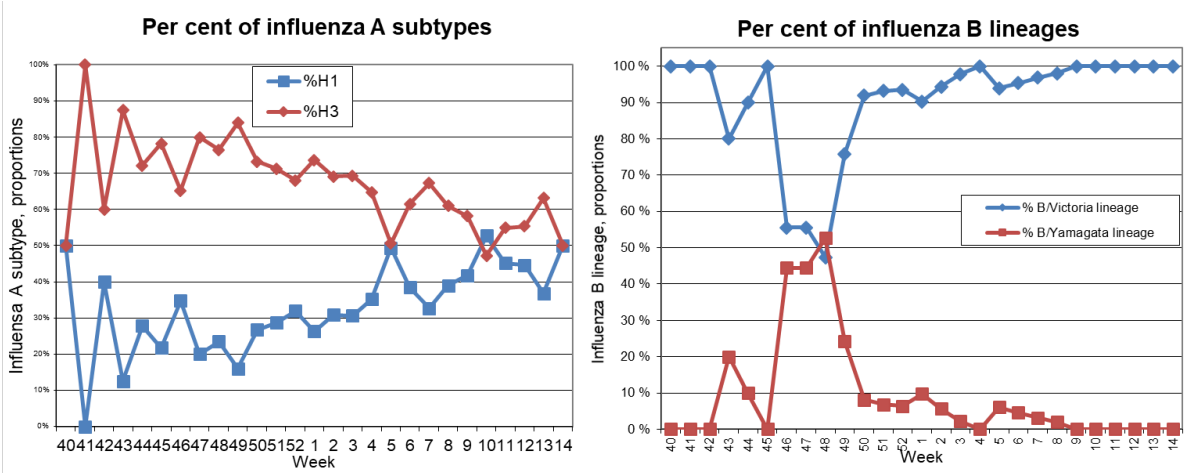


Figure 9. Weekly proportions of influenza A subtypes (left panel), among influenza A viruses that have been tested for both H1 and H3; and influenza B lineages. Proportions after week 14 are not displayed, due to very low number of viruses analysed.

Table 1: Weekly incidence of influenza-like illness (ILI), total number of specimens tested for influenza, proportion of specimens positive for influenza virus, and influenza virus detections per type/subtype/lineage (sentinel plus non-sentinel), in Norway from week 40/2019 through week 35/2020.

week	Clinical surveillance % ILI	*Virus detections*								
		Specimens	% positive	A *not subtyped*	A(H1) pdm09	A(H1) pdm09*	A(H3)	B *not lineage typed*	B/Victoria lineage	B/Yamagata lineage
40	0,22 %	3670	0,7 %	10	6	1	1	6	3	0
41	0,24 %	3837	0,5 %	10	0	0	5	2	1	0
42	0,29 %	4154	1,0 %	13	10	6	9	6	3	0
43	0,30 %	4230	0,9 %	10	6	2	14	3	4	1
44	0,32 %	4250	1,1 %	11	6	5	13	8	9	1
45	0,35 %	4659	1,3 %	26	8	5	18	5	5	0
46	0,38 %	4758	2,0 %	36	20	8	15	16	5	4
47	0,42 %	4765	2,8 %	34	22	11	44	15	10	8
48	0,44 %	4950	4,0 %	73	29	12	39	39	9	10
49	0,52 %	5354	4,6 %	93	27	8	42	56	22	7
50	0,60 %	6221	6,7 %	148	53	19	52	125	34	3
51	0,71 %	6553	10,0 %	326	67	25	62	155	41	3
52	1,14 %	3461	13,4 %	241	57	23	49	86	29	2
1	1,27 %	5059	13,7 %	340	81	31	87	146	37	4
2	1,17 %	7838	12,1 %	430	106	45	101	261	50	3
3	1,01 %	7187	11,9 %	341	127	46	104	240	45	1
4	1,08 %	6695	15,1 %	414	135	50	92	301	66	0
5	1,27 %	6988	16,9 %	432	174	77	79	429	62	4
6	1,38 %	7338	19,6 %	576	176	53	85	533	62	3
7	1,48 %	7493	21,3 %	666	156	50	103	606	62	2
8	1,57 %	7638	20,9 %	686	151	53	83	628	50	1
9	1,46 %	7124	19,7 %	518	161	51	71	606	47	0
10	1,55 %	7315	15,7 %	439	160	66	59	436	52	0
11	1,85 %	10942	8,8 %	335	131	37	45	412	35	0
12	1,66 %	11569	3,6 %	142	68	33	41	148	19	0
13	1,10 %	9383	1,5 %	30	12	7	12	70	15	0
14	0,65 %	9108	0,64 %	30	5	3	3	19	1	0
15	0,38 %	6591	0,06 %	1	0	0	0	2	1	0
16	0,30 %	7564	0,05 %	2	0	0	1	1	0	0
17	0,17 %	7629	0,05 %	2	0	0	0	2	0	0
18	0,16 %	6902	0,06 %	2	0	0	0	2	0	0
19	0,13 %	6589	0,03 %	1	0	0	0	1	0	0
20	0,11 %	5349	0,02 %	0	0	0	0	1	0	0
21		3965	0,08 %	1	0	0	0	2	0	0
22		3842	0,08 %	2	0	0	1	0	0	0
23		3122	0,00 %	0	0	0	0	0	0	0
24		2897	0,00 %	0	0	0	0	0	0	0
25		2274	0,00 %	0	0	0	0	0	0	0
26		2407	0,00 %	0	0	0	0	0	0	0
27		2540	0,00 %	0	0	0	0	0	0	0
28		2335	0,00 %	0	0	0	0	0	0	0
29		2112	0,00 %	0	0	0	0	0	0	0
30		1945	0,00 %	0	0	0	0	0	0	0
31		2371	0,04 %	0	0	0	0	1	0	0
32		2378	0,00 %	0	0	0	0	0	0	0
33		2129	0,00 %	0	0	0	0	0	0	0
34		1988	0,00 %	0	0	0	0	0	0	0
35		2037	0,00 %	0	0	0	0	0	0	0
Total	Total			6421	1954	727	1330	5369	779	57
week	% ILI	*Specimens*	% positive	A *not subtyped*	A(H1) pdm09	A(H1) pdm09*	A(H3)	B *not lineage typed*	B/Victoria lineage	B/Yamagata lineage
			Type A:	9705			Type B: 6204			

Age distribution of the different viruses

Age profiles for the different subtypes and lineages generally indicate that the age patterns this season (Figure 10) do not differ from recent seasons (1). Infants are strongly represented among cases with A(H1N1) infection, and persons 60 years and older are strongly represented among cases with A(H3N2) infection, together with infants. Children below 15 are the ones most affected by B/Victoria-lineage viruses. For B/Yamagata-lineage viruses, there is less data. The pattern from previous seasons, indicating that the elderly are the group most affected by this virus, is less apparent now, but this should be interpreted with caution.

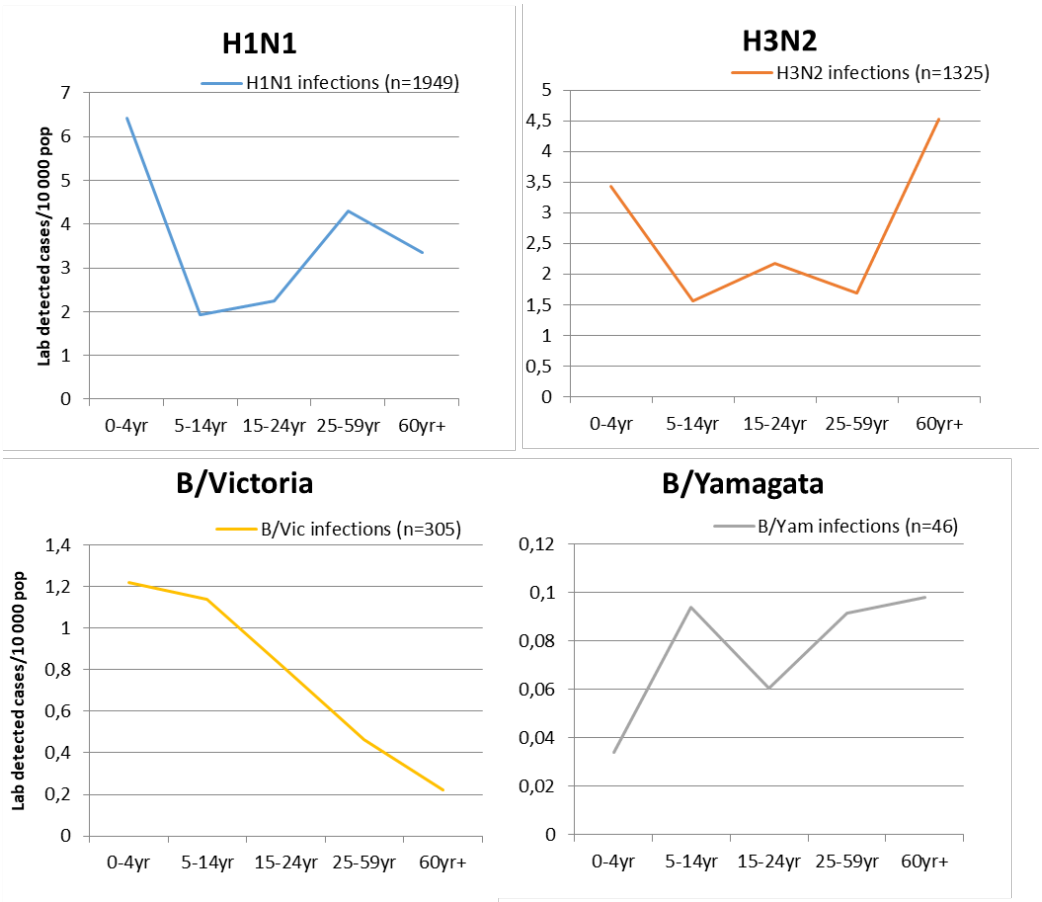


Figure 10. Cumulative incidence per 10 000 population of subtype/lineage detections by age group, based on viruses subtyped in Norwegian laboratories in the 2019/20 influenza season. Since the number of viruses subjected to type, subtype and variant testing differs widely, the incidences are comparable between age groups in the same panel, but incidences are not comparable between the panels.

Genetic characterisation of the viruses in circulation

From week 40/2019 to week 35/2020, the influenza laboratory received 2258 influenza positive samples for further analysis (14.2% of all positives in Norway). 13.3% (301) of these were further characterised to look at genetic markers for genetic drift and virulence. 9.3% (209) of the positive samples were tested for antiviral resistance either genetically (103) or by neuraminidase inhibitor susceptibility (106). 140 viruses were shipped to the WHO Collaborative Centre in London (Francis Crick Institute) for further analysis (making up 6% of all positive samples received at NIPH). In addition, 248 HA gene sequences were published in the GISAID (Global Initiative on Sharing All Influenza Data) sequence database (constituting 11% of all positive samples at NIPH).

H3N2

Although some viruses of the 3C.3a northern vaccine candidate group of viruses were seen in the middle of the outbreak, the most prevalent influenza H3N2 viruses this season in Norway have been the 3C.2a1b genetic group, A/South Australia/34/2019-like viruses, with the T131K substitution, more similar to the vaccine candidate for the Southern hemisphere. This group of viruses can be divided in three based on key amino acid differences. The H3N2 3C.2a1b viruses appearing in Norway during the summer months of 2019, possessing Q197R and K207R in HA slightly outnumbered the 3C.2a1b Clade A/Oman/4262/2019 group of viruses possessing Y94N and some also with Y94S, and with F193S. Most of the recent H3 viruses have been in the Q197R+K207R 3C2a.1b group (Figure 11) but with one additional I214T substitution.

The A/Hong Kong/2875/2019-like viruses possessing the S137F substitution caused a small local outbreak in the southern part of Norway early in the season. Some very few viruses in the 3C.2a1b+T135K- group have also possessed the substitution G186D. We did see a somewhat higher proportion of hospitalised patients infected with the 3C.3a viruses than other subgroups of H3N2 viruses (not shown).

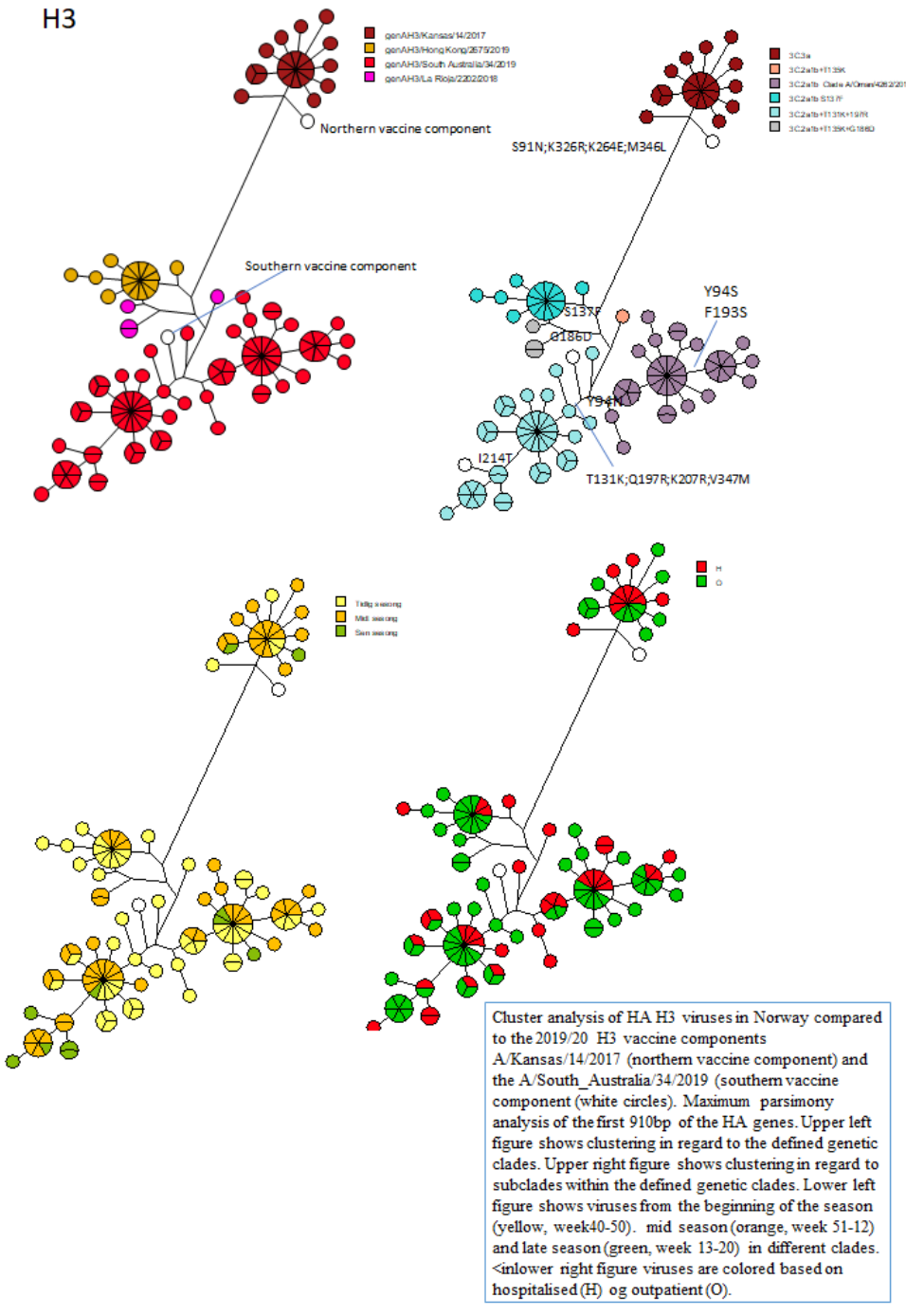


Figure 11. Cluster analysis of the HA gene of influenza A(H3N2) viruses, season 2019/20 in Norway, up to week 35 2020.

H1N1

The analysed HA sequences of the H1N1 viruses were all characterised as clade 6B.1A A/Brisbane/02/2018-like viruses. The major group of H1 viruses fell in the A/Norway/3433/2018 6B.1A5A subgroup of viruses. The viruses within this subgroup with the K130N and N156K were more prominent from the middle of the season. Only a small proportion

of viruses belonged to the 6B.1A7 subgroup, mainly viruses from the north of Norway. Some viruses were also seen belonging to the 6B.1A5B subgroup (Figure 12)

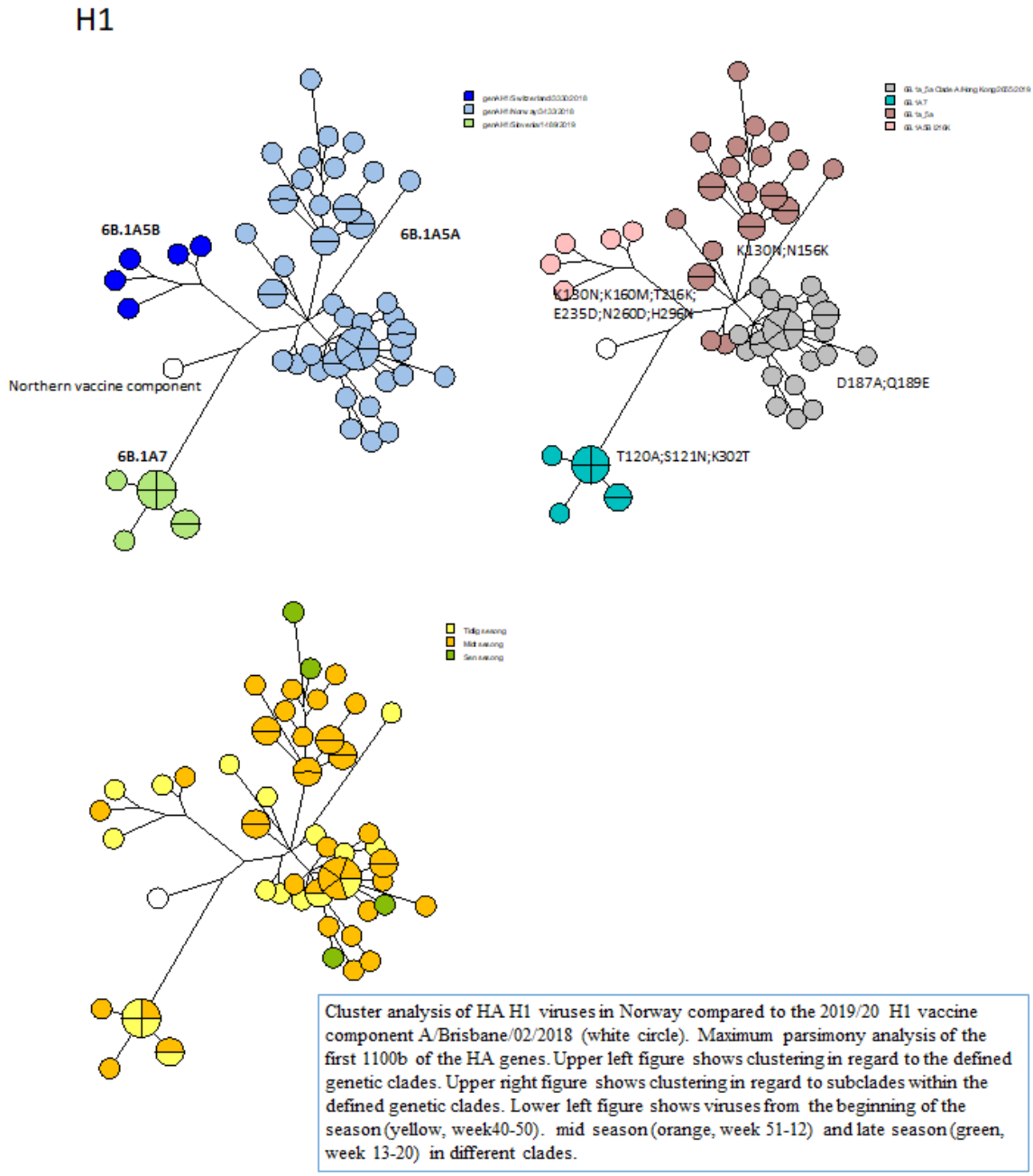


Figure 12. Cluster analysis of the HA gene of influenza A(H1N1)pdm09 viruses season 2019/20 in Norway, up to week 35 2020.

B-Yamagata

Influenza B-Yamagata viruses characterised are all clade 3 viruses with very few amino acid differences. Most of the viruses possessed the N164K substitution. A smaller group of viruses from the beginning of the season possessed D232N (Figure 13).

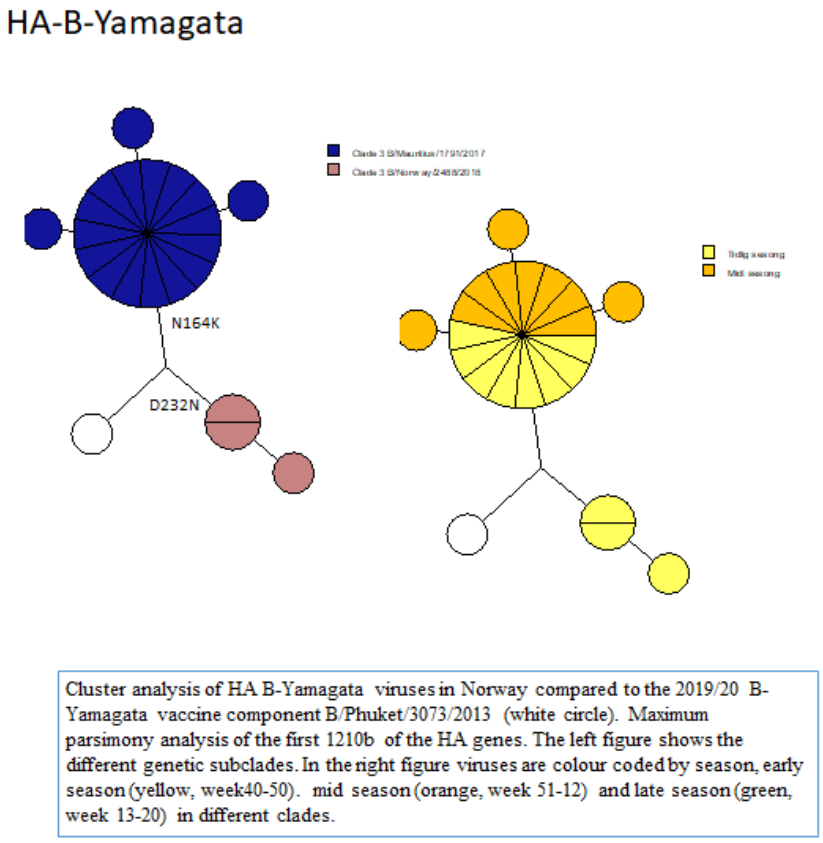
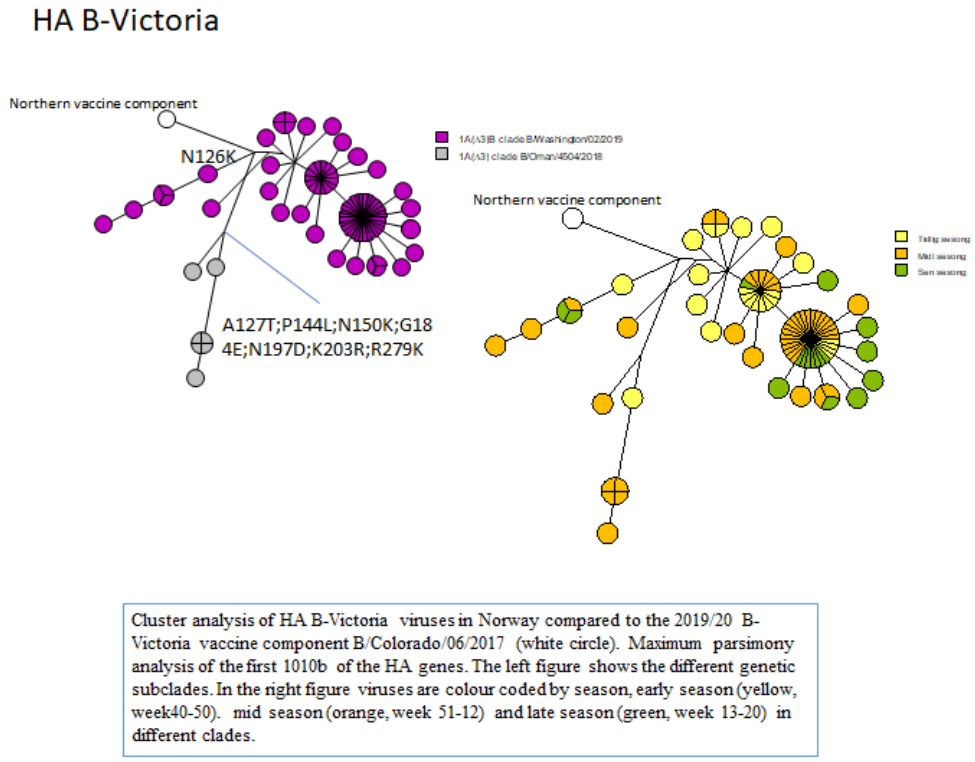


Figure 13. Cluster analysis of the HA gene of influenza B-Yamagata viruses season 2019/20 in Norway, up to week 35 2020.

B-Victoria

All the few influenza B-Victoria viruses collected and analysed this season were the triple deletion variant viruses, amino acids 162 to 164 (Δ3), belonging to the clade 1A(Δ3)B subgroup of viruses B/Washington/02/2019. The majority of the viruses possessed the E128K and G133R substitutions in HA. A smaller, more recent, group of viruses possessed a number of substitutions: A127T;P144L;N150K;G184E;N197D;K203R;R279K. This far, these have only been seen in central Norway (Figure 14). In addition, some few more recent viruses also possessed N126K.



Cluster analysis of HA B-Victoria viruses in Norway compared to the 2019/20 B-Victoria vaccine component B/Colorado/06/2017 (white circle). Maximum parsimony analysis of the first 1010b of the HA genes. The left figure shows the different genetic subclades. In the right figure viruses are colour coded by season, early season (yellow, week40-50). mid season (orange, week 51-12) and late season (green, week 13-20) in different clades.

Figure 14. Cluster analysis of the HA gene of influenza B-Victoria viruses season 2019/20 in Norway, up to week 35 2020.

Antiviral susceptibility

No resistance towards neuraminidase inhibitors like oseltamivir and zanamivir has so far been detected, out of 134 viruses analysed (Table 2).

Table 2: Resistance to neuraminidase inhibitor drugs

pr. 26/08-20	Oseltamivir (Tamiflu®)		Zanamivir (Relenza®)	
Virus	Tested	Oseltamivir-resistant virus	Tested	Zanamivir-resistant virus
H3	63	0 / (0 %)	60	0 / (0 %)
B	42	0 / (0 %)	42	0 / (0 %)
H1	103	0 / (0 %)	32	0 / (0 %)
Resistance to oseltamivir and zanamivir detected either by sequence analysis or by neuraminidase susceptibility assay				

Vaccine distribution and coverage

A total of 1 031 020 influenza vaccine doses have been distributed in the 2019/20 season; 813 020 of these were specifically intended for persons in medical risk groups and health care personnel involved in direct patient care. The number of distributed doses has increased by 16 % compared to the 2018/19 season and has doubled in five years (Figure 15).

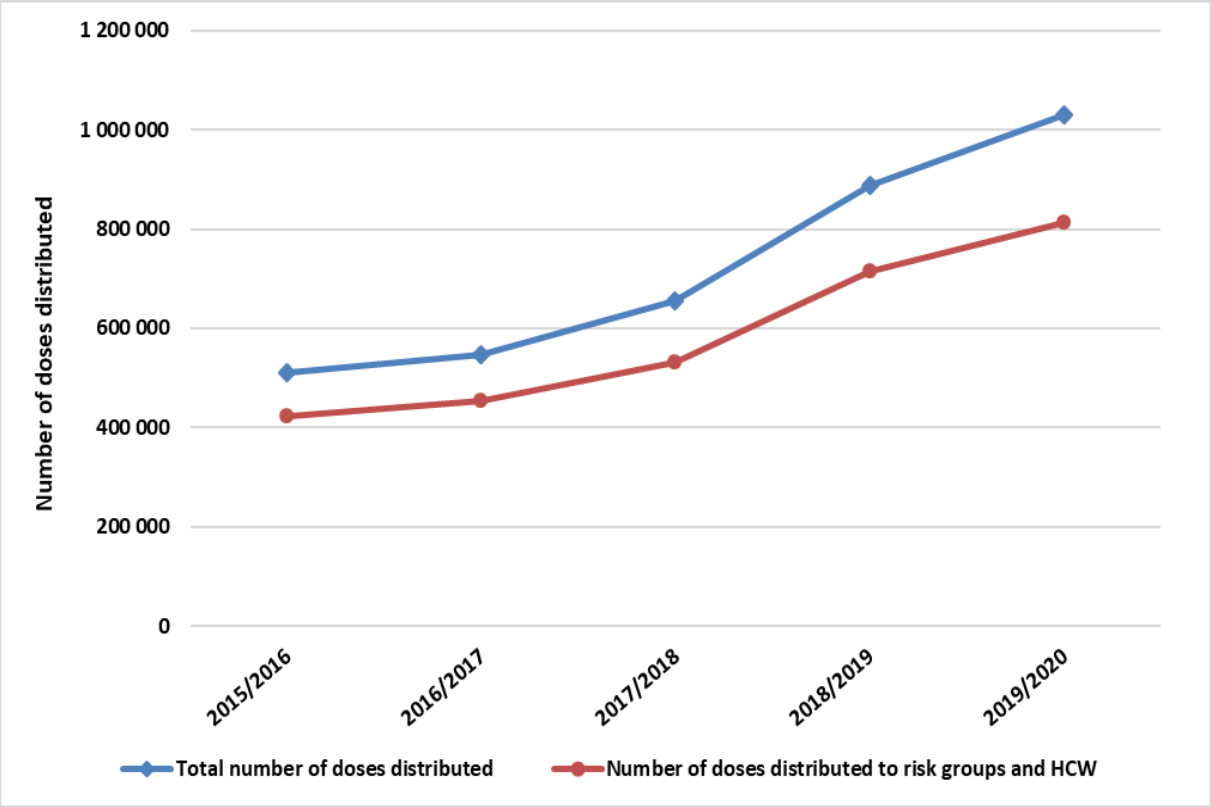


Figure 15: Influenza vaccine doses (seasonal) distributed in Norway, 2015 through July 2020. HCW = Health Care Workers.

According to the Norwegian Immunization Registry SYSVAK, at least 41 % of the population above 65 years of age received an influenza vaccine this season. Only about 78 % of the doses used is registered in SYSVAK, due to underreporting and technical issues. Vaccine coverage is therefore estimated for the various risk groups based on survey data from Statistics Norway. However, these estimates will not be available until October 2020.

Population immunity against recent influenza viruses, August 2019

In August each year, the National Influenza Seroepidemiology Programme solicits approximately 2000 anonymised convenience 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 (HI) test to determine the antibody immunity against relevant circulating influenza viruses. As an austerity measure, only a subset of 1054 sera were analysed for 2019. The main findings are shown in figure 16, table 3, and summarised as follows:

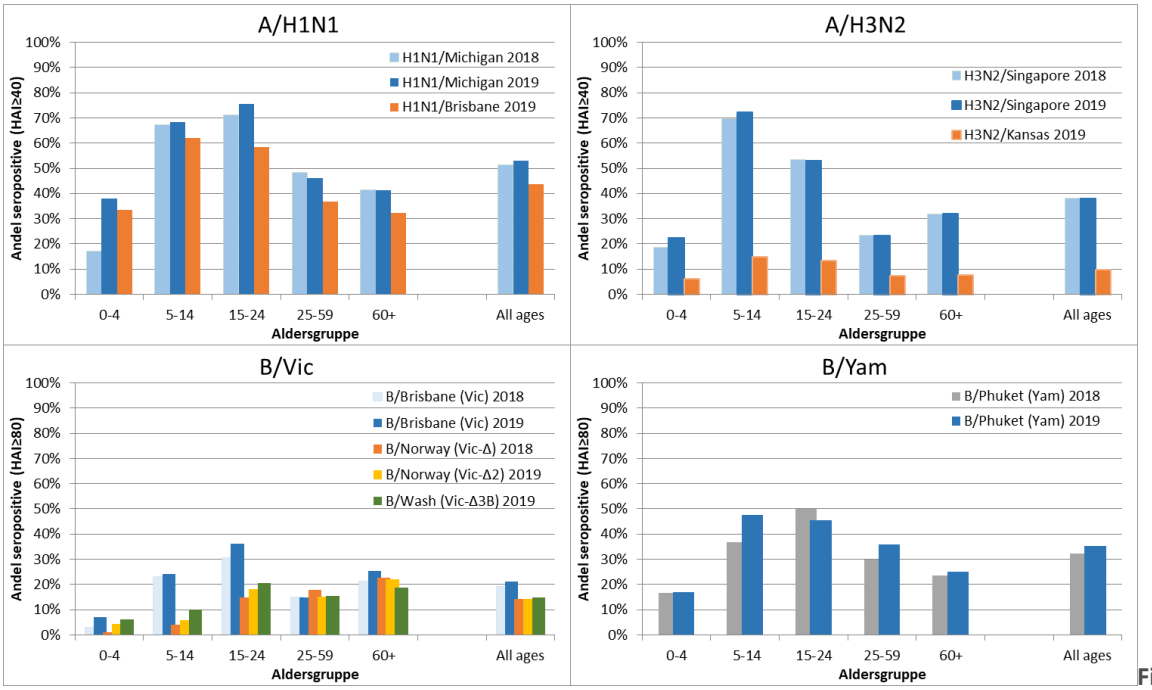


Fig 15. Seroprevalence in August 2019 to current influenza A and B reference and vaccine strains for 'All ages' and in various age groups. For comparison, seroprevalences to some virus strains in August 2018 are also shown. Michigan= A/Michigan/45/2015 (H1N1)pdm09 clade 6B.1; H1N1/Brisbane= A/Brisbane/02/2018 (H1N1)pdm09 clade 6B.1A1; Singapore= A/Singapore/INFIMH-16-0019/2016 (H3N2) clade 3C.2a1 ; Kansas= A/Kansas/14/2017 (H3N2) clade 3C.3a; B/Brisbane= B/Brisbane/60/2008 (Victoria lineage); B/Norway= B/Norway/2409/2017 (Victoria lineage, amino acid 162-163 deletion variant); B/Wash=B/Washington/02/2019 (Victoria lineage, amino acid 162-164B deletion variant); B/Phuket= B/Phuket/3073/2013 (Yamagata lineage).

For A(H1N1) viruses, the comparatively strong population immunity that has been accumulated in recent years had been maintained in most age groups. There was a marked increase since 2018 in the proportion of people with protective antibody levels (seroprevalence) in the youngest age group in which many individuals would have experienced their first A(H1N1) exposure last winter. Seroprevalence against the more recent subclade 6B.1A1 A/Brisbane/02/2018 variant was slightly lower than against the clade 6B.1 virus A/Michigan/45/2015.

For A(H3N2) viruses, the seroprevalence against clade 3C.3a viruses observed in 2017 and 2018 was essentially maintained. The seroprevalence was quite high in the 5-24 year olds. Perhaps importantly, our data appear to indicate that population immunity against recent clade 3C.3a

viruses, represented by the current vaccine virus A/Kansas/14/2017, is very poor (10% seroprevalence overall). If this is so, the current vaccine virus is well placed to address a significant vulnerability in the population immunity.

The seroprevalence against B/Victoria-lineage viruses remained low, with overall seroprevalence of 21 % against the previous B/Victoria vaccine component B/Brisbane/60/2008. Interestingly, in most age groups there was little difference in seroprevalence against the mother variant B/Brisbane/60/2008, and against the two newly emerged deletion variants, represented by B/Norway/2409/2017 (1A(Δ2) group) and the current vaccine virus B/Washington/02/2019 (1A(Δ3)B group). The exception was for those between 5 and 25 years old, where seroprevalence against B/Brisbane/60/2008 was markedly higher. The seroprevalences differed little between the 1A(Δ2) group and 1A(Δ3)B groups, and individual sera tended to have similar titres against the two antigens (data not shown).

For the B/Yamagata-lineage viruses, represented by the vaccine virus for tetravalent vaccines, B/Phuket/3070/2013, the seroprevalence changed little from 2018. Overall seroprevalence was 35%, with highest proportions in the 5-24 year olds.

Table 3. Influenza seroepidemiology results in August 2019 - Comparison between age groups.
For comparison data from studies performed for the preceding years 2015-2018 are also included.

Influenza strains (Year[$])	Age groups						
	0-4	5-14	15-24	0-24	25-59	60+	All ages
H1 X-179A/A(H1N1)pdm09 (2015)	24	53	58	50	30	36	39
H1 South Africa/3626/13 (2015)[1)]	35	62	57	55	31	22	40
H1 X-179A/A(H1N1)pdm09 (2016)	30	66	62	56	38	36	46
H1 Slovenia/2903/15 (2016)	34	66	68	60	38	33	47
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/02/18 (2019)*	***34***	***62***	***58***	***54***	***37***	***32***	***44***
H3 Texas/50/12 (2015)	35	79	54	60	35	44	47
H3 Switzerland/9715293/13 (2015)	33	59	31	42	30	40	37
H3 Hong Kong/5738/14 (2015)[1)]	28	68	47	51	27	29	38
H3 Switzerland/9715293/13 (2016)	18	60	29	39	21	33	31
H3 Hong Kong/5738/14 (2016)	14	53	26	34	14	22	24
H3 Hong Kong/5738/14 (2017)	28	78	59	60	30	43	45
H3 Norway/3806/16 (2017) [1)]	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***
B/Vic Brisbane/60/08 (2015)[2)]	2	32	25	23	17	32	23
B/Vic Brisbane/60/08 (2016)	9	28	15	19	9	15	15
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/Yam Massachusetts/2/12 (2015)[3)]	12	29	58	38	36	33	37
B/Yam Phuket/3073/13 (2015)[3)]	12	31	43	32	23	28	28
B/Yam Phuket/3073/13 (2016)	5	23	39	25	26	20	24
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***
Sera analysed (n): 2015 Aug	178	353	363	894	788	409	2091
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**

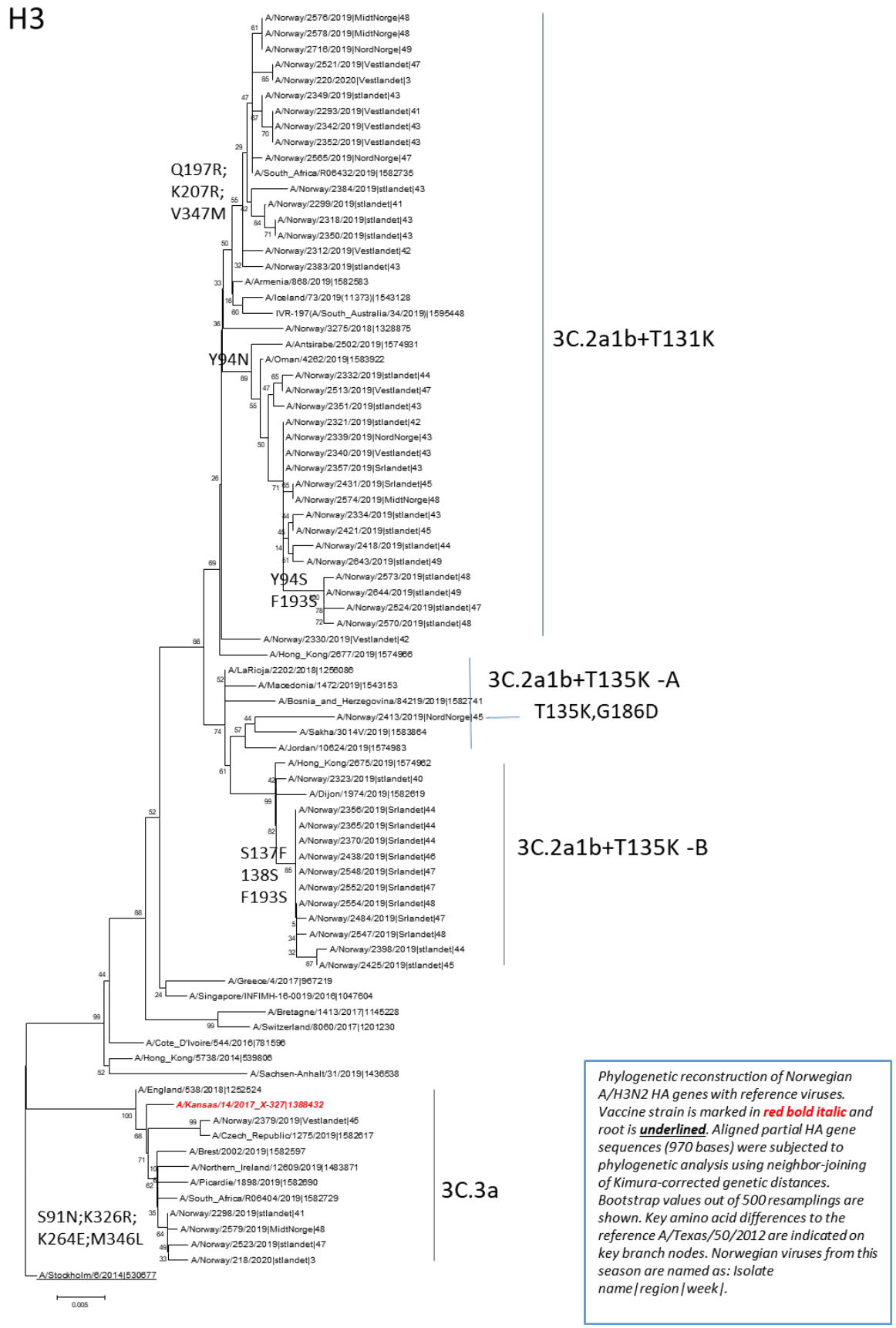
[$]Year of serum collection and HI analysis.

*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 2019-2020.

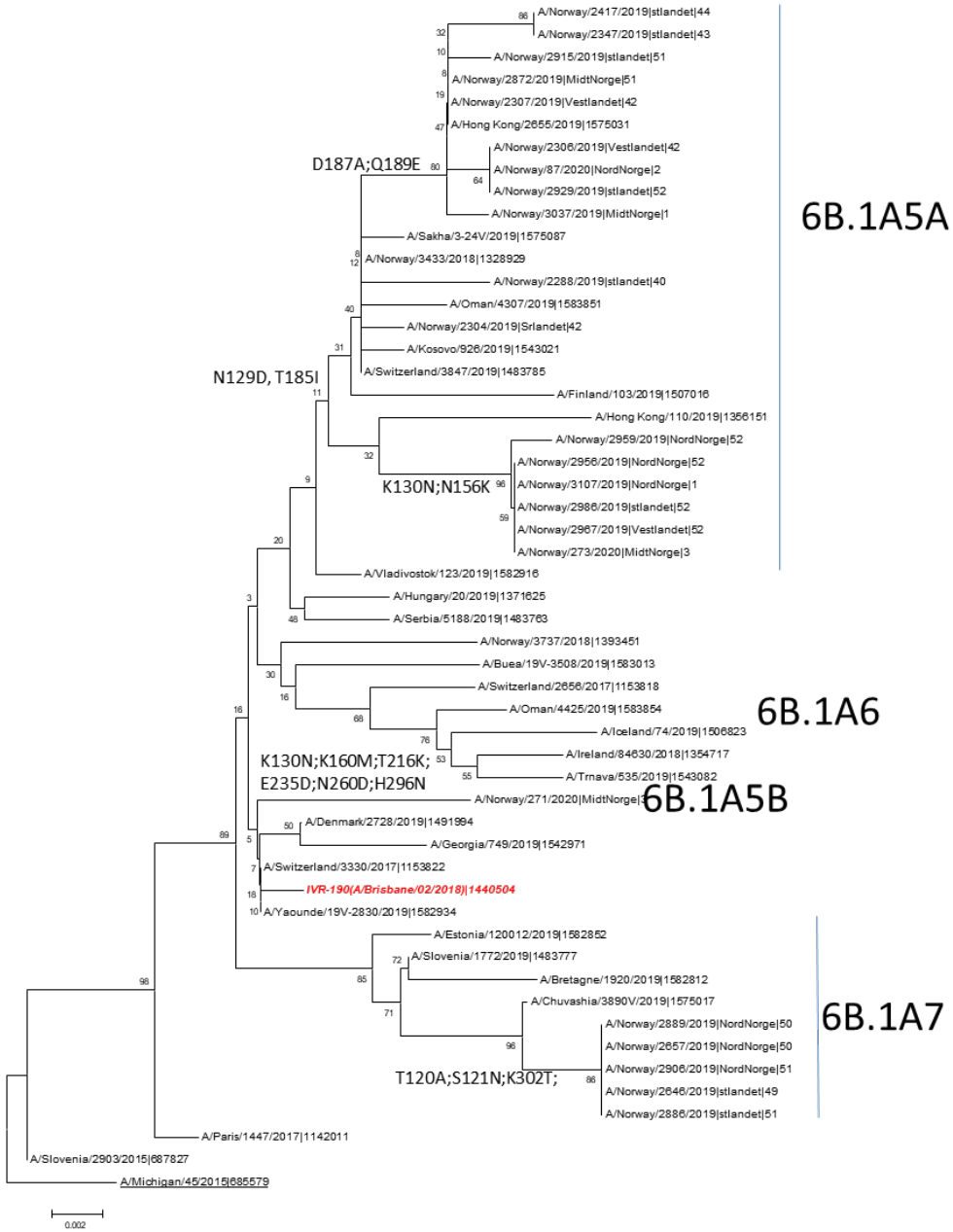
B/Yam: B/Yamagata/16/1988 lineage; **B/Vic**: B/Victoria/2/1987 lineage

Phylogeny (not updated since week 4 2020 due to COVID-19 workload)



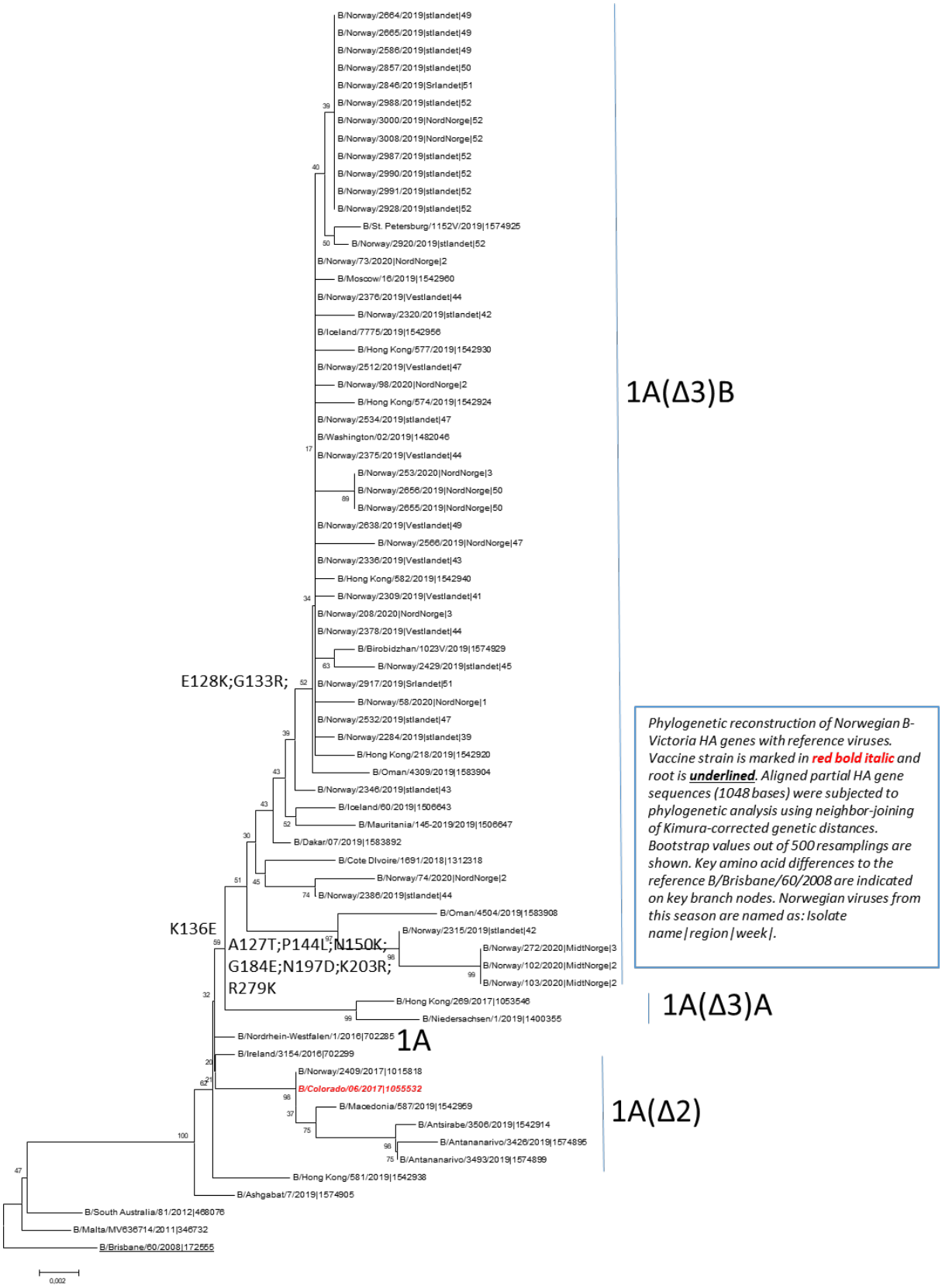
*Phylogenetic reconstruction of Norwegian A/H3N2 HA genes with reference viruses. Vaccine strain is marked in **red bold italic** and root is **underlined**. Aligned partial HA gene sequences (970 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. Bootstrap values out of 500 resamplings are shown. Key amino acid differences to the reference A/Texas/50/2012 are indicated on key branch nodes. Norwegian viruses from this season are named as: Isolate name|region|week|.*

H1



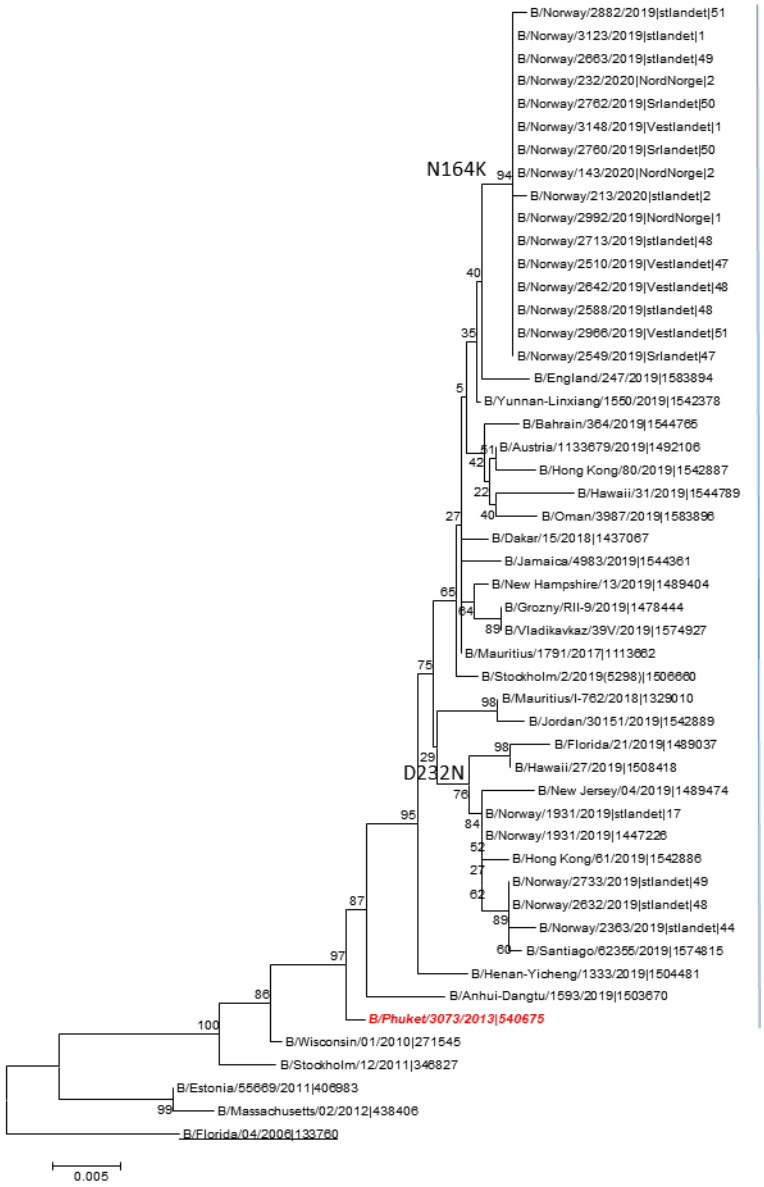
*Phylogenetic reconstruction of Norwegian A/H1N1 HA genes with reference viruses. Vaccine strain is marked in **red bold italic** and root is **underlined**. Aligned partial HA gene sequences (1056 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. Bootstrap values out of 500 resamplings are shown. Key amino acid differences to the reference A/Michigan/45/2015 are indicated on key branch nodes. Norwegian viruses from this season are named as: Isolate name|region|week|.*

HA B-Victoria



*Phylogenetic reconstruction of Norwegian B-Victoria HA genes with reference viruses. Vaccine strain is marked in **red bold italic** and root is **underlined**. Aligned partial HA gene sequences (1048 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. Bootstrap values out of 500 resamplings are shown. Key amino acid differences to the reference B/Brisbane/60/2008 are indicated on key branch nodes. Norwegian viruses from this season are named as: Isolate name|region|week|.*

HA B-Yamagata



3

*Phylogenetic reconstruction of Norwegian B-Yamagata HA genes with reference viruses. Vaccine strain is marked in **red bold italic** and root is **underlined**. Aligned partial HA gene sequences (1010 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. Bootstrap values out of 500 resamplings are shown. Key amino acid differences to the reference B/Phuket/3073/2013 are indicated on key branch nodes. Norwegian viruses from this season are named as: Isolate name|region|week|.*

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1 Bragstad K, Paulsen TH, Tønnessen R, Klüwer B, Rydland KM, Hungnes O. "Norway National Influenza Centre – Influenza Virological and Epidemiological Information prepared for the WHO Consultation on the Composition of Influenza Virus Vaccines for the Southern Hemisphere 2020., September 2019 ". Report 2019. Oslo: Norwegian Institute of Public Health, 2019. https://www.fhi.no/publ/2019/influenza-virological-and-epidemiological-information-prepared-for-the-who-/

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With best regards,

Karoline Bragstad, Trine Hessevik Paulsen, Ragnhild Tønnessen, Birgitte Klüwer, Kjersti Rydland, Torstein Aune, and Olav Hungnes

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7 September 2020

Appendices

Methods

Influenza-like illness

Norwegian ILI surveillance data is provided by NorSySS (Norwegian Syndromic Surveillance System). NorSySS 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. NorSySS has been in operation since 2014 and is supported by retrospective data from the 2006-07 season and onwards.

Virological surveillance.

A network of volunteer sentinel physicians throughout the country collects specimens from patients with ILI for analysis at the National Influenza Centre.
In addition, medical microbiology laboratories that perform influenza diagnostics weekly report the number of positives and the number of specimens tested, according to virus type/subtype, detection method and patient age group. 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. Starting in early 2020, in response to the COVID-19 pandemic, a new laboratory database has been established in the NIPH, that receives diagnostic testing outcomes for respiratory pathogens in near real-time. This source has been used to populate the influenza virological data set after the regular weekly reporting from the laboratories ceased in week 20/2020.

Surveillance of laboratory-confirmed influenza in hospitalised patients

As an extension to the basic weekly reporting of influenza diagnostic testing outcomes, nine medical microbiology laboratories stratify their report into hospitalised patients and outpatients. Together, these laboratories cover approximately 68% of the Norwegian population, and report each week the number of influenza virus detections in hospitalised patients (all wards) as well as outpatients according to influenza type (A, B) and age group. This extended reporting constitutes the basis for the surveillance of laboratory confirmed influenza in hospitalised patients. This is the sixth season this surveillance system is in operation.

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. Currently, only anonymised data are reported from NICR to the NIPH.

Mortality monitoring

The Norwegian Mortality Monitoring system (NorMOMO) is used for weekly monitoring of all-cause mortality. The system has been in operation since 2015 and it is based on the algorithm developed by the EuroMOMO network.

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. The sera are tested by the haemagglutination-inhibition (HI) test to determine the antibody immunity to relevant circulating influenza viruses. HI titres ≥40 against the influenza A strains and ≥80 against ether-treated influenza B strains are considered as protective levels and recorded as seropositive in the analysis.

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