NIPH
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REPORT

2019

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

Geneva, September 2019

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Published by Norwegian Institute of Public Health
Division of Infection Control and Environmental Health
Department of Influenza
September 2019

Title:
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

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Ordering:
The report can be downloaded as pdf at www.fhi.no/en/publ/

Graphic design template:
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ISBN digital 978-82-8406-031-6

Citation: 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". [Norsk influensarapport til WHOs møte om sammensetning av influensavaksinen for sørlige halvkule 2020] Report 2019. Oslo: Norwegian Institute of Public Health, 2019.

Content

The 2018-2019 influenza season, Norway

Summary

- Seroepidemiology data from August 2018 indicate that immunity in Norway against circulating influenza A(H1N1) and A(H3N2) viruses was quite strong. Also for the B/Yamagata-lineage virus that caused the preceding winter's influenza outbreak, there was a marked increase in people with antibody at protective levels.
- Added to this came the immunity due to the subsequent influenza vaccination campaign in the autumn. Rates of vaccination were raised considerably that year.
- The seasonal influenza outbreak began in week 52. It reached medium intensity, a level it remained at for three weeks. The flu peak was reached in week 7. The outbreak was over in week 13 and had a duration of 13 weeks.
- 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).
- As in earlier A(H1N1)pdm09 dominated seasons, young children were more likely than others to be diagnosed with influenza infection.
- Among the few influenza B viruses, the B/Victoria-lineage was slightly more frequent than the B/Yamagata-lineage. Whereas B/Yamagata-lineage viruses were more common in the beginning, only B/Victoria-lineage viruses have been observed since week 23.
- The majority of the H1N1 viruses were characterised as 6B.1A5 A/Switzerland/3330/2017 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).
- There has been a number of different subgroups of H3N2 viruses circulating also this season, but the main group has been the 3C.2a1b viruses. During the summer, viruses in this group carrying the Q197R together with K207R have become more prominent.
- All influenza B/Yamagata-lineage viruses were HA clade 3 viruses. Two influenza B-Yamagata viruses have been detected that possess a large number of substitutions in both HA and NA.
- The African triple deletion variant has been most prevalent among the B/Victoria-lineage viruses this season.
- About 4 400 patients with laboratory-confirmed influenza were hospitalised. Compared with the previous season, there were far fewer hospitalisations, less influenza patients requiring intensive care unit (ICU) admission, and fewer 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). There were fewer hospitalised elderly this season. However, in young children, the hospitalisation rate was relatively high.

A look back at the season before

The previous influenza outbreak of 2017/18 started in mid-December and lasted unusually long. Although intensity, measured as weekly incidence of ILI, only reached medium level, the cumulative magnitude was larger than in the preceding seasons.[1] The outbreak was dominated by influenza B Yamagata-lineage viruses, antigenically similar to the reference/vaccine virus B/Phuket/3073/2013. A lower number of influenza A(H3N2) (clade 3C.2a2 in majority) circulated at the same time. By week 12/2018, influenza B cases had decreased significantly, while influenza A(H3N2) persisted longer and was predominant until the end of the season. The older segments of the population accounted for a high proportion of both the B/Yamagata and A(H3N2) cases. A significantly larger number was hospitalised with influenza that season compared to the preceding three seasons due to the protracted outbreak. Excess all-cause mortality was observed in the elderly during several weeks.

Despite very few cases of influenza B/Victoria-lineage infection that season, the novel two-amino acid HA deletion variant represented a larger proportion than in the preceding 2016/17 season, and increased during the outbreak. The moderate number of H1N1 viruses that circulated belonged to subclade 6B.1.

The last time influenza A(H1N1)pdm09 viruses predominated was in the 2015/16 season.

The 2018/19 season

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

Influenza-like illness (ILI) in primary health care

The seasonal influenza outbreak began in week 52. It reached medium intensity, a level at which it remained for three weeks. The outbreak peaked in week 7, was over in week 13 and had a duration of 13 weeks (Figure 1).

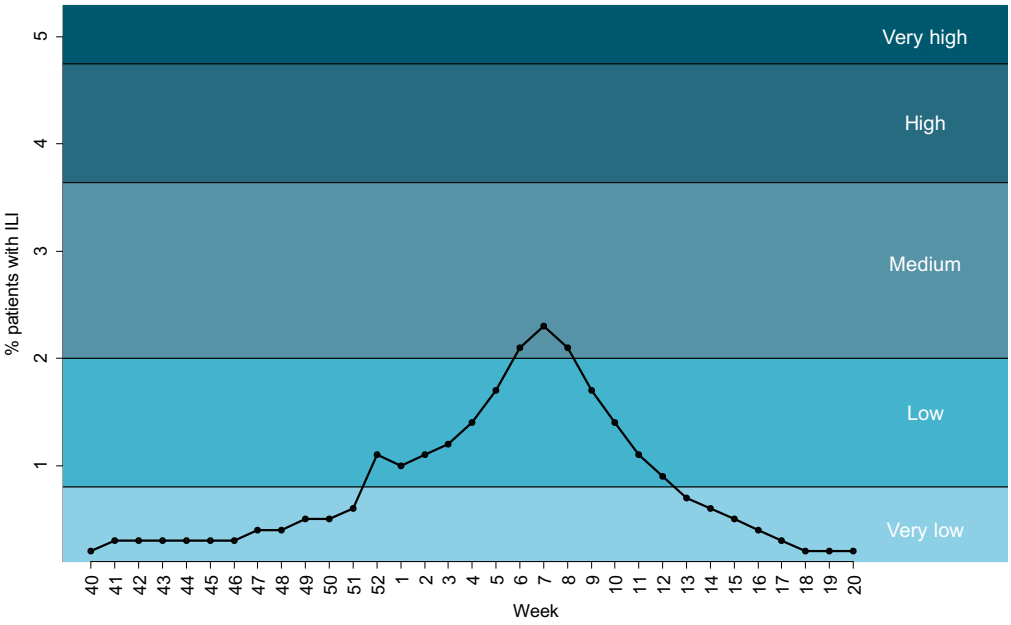


Figure 1: Level of influenza intensity (by present-season MEM intensity thresholds) depicted as weekly proportion of patients in general practice and emergency clinics presenting with ILI, Norway 2018-2019 season

The 2018/19-outbreak in Norway was of lesser magnitude than average, measured by ILI consultations (Figure 2). The total number of physical consultations and consultations by telephone in the 2018/19-outbreak was 12 % lower than average, and 43 % lower than the 2017/18-season.

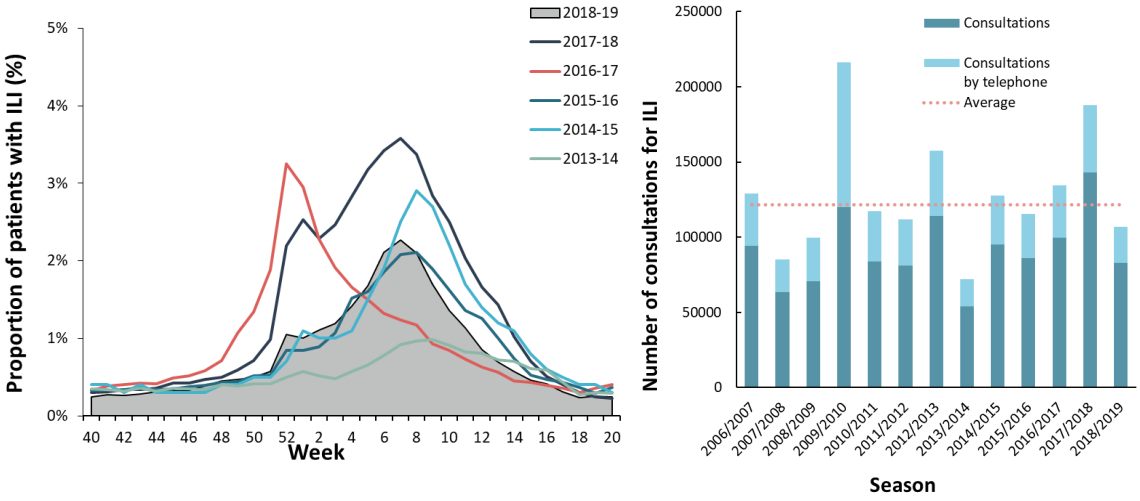


Figure 2: Left panel: Weekly incidence of ILI, Norway 2018-2019 season (grey). The graph shows the proportion of patients in general practice and emergency clinics presenting with ILI, by calendar week. The five previous seasons are also shown. Right panel: Number of ILI face-to-face consultations and consultations by telephone by season in general practice and emergency clinics from 2006/07 to 2018/19. The average was calculated from seasons 2006/07 throughout 2017/18 with the pandemic of 2009/10 excluded.

Local outbreaks of influenza in health care institutions

Eighteen local outbreaks in health care institutions were reported in the period January throughout March 2019, all caused by influenza A. Information about subtype was only available for five of the outbreaks, H3N2 reported from all and H1N1 in addition in one of the outbreaks. 142 residents/patients were reported ill with suspected or lab-confirmed influenza, of which 20 died. The number of ill health care workers was reported in six of the outbreaks, and in this selection the proportion ill health care workers was 41 %. The reporting on outbreaks from Norwegian health care institutions is not exhaustive.

Laboratory-confirmed influenza hospitalisations

From week 40/2018 through week 20/2019, influenza virus was detected in 2 978 hospitalised patients. From this it was estimated that about 4 400 patients with laboratory-confirmed influenza was hospitalised in Norway, compared to 7 600 in 2017-2018. About 99 % of the detections were typed as influenza A. The hospitalisation rate started to increase in week 49, reached a temporary peak in week 1 and further increased from week 4 until the peak was reached in week 7 (Figure 3). The cumulative hospitalisation rate was much lower compared to the two preceding seasons, but somewhat higher than in 2015-2016, the last season when A(H1N1)pdm09 predominated in Norway. The highest cumulative weekly hospitalisation rates were found in the elderly (60 years or older) and in young children (0-4 years) (Figure 3). Compared with the preceding season, the hospitalisation rate in the elderly was much lower. However, in children, the rate was relatively high, but still lower than during the large and long-lasting

B-Yam outbreak in 2017-2018 and the (H1N1)pdm09 outbreak in 2015-2016.

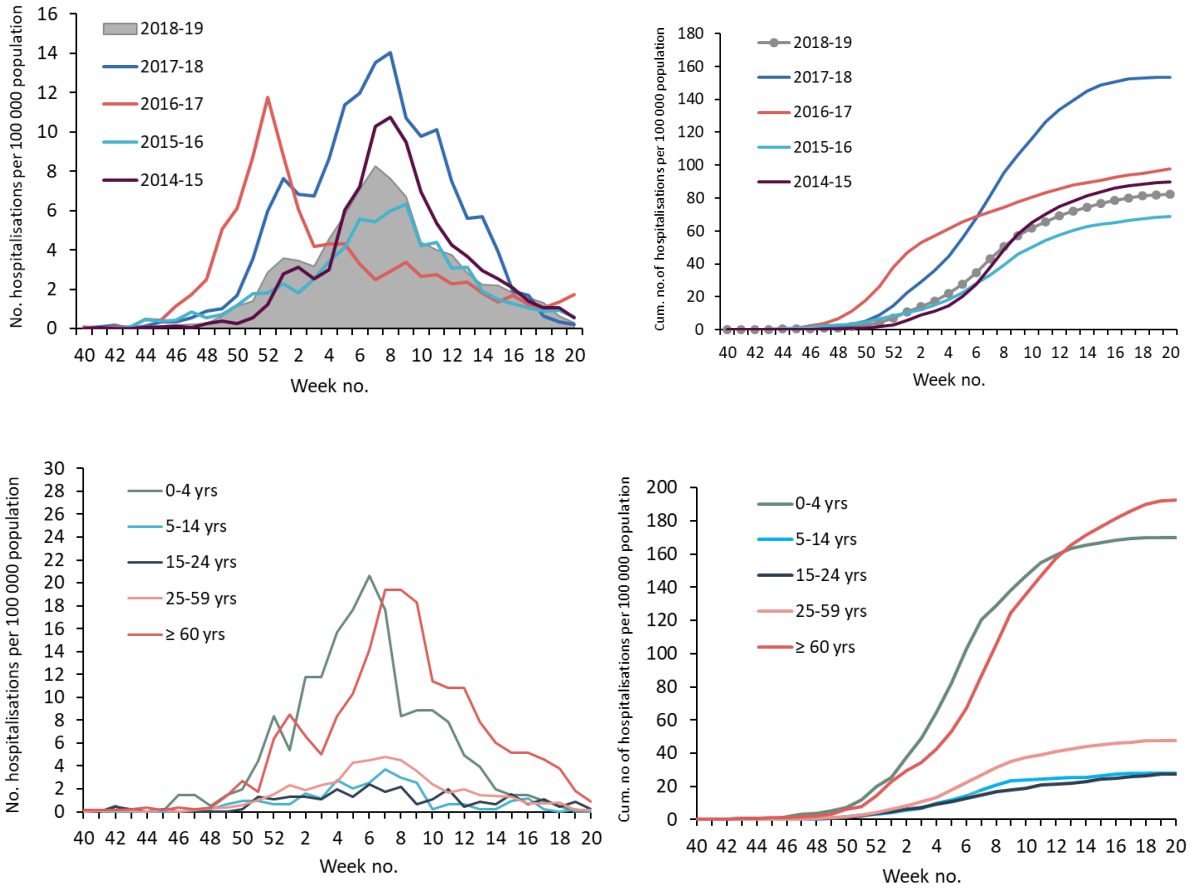


Figure 3: Influenza-confirmed hospitalisations in Norway. Upper left- and right-hand panel: Weekly and weekly cumulative rate of hospitalised patients with confirmed influenza per 100 000 population compared to the previous four influenza seasons. Lower left- and right-hand panel: Weekly and weekly cumulative rate of hospitalised patients with confirmed influenza per 100 000 population per age group The figures are based on data from nine sentinel medical microbiological hospital laboratories, offering influenza diagnostics to about 68 % of the population in Norway.

Influenza patients in intensive care units

During the influenza season in 2018-19, a total of 260 ICU treated influenza (67 suspected and 193 confirmed) patients were registered by the Norwegian Intensive Care Registry. The number of patients with laboratory-confirmed influenza admitted to ICUs was lower than in the previous two seasons (Figure 4). This corresponds to fewer influenza hospitalisations in general. However, due to a change in the reporting method in 2018-19, caution must be taken when comparing this season's ICU numbers with the numbers from previous seasons.

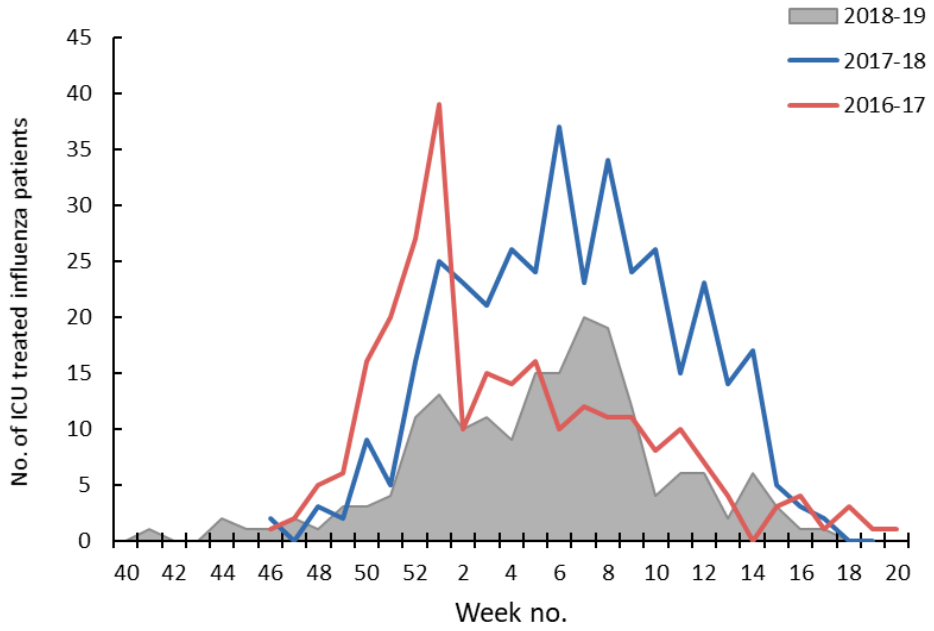


Figure 4: Number of patients in ICU with confirmed influenza (ICD-10 code J10) week 46-20 seasons 2016-2017 and 2017-2018, and week 40 to 20 in 2018-2019. I the first two seasons, the numbers were based on email registrations to The Norwegian Intensive Care Registry. From 2018-2019 a new influenza reporting scheme has been used. The numbers were last updated week 20, and may have adjusted due to delayed reporting. For 2018-2019, 11 cases have been excluded due to uncertain date of registration.

Excess all-cause mortality

From week 40 2018 through week 20 2019, the level of all-cause mortality has been within normal expected ranges. Excess all-cause mortality was registered only in week 7/2019.

Laboratory confirmed influenza: Virological surveillance

Altogether, 191 807 patients in Norway tested for influenza have been recorded during weeks 40/2018 - 35/2019, resulting in 21 092 detections of influenza A and a mere 207 detections of influenza B. There was a gradual increase in the detections of influenza viruses since the beginning of October, with a more marked increase in weeks 49 – 52/2018. After the usual stagnation during the first weeks of January, the increase resumed towards a peak in week 7/2019. The subsequent decline reached very low level somewhat earlier than in many previous seasons. Weekly totals and proportions of influenza positives are shown in Figure 6 and Table 1. Sporadic cases of laboratory verified influenza have occurred every week through the summer.

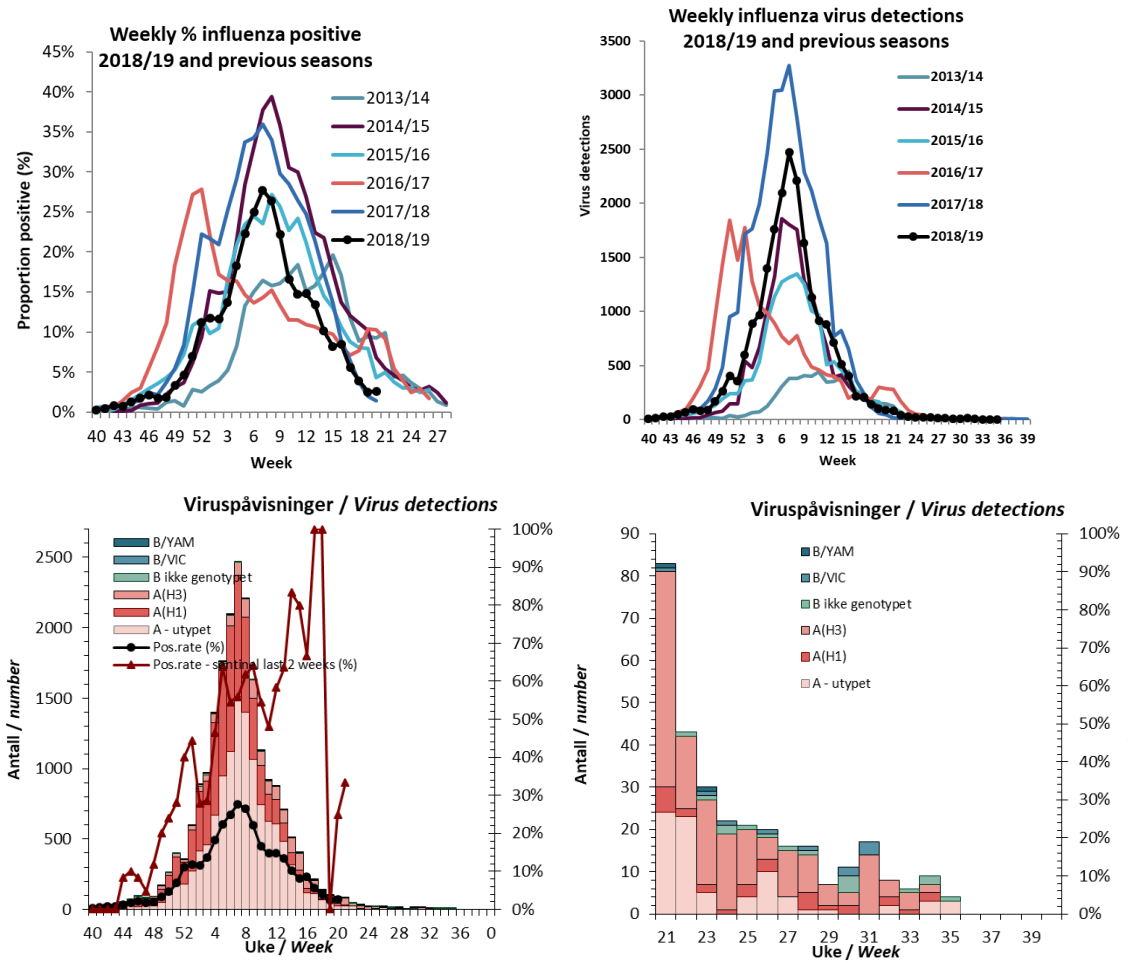


Figure 6: Laboratory detections, Norway 2018-2019. Upper left-hand panel: Weekly proportion of influenza virus positive specimens, with previous season proportions shown for comparison. Upper right-hand panel: Weekly number of influenza virus detections, with previous season numbers shown for comparison. Lower panels: 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 right-hand panel shows the summer weeks only.

The proportion of type B viruses was unusually low. During the first few weeks, there was a slight majority of A(H3N2) viruses. After clear A(H1N1) predominance during the main outbreak period, A(H3N2) viruses were again in clear majority during spring and most of the summer weeks (Figure 7, 8).

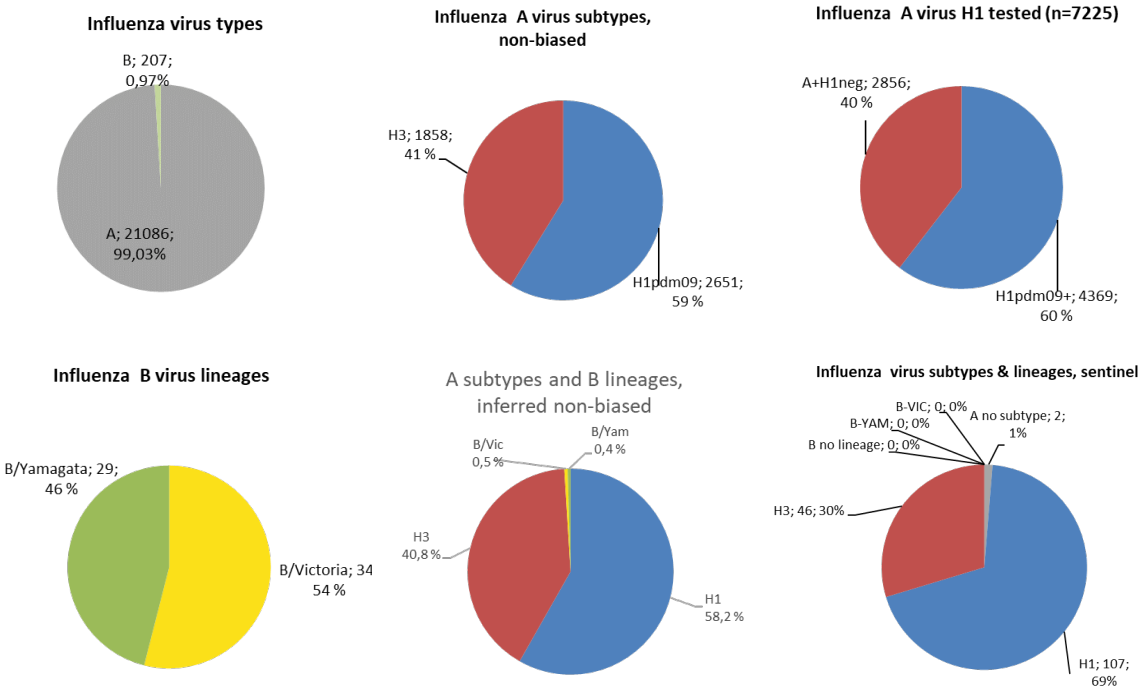


Figure 7. Proportions of 2018/19 season influenza virus subtypes and lineages among viruses analysed in Norway, by 9th September 2019. All-laboratories proportions of A/B type, A subtypes and B lineages are shown in the first four diagrams. The subtype and lineage frequencies are superimposed on type distributions in the lower middle 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. A similar proportion is obtained through an alternative approach that uses data from a higher number of laboratories that test all A positives for H1 but not H3, shown in the top-right diagram, where A positives testing negative for H1 serve as a proxy for H3. The sentinel data are not subtype biased in this way but the numbers are more limited, and there are few samples from late in the season.

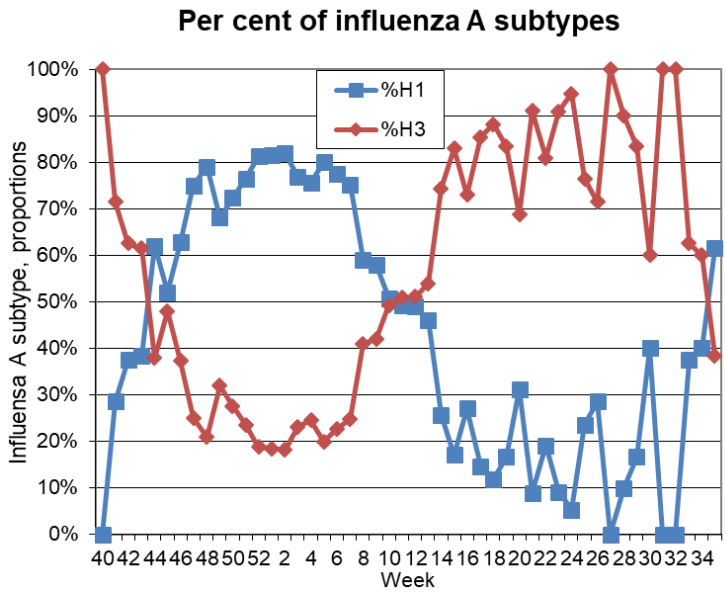


Figure 8. Weekly proportions of subtype H1 and H3, respectively, among influenza A viruses that have been tested for both H1 and H3. The main outbreak (% positives >10%) was weeks 52 - 14

The A(H1N1)pdm09 predominance represents a continuation of a pattern of H1N1 predominance every third season since the virus emerged with the 2009 pandemic (Figure 9). In addition to these 3-year-interval major H1N1pdm09 outbreaks, this virus also predominated during the 2013-14 season but that was a very small outbreak (cf. Fig 2 & 6), with little expected impact on population immunity.

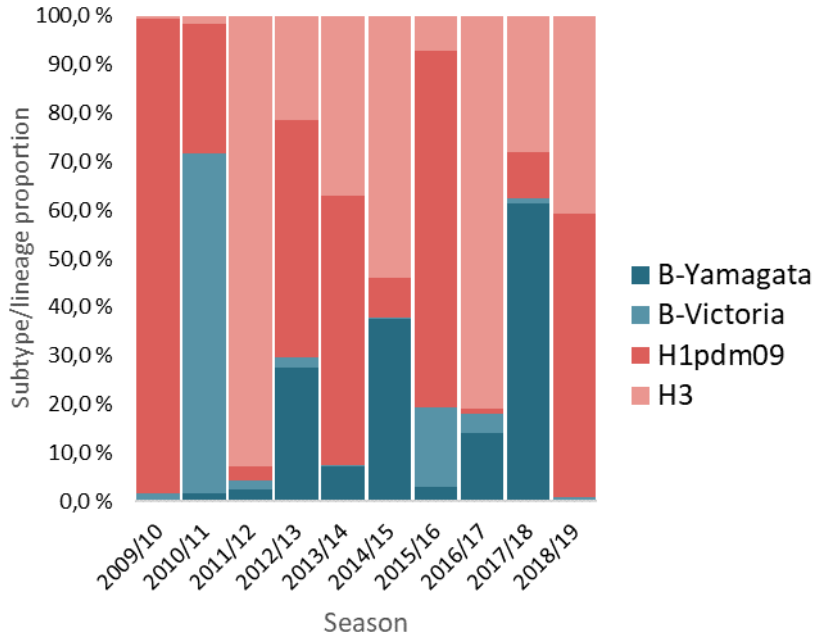


Figure 9: Predominance of influenza viruses in Norway, seasons 2009 to 2019. Proportions of influenza A subtypes and B lineages were superimposed on type A and B proportions, as described for figure 7.

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, 2018/2019 season.

		Virus detections								
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
40	0,2 %	3459	0,2 %	0	0	0	4	3	0	1
41	0,3 %	3465	0,5 %	4	5	2	5	2	0	1
42	0,3 %	3531	0,8 %	3	11	6	10	4	0	2
43	0,3 %	3698	0,7 %	5	12	5	8	0	0	2
44	0,3 %	3852	1,3 %	8	29	18	11	2	0	0
45	0,3 %	4140	1,7 %	23	34	13	12	2	0	0
46	0,3 %	4312	2,1 %	16	55	32	19	2	0	0
47	0,4 %	4541	1,8 %	35	39	18	6	2	0	0
48	0,4 %	4832	1,9 %	22	60	34	9	0	0	0
49	0,5 %	5015	3,3 %	48	93	49	23	1	1	0
50	0,5 %	5636	4,7 %	104	137	55	21	2	0	0
51	0,6 %	5804	7,0 %	180	191	91	28	6	0	0
52	1,1 %	3178	11,2 %	181	155	78	18	0	1	1
1	1,0 %	5084	11,8 %	275	290	119	27	5	0	2
2	1,1 %	7615	11,6 %	415	423	167	37	8	0	1
3	1,2 %	7093	13,7 %	459	452	150	45	11	0	2
4	1,4 %	7633	18,3 %	667	657	188	61	10	1	2
5	1,7 %	7894	22,3 %	948	750	205	51	9	2	0
6	2.1 %	8389	25,0 %	1120	893	261	76	6	1	1
7	2.3 %	8901	27,7 %	1514	857	279	92	6	0	0
8	2,1 %	8370	26,4 %	1403	671	189	131	2	1	0
9	1,7 %	7366	22,2 %	1064	436	177	128	5	0	0
10	1,4 %	6809	16,6 %	746	273	105	102	5	1	0
11	1,1 %	6224	14,7 %	624	191	91	94	5	1	0
12	0,9 %	5929	14,8 %	608	172	89	93	2	1	1
13	0,7 %	5302	13,4 %	485	131	76	89	4	0	1
14	0,6 %	5041	10,1 %	315	86	37	107	2	0	1
15	0,5 %	4877	8,2 %	234	46	24	117	3	2	0
16	0,4 %	2548	8,5 %	118	32	23	62	3	2	0
17	0,3 %	3801	5,6 %	111	24	12	70	2	4	1
18	0,2 %	3610	3,9 %	65	7	7	52	8	4	6
19	0,2 %	3981	2,5 %	55	10	6	30	3	2	0
20	0,2 %	3505	2,6 %	22	20	20	44	3	0	2
21	0,2 %	2526		24	6	5	51	0	1	1
22	0,2 %	2221		23	2	4	17	1	0	0
23	0,2 %	1292		5	2	2	20	1	1	1
24	0,2 %	998		0	1	1	18	2	1	0
25	0,1 %	1261		4	3	4	13	1	0	0
26	0,2 %	1243		10	3	2	5	1	1	0
27	0,1 %	1212		4	0	0	11	1	0	0
28	0,1 %	933		1	4	1	9	1	1	0
29	0,1 %	492		1	1	1	5	0	0	0
30	0,1 %	651		0	2	2	3	4	1	0
31	0,1 %	895		0	0	0	14	0	2	0
32	0,1 %	988		2	2	0	4	0	0	0
33	0,1 %	450		0	3	3	5	0	0	0
34	0,1 %	709		2	2	2	3	0	0	0
35	0,2 %	501		0	1	8	5	0	0	0
Total	Total	191807		11953	7274	2661*	1865	140	38	29
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:	21092			Type B:	207		

*To reduce effect of subtype testing bias, only H1pdm09 positives tested for both H1pdm09 and H3 are included here.

Age distribution of the different viruses

Age profiles for the A(H1N1) and A(H3N2) viruses 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. Analysis of viruses tested for both subtypes indicate that, even with overall predominance of A(H1N1), people 60 years and older were more likely to be diagnosed with A(H3N2) viruses (data not shown).

Although the numbers are very low, the age profiles for influenza B/Yamagata and B/Victoria are also consistent with previous seasons, with B/Victoria-lineage viruses affecting the younger age groups while the elderly are more affected by the B/Yamagata-lineage viruses.

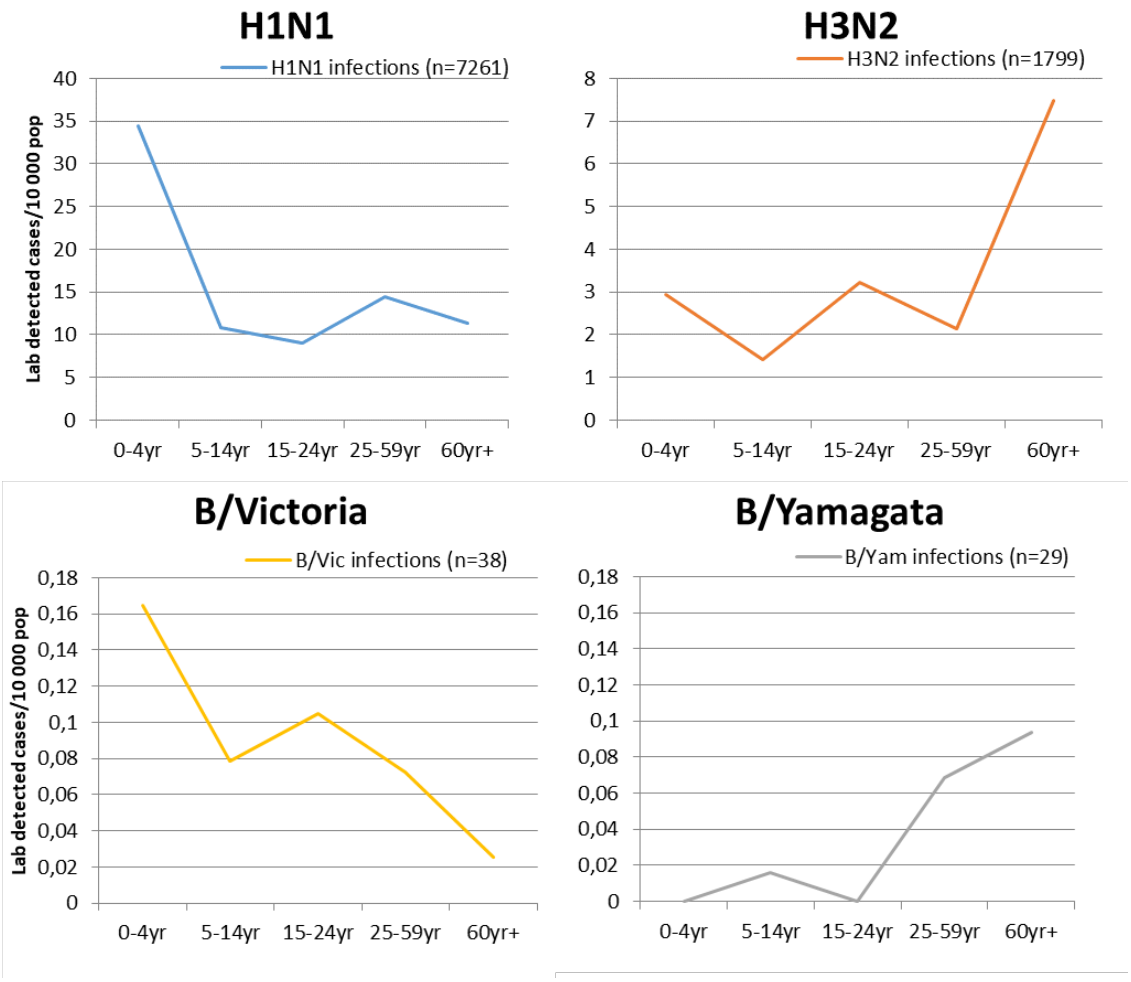


Figure 10. Cumulative frequency per 10 000 population of subtype/lineage detections by age group, based on viruses subtyped in Norwegian laboratories in the 2018/19 influenza season. Since the number of viruses subjected to type, subtype and lineage testing differs widely, the frequencies are comparable between age groups in the same panel, but frequencies are not comparable between the panels.

Genetic characterisations of the viruses in circulation

From week 40/2018 to week 35/2019, the influenza laboratory received 2,902 samples for further analysis. Of these, 2,558 samples were positive for influenza virus. 13% of these were further characterized to look at genetic markers for genetic drift and virulence. 14.5% of the positive samples were tested for antiviral resistance. 134 viruses were shipped to the WHO Collaborative Centre in London (Francis Crick Institute) for further analysis (making up 5.3% of all positive samples submitted to NIPH). In addition, 191 HA gene sequences were published in the GISAID (Global Initiative on Sharing All Influenza Data) sequence database (constituting 7.54% of all positive samples submitted to FHI).

H1N1

The analysed H1N1 viruses were all characterised as clade 6B.1A/Michigan/45/2015 viruses and the major group of H1 viruses possessed the following substitutions: S74R, N129D, S183P, S185I, R223Q and N260D and grouped phylogenetically together with the A/Switzerland/3330/2017 group of viruses, (see phylogenetic tree at the end of the report). These viruses have been assigned to the 6B.1A_5 clade. Also viruses possessing the key substitutions K302T, I404M and N496S (Figure 11), grouping together with clade A/Dnipro/409/2018 reference strain were circulating especially in the middle of the season, assigned to the 6B.1A_7 clade. From the middle of the season 6B.1A_6 clade A/Switzerland/2656/2017 viruses started to circulate in Norway. During the summer months H1 viruses forming a new subgroup under 6B.1A_5 emerged, possessing K130N;K160M;T216K;E235D;H296N and V321I in HA.

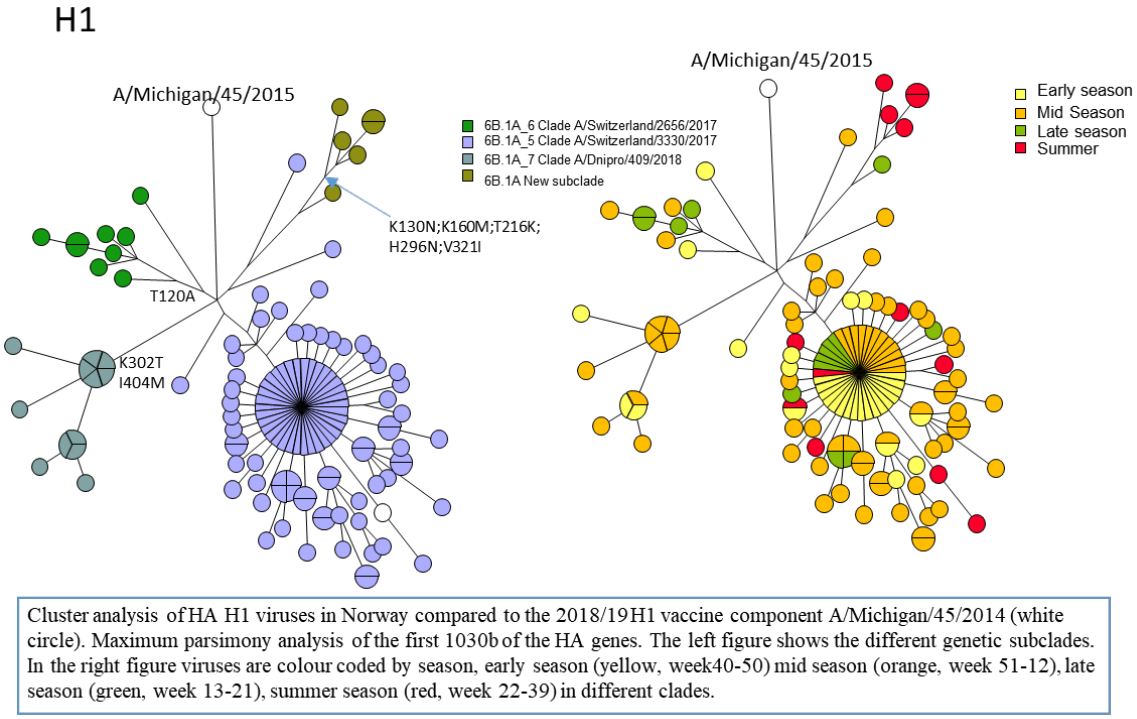


Figure 11. Cluster analysis of the HA gene of influenza A(H1N1)pdm09 viruses season 2018/19 in Norway, up to week 35 2019.

The NA genes of the most recent H1 viruses have not yet been characterised, but the NA genes analysed made the same phylogenetic grouping as for HA (Figure 11)

The N1 gene of the major clade 6B.1A_5 of A/Switzerland/3330/2017-like viruses possessed the key amino acid substitutions Q51K, V67I, F74S and S95N and formed the same phylogenetic clustering as the HA genes. The NA of the clade 6B.1A_7 H1 viruses possessed I188 and M314I with or without S12L in NA. The clade 6B.1A_6 viruses possessed P93H, I216V and I264T.

H3N2

The most dominating H3 viruses this season were the 3C.2a1b A/Alsace/1746/2018 viruses, however these divide into two almost equally prevalent subgroups; the A/Iceland/78/2018 subgroup with the A106V and T131K key substitutions and the A/LaRioja/2202/2018 subgroup with the T128A and T135K substitutions together with either I48R, D53N or S198P (Figure 12) (see also phylogenetic tree at the end of the report). The clade 3C.2a1b A/Iceland/78/2018 group of viruses were more prominent late in the season. In mid and late season some few viruses representing the 3C.2a, 3C.2a4 and the more diverse 3C.3a subgroup occurred. However; some of the more recent H3 viruses occurring during the summer months in Norway were viruses in the 3C.2a1b subgroup possessing Q197R and K207R in HA.

The N2 gene of all 3C.2a1b viruses possessed P126L in NA. The A/Iceland/78/2018-like viruses possessed in addition the key amino acid substitution S315R while the A/LaRioja/2202/2018 viruses possessed wither G93S or Y155H in NA. (The NA genes of the latest viruses have not yet been characterised.)

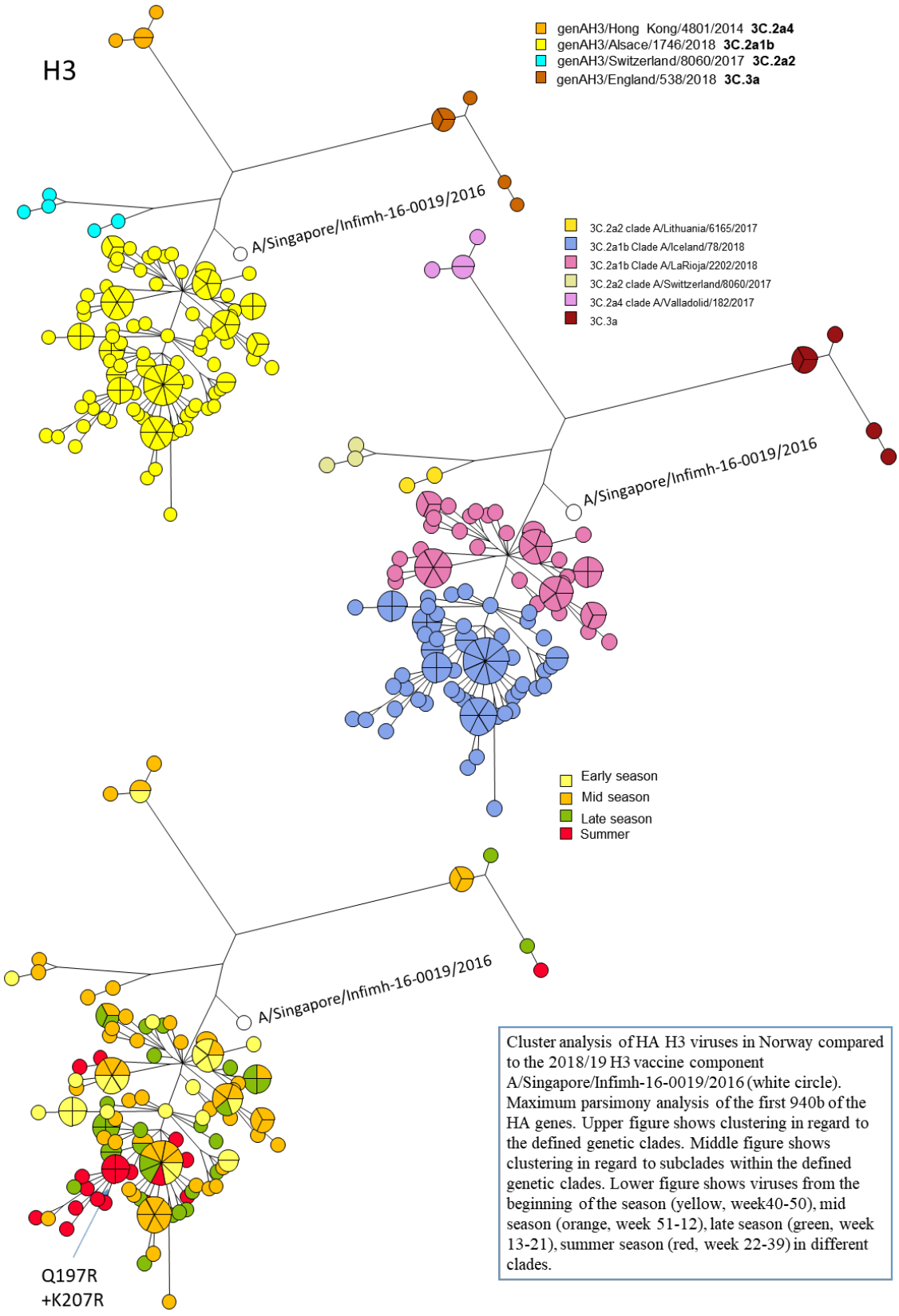


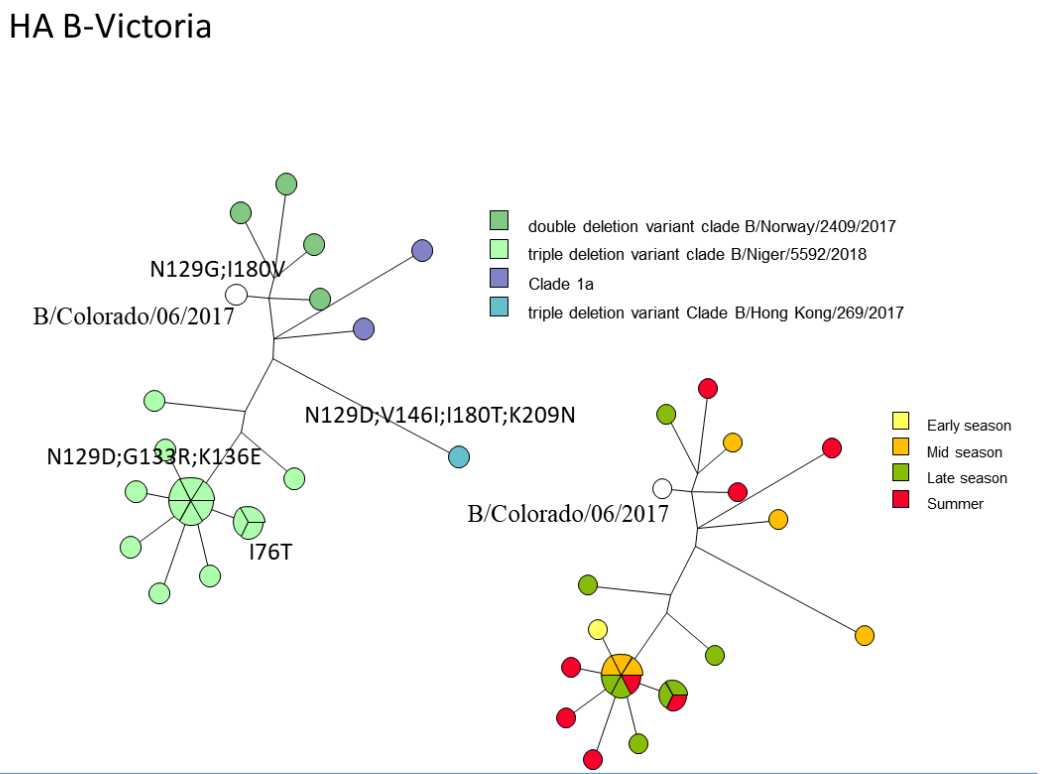
Figure 12. Cluster analysis of the HA gene of influenza A(H3N2) viruses season 2018/19 in Norway, up to week 35 2019.

B-Yamagata

Influenza B-Yamagata viruses characterised are all clade 3 viruses with a few amino acid differences. Two viruses with unsuspectedly many substitutions (G141R;K149E;S150I;D196I;D232N;P240Q) were found in week 3 and 23. See phylogenetic tree at the end of the report. Also the NA of these viruses were different compared to the others, possessing the substitutions K186;I248V;T311S;G346R;G378E and K436R in NA (not shown).

B-Victoria

The majority of the few influenza B-Victoria viruses collected and analysed this season were the triple deletion variant viruses, amino acids 162 to 164 (Δ3). The triple deletion variant viruses separated into two different subgroups, the clade B/Niger/5592/2018 as the most prevalent and one single virus in the B/Hong Kong/269/2017 subgroup. Only 4 double deletion variants, amino acids 162 to 163 (Δ2), have been detected and characterised. Also only two single B-Victoria of the clade 1a without deletions were detected (Figure 13)



Cluster analysis of HA B-Victoria1 viruses in Norway compared to the 2018/19 H1 vaccine component B/Colorado/06/2017 (white circle). Maximum parsimony analysis of the first 1005b 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), late season (green, week 13-21), summer season (red, week 22-39) in different clades.

Figure 13. Cluster analysis of the HA gene of influenza B-Victoria viruses season 2018/19 in Norway, up to week 36 2019.

Antiviral susceptibility

No resistance towards neuraminidase inhibitors like oseltamivir and zanamivir has so far been detected, out of 381 viruses analysed for susceptibility to oseltamivir and 215 to zanamivir (Table 2).

Table 2: Resistance to neuraminidase inhibitor drugs

per. 10/09-19	Oseltamivir (Tamiflu®)		Zanamivir (Relenza®)	
Virus	Tested	Oseltamivir-resistant virus	Tested	Zanamivir-resistant virus
H3	108	0 / (0 %)	107	0 / (0 %)
B	26	0 / (0 %)	26	0 / (0 %)
H1	247	0 / (0 %)	82	0 / (0 %)
Resistance to oseltamivir and zanamivir detected either by sequence analysis or by neuraminidase susceptibility assay				

The last virus with reduced susceptibility to neuraminidase inhibitors observed in Norway was a double-deletion B/Victoria-lineage virus from August 2018, B/Norway/3241/2018, harbouring the substitution D197N in the neuraminidase gene.

Vaccine distribution and coverage

A total of 888 000 influenza vaccine doses have been distributed this season; 715 000 of these were specifically meant for persons in medical risk groups and health care personnel involved in direct patient care. These numbers represent an increase in distributed doses of 55-60 % over the last two years (Figure 14).

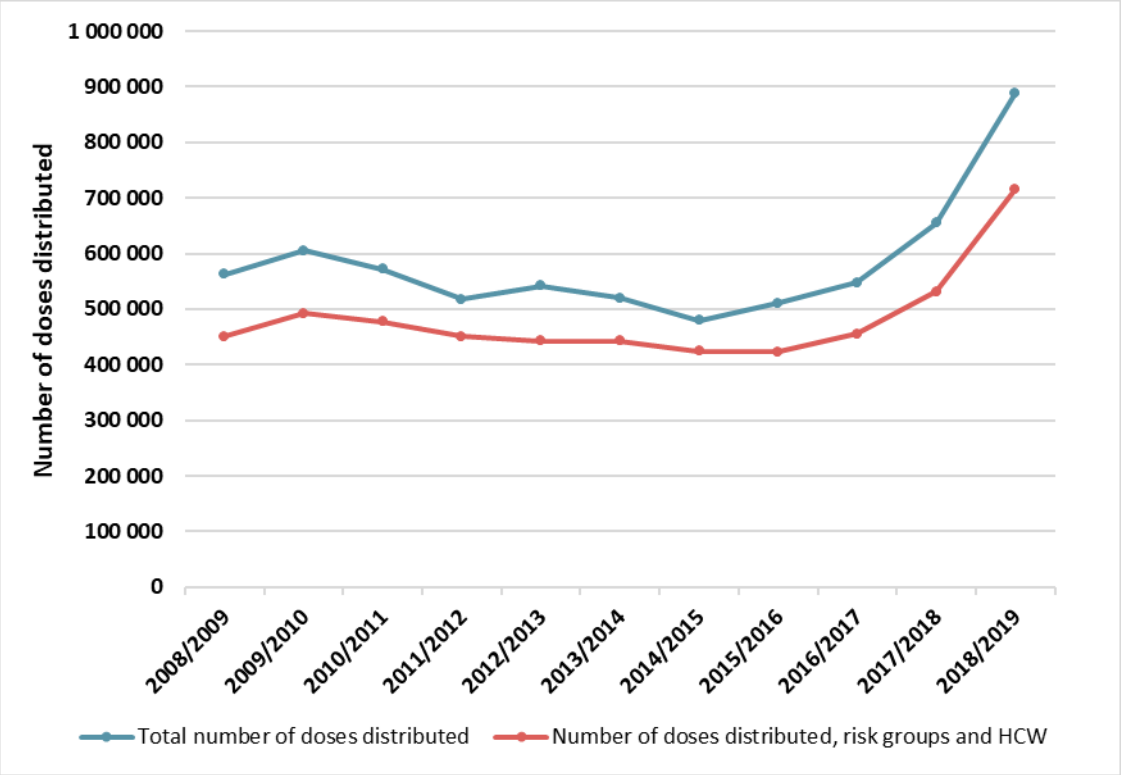


Figure 14: Influenza vaccine doses (seasonal) distributed in Norway, 2008 through 2019 as per 7th June. HCW = Health Care Workers.

Estimates of vaccine coverage in the various risk groups in the current season will not be available until October/November 2019.

Population immunity against recent influenza viruses, August 2018

The National Influenza Seroepidemiology Programme annually in August collects about 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 1178 sera were analysed this year. The main findings are shown in figure 15, table 3, and summarised as follows:

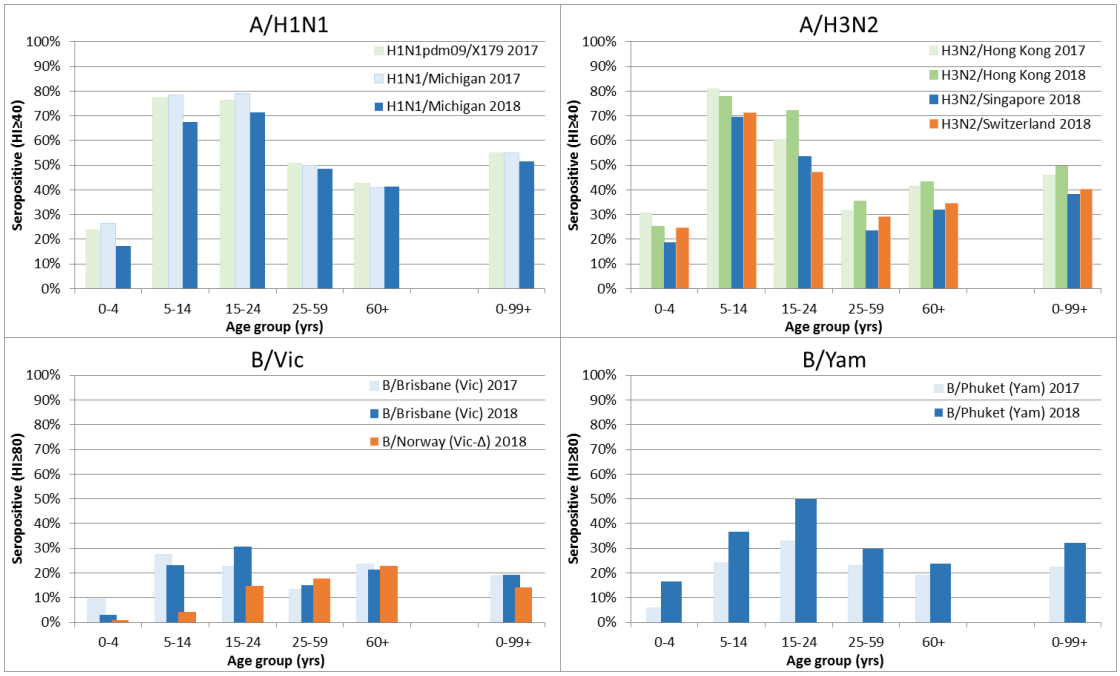


Fig 15. Seroprevalence in August 2018 to current influenza A and B reference and vaccine strains for 'All ages' (0-99+) and in various age groups. For comparison, seroprevalences to some virus strains in August 2017 are also shown. X179A= A/California/07/2009 (H1N1)pdm09; Michigan= A/Michigan/45/2015 (H1N1)pdm09 clade 6B.1; Hong Kong = A/Hong Kong/5738/2014 (H3N2) clade 3C.2a; Singapore= A/Singapore/INFIMH-16-0019/2016 (H3N2) clade 3C.2a1 ; Switzerland= A/Switzerland/8060/2017 (H3N2) clade 3C.2a2; B/Brisbane= B/Brisbane/60/2008 (Victoria lineage); B/Norway= B/Norway/2409/2017 (Victoria lineage, amino acid 162-163 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, even though circulation of this virus was limited during the previous season. However, for those below 25 years old, the proportion of people with protective antibody levels (seroprevalence) had fallen by 10 percentage points since 2017.

Similarly, for A(H3N2) viruses, the comparatively strong population immunity observed in 2017, stemming from previous outbreaks and vaccination, was essentially maintained. The seroprevalence may be somewhat lower against some more recent genetic variants, particularly in the 15-24 years age group.

The seroprevalence against B/Victoria-lineage viruses remained low with overall seroprevalence of 20 % against the previous B/Victoria vaccine component B/Brisbane/60/2008.

Interestingly, the seroprevalence against a newly emerged "double deletion" variant, represented by B/Norway/2409/2017 in our analysis, shows a different and reduced pattern for those below 25 years old, and particularly those younger than 15 years. For those 25 years and older the seroprevalence against the two virus variants was similar.

B/Yamagata-lineage viruses predominated last winter, and the seroprevalence against the current variant B/Phuket/3070/2013 increased since 2017 in all age groups. The largest increase occurred in people younger than 25 years, with more modest increases in other age groups.

Table 3. Influenza seroepidemiological results in August 2018 - Comparison between age groups.
For comparison data from studies performed for the preceding years 2014-2017 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 (2014)	**27**	**52**	**58**	**49**	**31**	**30**	39
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*
H3 Switzerland/9715293/13 (2014)[1)]	20	**31**	**24**	26	**12**	27	21
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*
B/Vic Brisbane/60/08 (2014)	**4**	**20**	12	13	**10**	**21**	14
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/VicΔ Norway/2409/17 (2018)*	***1***	***4***	*15*	***7***	***18***	***23***	*14*
B/Yam Phuket/3073/13 (2014) [1)]	**2**	17	**39**	21	18	16	21
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*
Sera analysed (n): 2015 Aug	178	353	363	894	788	409	2091
[1)]Sub-panel (n) of 2015 sera (SA+HK)	91	145	130	366	282	156	804
[2)]Sub-panel (n) of 2015 sera (Brisb)	132	279	298	709	654	332	1695
[3)]Sub-panel (n) of 2015 sera (Mass+Phu)	75	183	209	467	462	232	1161
Sera analysed (n): 2016 Aug	188	351	333	874	745	411	2028
Sera analysed (n): 2017 Aug	189	318	353	860	797	436	2093
[1)]Sub-panel (n) of 2017 sera (Norway/3806/16)	162	276	315	713	753	390	1856
Sera analysed (n): 2018 Aug	155	251	236	642	501	275	1418
[1)]Sub-panel (n) of 2018 sera (Hong Kong/5738/14)	84	125	114	323	251	137	711
[1)]Sub-panel (n) of 2018 sera (Switz./8060/17)	50	85	84	218	166	92	477

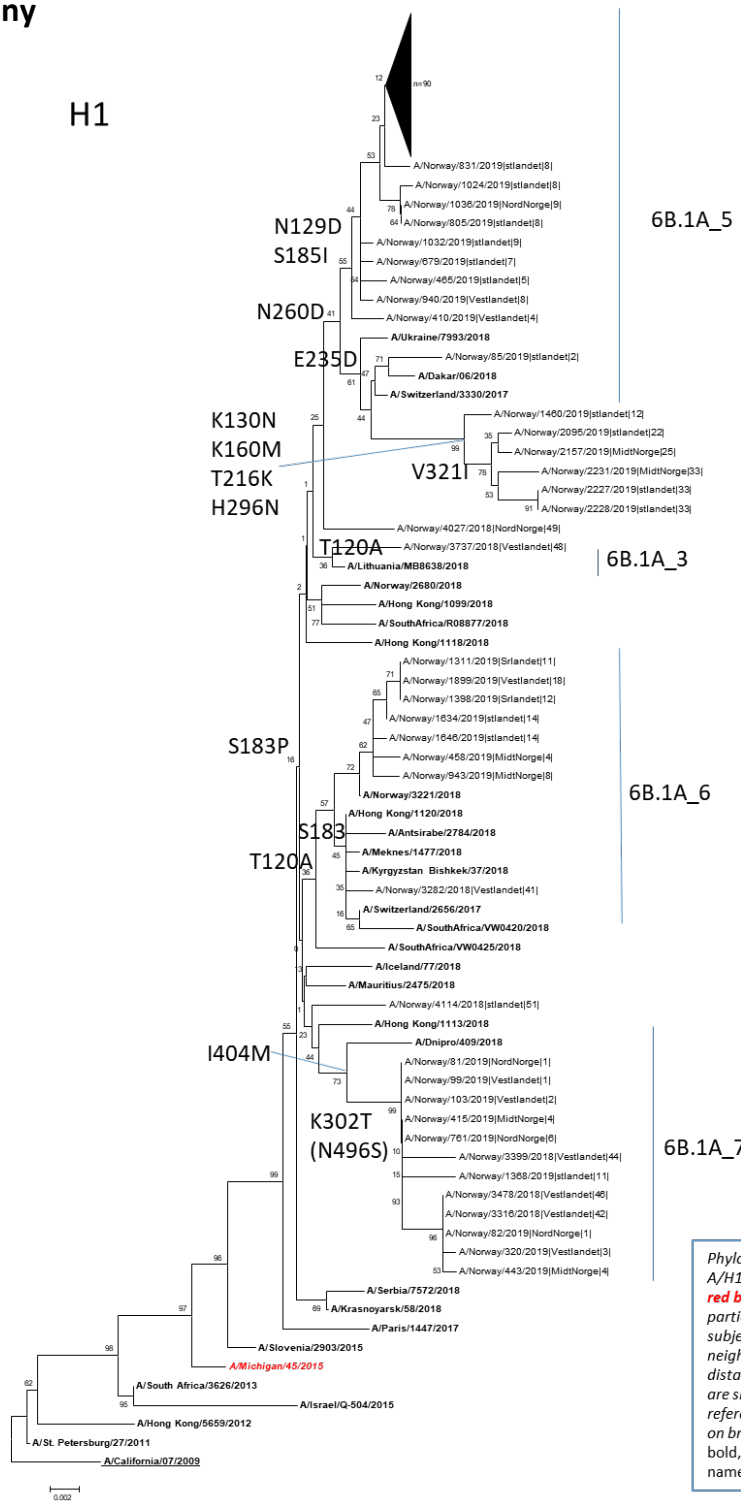
[$]Year of serum collection and HI analysis.

*All entries are per cent of sera having HI titres ≥ 40 for the A strains and ≥ 80 for the ether-treated B strains. The resulting data are weighted according to age group distribution and population density of various counties in Norway.

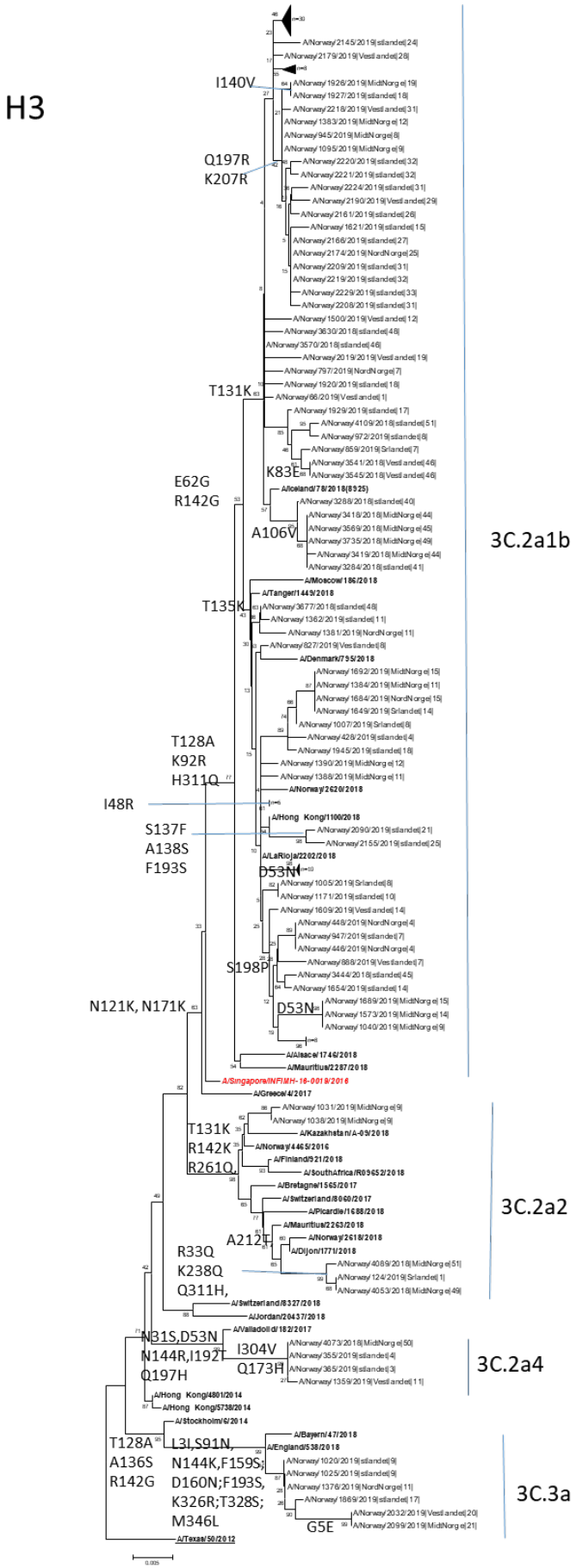
**(Corresponding to) components of the Northern hemisphere influenza vaccine (trivalent/quadrivalent) for the season 2018-2019.

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

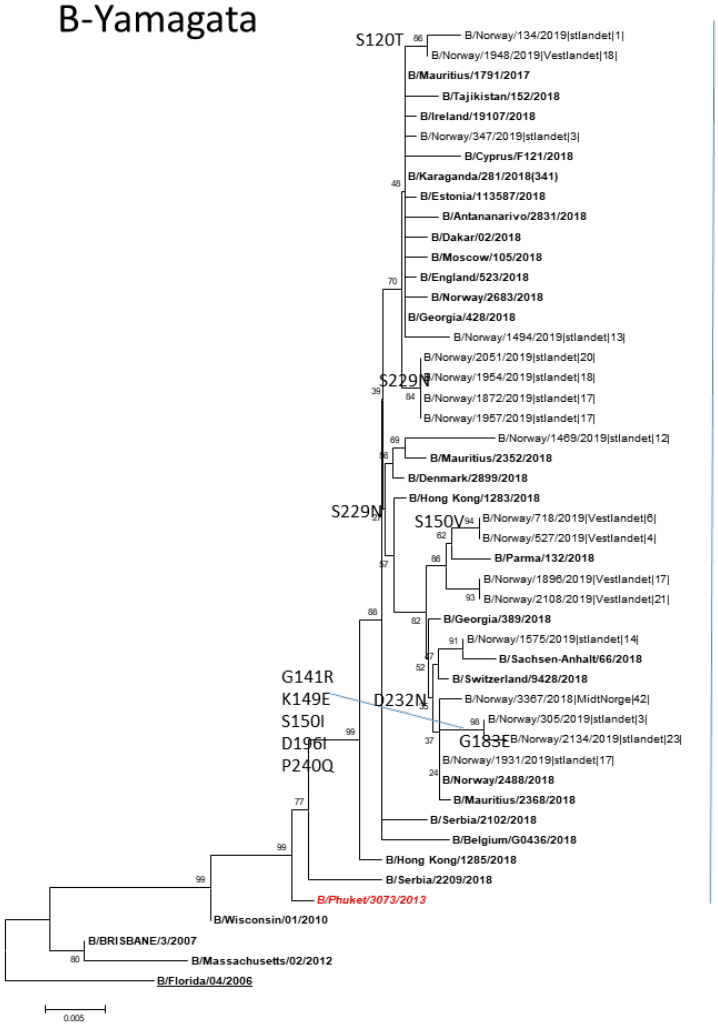
Phylogeny



*Phylogenetic reconstruction of Norwegian A/H1N1 HA genes. Vaccine strain is marked in **red bold italic** and root is **underlined**. Aligned partial HA gene sequences (1030 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. Bootstrap values of 500 resamplings are shown. Key amino acid differences to the reference A/California/07/2009 are indicated on branch nodes.* Reference viruses are in bold, Norwegian viruses from this season are named as: Isolate name|region|week|.



Phylogenetic reconstruction of Norwegian A/H3N2 HA genes. Vaccine strain is marked in ***red bold italic*** *and root is* ***underlined****. Aligned partial HA gene sequences (1040 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.* Reference viruses are in bold, Norwegian viruses from this season are named as: Isolate name|region|week|.



Clade 3

*Phylogenetic reconstruction of Norwegian B-Yamagata HA genes. Vaccine strain is marked in **red bold italic** and root is **underlined**. Aligned partial HA gene sequences (1067 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/Florida/04/2008 are indicated on key branch nodes.* Reference viruses are in bold, Norwegian viruses from this season are named as: Isolate name|region|week|.

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Acknowledgements

The work presented relies heavily on the essential contributions by the sentinel physicians, Norwegian medical microbiology laboratories, the Norwegian Intensive Care Registry and intensive care units, other participants in Norwegian influenza surveillance, as well as the WHO Collaborating Centre for Influenza Reference and Research at the Francis Crick Institute, London, UK and other partners in the WHO Global Influenza Surveillance and Response System and the European Influenza Surveillance Network. Data on the incidence of influenza-like illness are provided by the Department of Infectious Disease Epidemiology and Modelling, Norwegian Institute of Public Health, which also assisted with mortality monitoring. Kristian Waalen, Ph.D., and Torstein Aune, M.Sc., have contributed important parts of the early season data and analysis but are no longer working in the NIC.

A number of sequences were accessed in the GISAID database EpiFlu and we gratefully acknowledge the contributions of all the people and institutions that have been developing and maintaining this sharing mechanism, as well as the authors, originating and submitting laboratories of the sequence data that we have used.

We furthermore gratefully acknowledge the excellent technical work performed by Valentina M. Johansen, Anne Maria Lund, Marie Paulsen Madsen, Remilyn Ramos-Ocao and Marianne Morken.

With best regards,

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

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10 September 2019

Appendices

Methods

Influenza-like illness

Influenza-like illness (ILI) in Norway is monitored through The Norwegian Syndromic Surveillance System (NorSSS). NorSSS is a population-based automated electronic system that daily provides data from all GPs and emergency clinics in primary health care in Norway. The Department of Influenza at the Norwegian Institute of Public Health (NIPH) receives data from the Norwegian Health Economics Administration (HELFO). NorSSS has been in operation since 2014 and is supported by retrospective data from the 2006-07 season and onwards.

Outbreaks in health care institutions

Local outbreaks of contagious disease in health care institutions are notifiable to the Norwegian Institute of Public Health. The reporting concerning suspected or lab-confirmed influenza in nursing homes and hospitals is known not to be complete, although we suspect the reporting is improving.

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.

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, from 2018-2019 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 fifth year 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. For the 2018-19 season an electronic form was developed that will enable the reporting of data that are more detailed. Currently, only limited 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.

NIPH

Published by the Norwegian Institute of Public Health
October 2019
P.O.Box 222- Skøyen
NO-0213 Oslo
Norway
Tel: + 47-21 07 70 00
The report can be downloaded as pdf
at www.fhi.no/en/publ/