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Influenza Epidemiological Information prepared for the WHO Consultation on the Composition of Influenza Virus Vaccines for Use in the 2018 Southern Hemisphere Influenza Season

Melbourne, September 2017

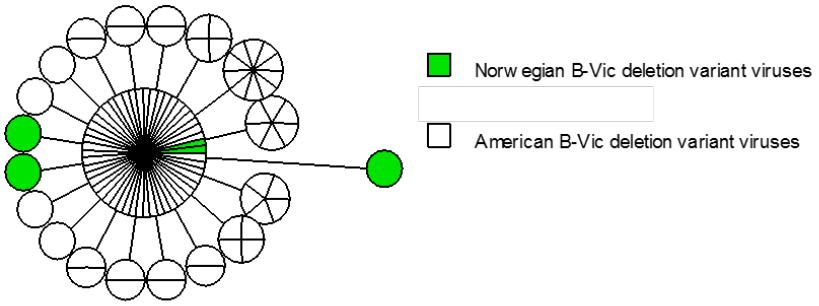


Figure 1: Maximum parsimony cluster analysis of influenza B-Victoria deletion variants in Norway (green) and the USA (white). The analysis suggests more than one introduction of influenza B-Victoria deletion variant viruses to Norway. For further information, see section 2, page 12.

Contents

1: The 2016-2017 influenza season, Norway

Summary

- The influenza season had an unusually early start in Norway and peaked already around New Year
  - Only the 2009 (pandemic) and 2003/04 (Fujian strain) peaks occurred earlier during last 20 years

- The number of samples tested for influenza reached the highest level ever with nearly 160 000 samples tested, but the all-country ILI incidence indicated medium intensity.

- There was strong (~ 95%) predominance of influenza A(H3N2), with very few A(H1N1)pdm09 viruses reported. Influenza B viruses, mostly of the Yamagata lineage, predominated in March-June and peaked very late, but numbers were not high and Yamagata did not predominate in all age groups.
- As in other A(H3N2)-dominated seasons, the elderly were particularly affected.
- Approximately as many people were hospitalised with flu this season as in 2014/15, but more elderly were admitted compared to the previous two seasons
- Significant excess mortality was observed in week 50/2016 to week 3/2017, as well as in week 5/2017 and 8/2017, particularly in the elderly. Fatal influenza cases were also reported from intensive care units.
- In contrast to most other countries in Europe, the A(H3N2) viruses in the ”mother” genetic group 3C.2a were in majority in Norway, with only a minority in sub-clade 3C.2a1. However; the proportion of 3C.2a1 viruses increased, in the off-season, during the summer months.
- Six B/Victoria lineage viruses, collected during April-June, carried the HA1 aa 162-163 deletion. This deletion variant has been reported to be antigenic different from the vaccine virus and currently circulating non-deleted viruses.
- As might be expected with an outbreak affecting a subpopulation with above-average vaccine coverage and a partially protective vaccine, influenza cases in vaccinated individuals were commonplace and more frequent this season than the season before.
- There was reduced protective antibody immunity against the H3N2 vaccine strain (A/Hong Kong/4801/14-like viruses) in August 2016 compared to the previous year. On the other hand, seroprevalence against the H1N1 vaccine strain (A/California/07/09), had risen to the highest observed since just after the influenza pandemic in 2009 (details on page 14).

A look back at the two preceding seasons

- The last H3N2 influenza outbreak in 2014/15 was of medium intensity and co-dominated by two influenza A(H3N2) genetic variants, in approximately equal numbers: the non-antigenic-drift 3C.3b group and the antigenic-drift 3C.2a group.
    - Accordingly, a proportion of the population is expected to have encountered H3N2 group 3C.2a viruses before
- The 2015/16 season was dominated by influenza A(H1N1)pdm09 viruses, mostly of the 6B.1 genetic group, and the outbreak was of medium intensity. Influenza B viruses, primarily of the B/Victoria/2/87 lineage, constituted a third of the cases and dominated towards the end of the season. Post-season predominance of A(H3N2) viruses through the summer months heralded the dominance of this virus in the present season.

Incidence of influenza-like illness

The incidence of 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.

The ILI consultation rate began to rise in week 45/2016, a few weeks after a marked increase in lab confirmed cases, and the epidemic threshold was reached in week 49. The peak came in week 52, which is considerably earlier than in the five previous seasons (Fig. 2, left). The clinical influenza activity was then at a medium level for the first time this season (Fig.2, right). In week 4/2017, the influenza activity returned to low intensity. Measured as the incidence of influenza-like-illness in primary care, the season reached medium intensity (Fig. 2, right). During this influenza season, eleven outbreaks in health care institutions have been reported with the last outbreak occurring in May 2017.

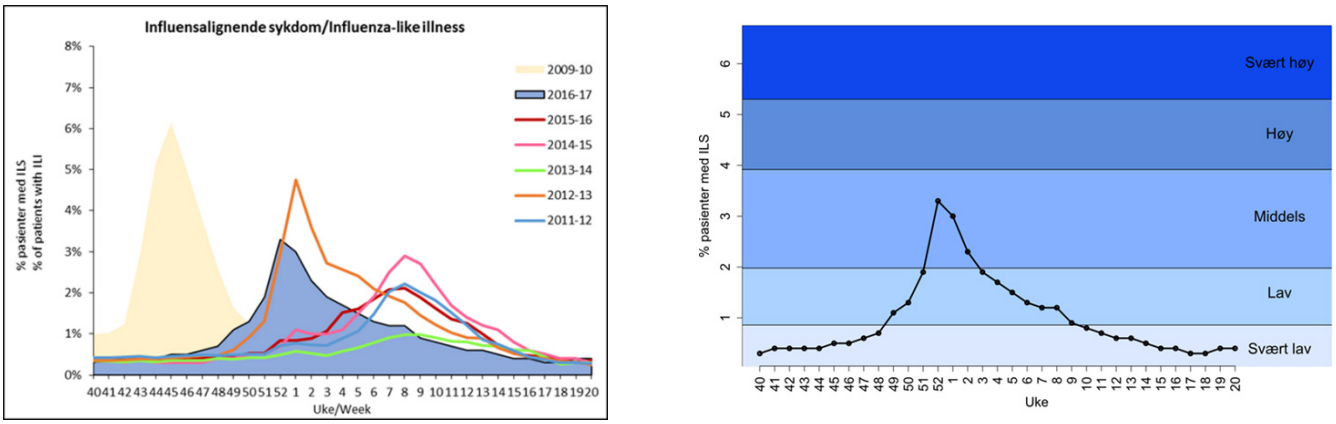
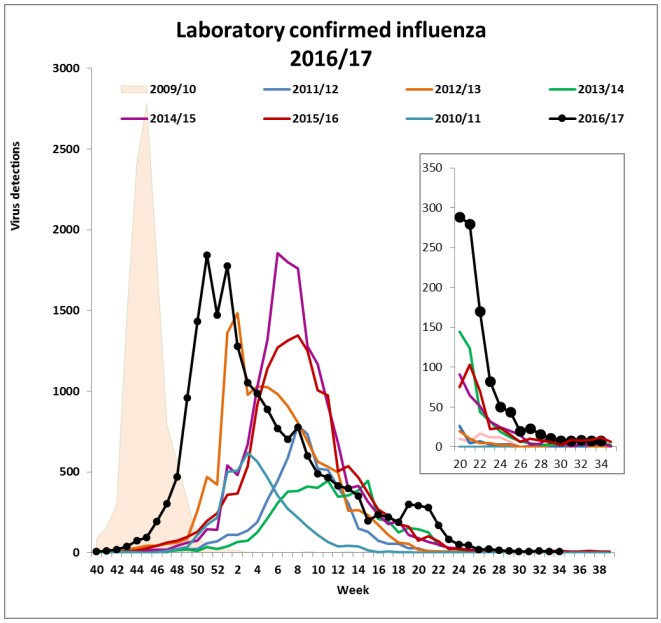


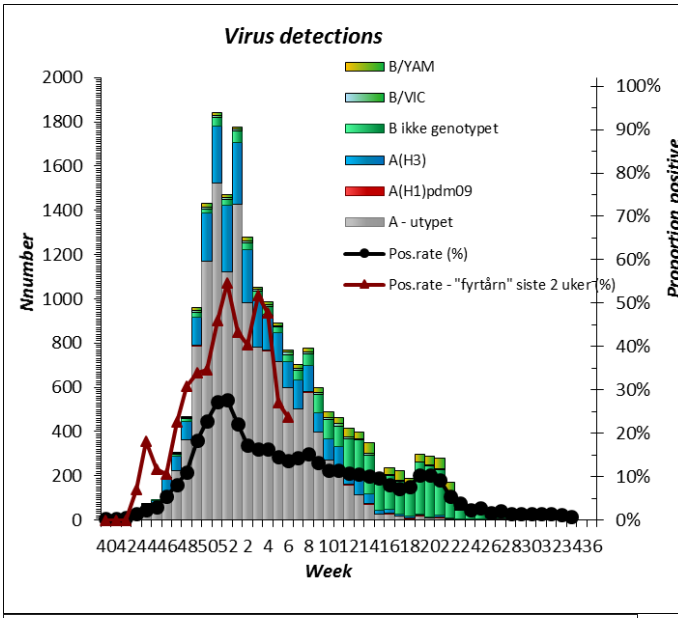
Figure 2: Weekly incidence of ILI, Norway 2016-2017. Proportion of patients in general practice and emergency clinics presenting with ILI, by calendar week. In the left-hand panel, a selection of previous seasons is also shown. In the right-hand panel, the ILI incidence is shown against the present-season MEM intensity thresholds

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, and in addition contribute positive specimens to the NIC for further characterisation. Even though most of these laboratories are in hospitals, the majority of specimens tested for influenza virus tend to be from outpatients attending general practitioners.

Sporadic cases of laboratory verified influenza were recorded weekly throughout the summer and early autumn 2016 (cf. our report for the September 2016 VCM). A clear increase in the numbers was noticed from early November onwards and already then indicated an early developing outbreak compared to previous seasons (Figure 3, table 1). From the outset, influenza A(H3N2) viruses were clearly predominating. The number of weekly detections crossed the 1000 mark in early December and the all-laboratories positivity rate exceeded 20 per cent during the peak weeks 50/2016 through 1/2017. The subsequent decline was slower than the pre-Christmas rise, and in some parts of the country the activity peaked several weeks after others. Whereas there was a steady post-peak decline of influenza A(H3N2) infections, the more limited number of influenza B cases continued to rise until a minor peak was reached in mid-May (figure 3). Influenza B outnumbered influenza A from week 12 and onwards. Influenza positive samples have been reported every week off-season until week 34.





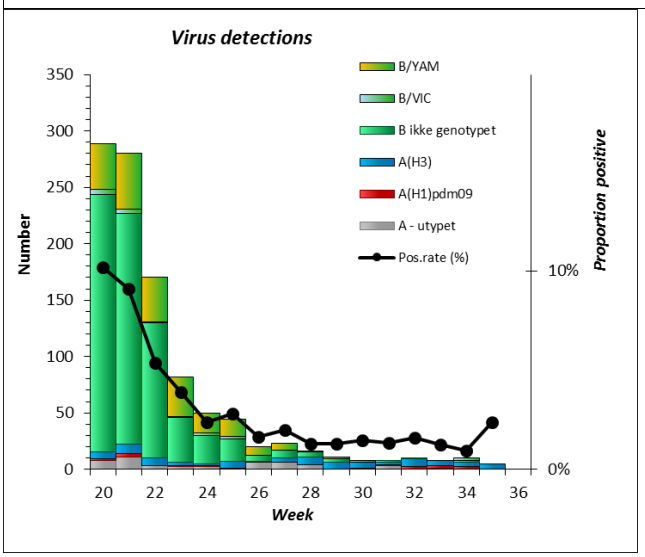


Figure 3: Laboratory detections, Norway 2016-2017. Left hand panel: Weekly numbers of influenza virus detections, with previous season numbers shown for comparison. The insert displays off-season numbers. Right hand panel: Weekly number of the different influenza viruses is displayed as stacked bars, and influenza virus positivity rates of sentinel specimens ("fyrtårn") and all lab testing, respectively, are shown as line graphs. Lower panel: off-season numbers of different influenza viruses.

By week 35 approximately 160 000 samples had been analysed for influenza at Norwegian medical microbiology laboratories this season (Figure 4). Among all reported influenza virus infections, 82% have been type A and 18% type B (figure 5). A(H3N2) constituted more than 99 % of the subtyped type A viruses, with very few (54 out of 3245) A(H1N1)pdm09 viruses. Among genotyped type B viruses, proportions differed between localities, but with a clear majority (79%) of Yamagata/16/88-lineage viruses in most localities and in the country as a whole.

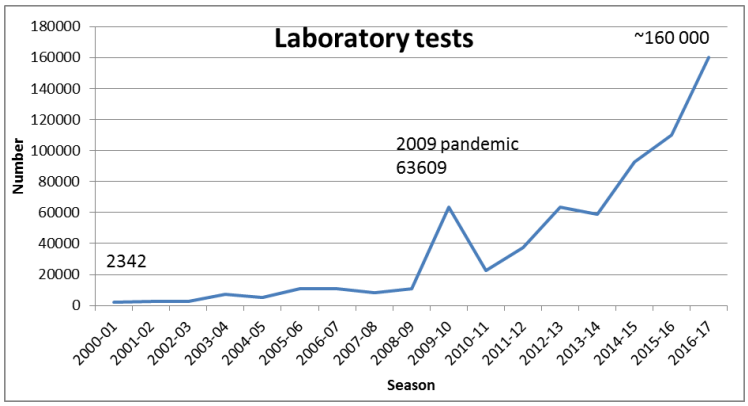
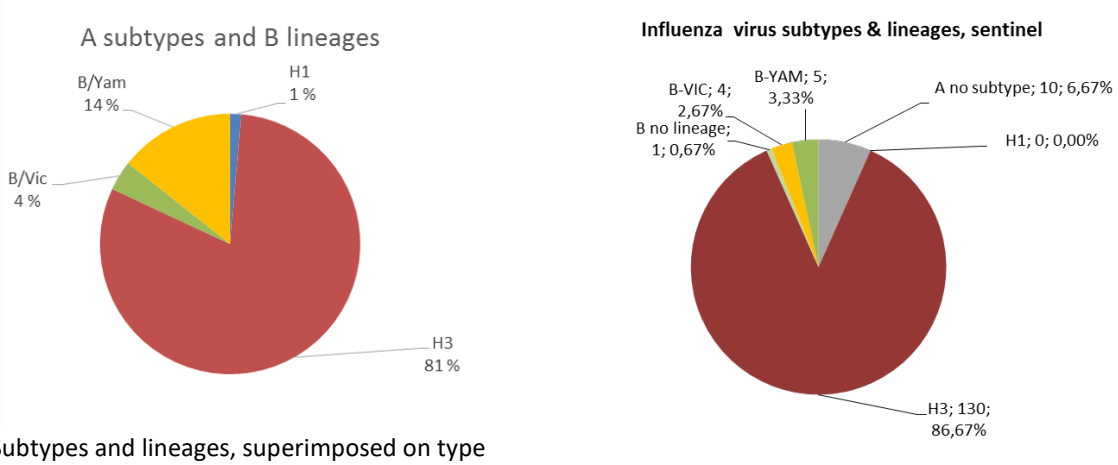


Figure 4. Number of tests for influenza virus carried out in Norwegian medical microbiology laboratories, as recorded in weekly reports to the NIC.



Subtypes and lineages, superimposed on type distribution

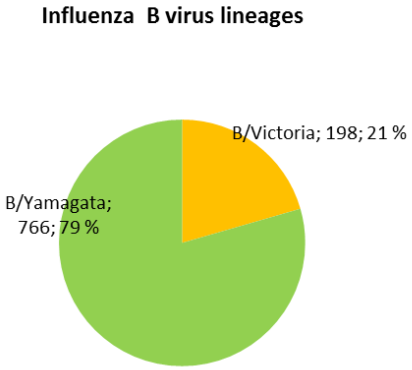


Figure 5. Proportions of 2016/17 season influenza virus subtypes and lineages among viruses analysed in Norway, by 8th of September 2017. In the upper left panel the all-laboratories subtype and lineage frequencies are superimposed on type distributions, for comparison with the distribution among sentinel specimen data. The relative frequencies are generally consistent. The proportion of the H1 subtype may be overestimated in the all-laboratories data because more than three times more viruses were tested for H1 than for H3. Sentinel data are not biased in this way but the numbers are more limited, and few samples were received late in the season when influenza B predominated and the B/Yamagata lineage proportion was higher.

Whereas there among the influenza B viruses was a clear majority of the B/Yamagata lineage, this varied considerably with age (Fig 6). The likelihood of being diagnosed with the B/Yamagata lineage was increasing with age; and the likelihood was similar between lineages in young children as well as in young adults.

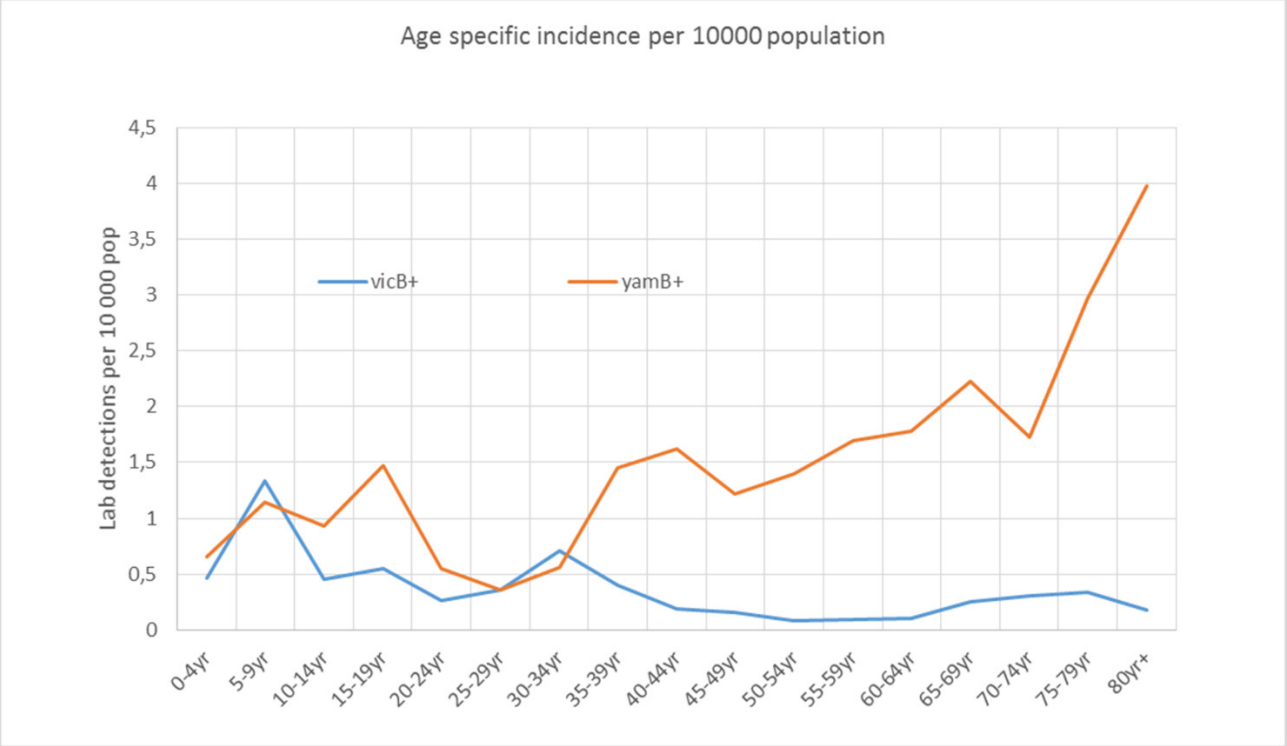


Figure 6: Incidence per 10 000 population of detected influenza B lineages, by 5-year age groups in Norway, 2016/17 season.

UKE/ *week*	Virusspåvisninger/*Virus detections*								ILS
	Prøver/ *Specimens*	% positive	A(utypet) *not subtyped*	A(H1) pdm09	A(H3)	B ikke genotypet *not lineage typed*	B/ Victoria lineage	B/ Yamagata lineage	
40	2274	0,4 %	5	0	2	1	0	0	0,3 %
41	2419	0,4 %	1	0	7	1	0	0	0,4 %
42	2686	0,6 %	9	0	7	1	0	0	0,4 %
43	2706	1,4 %	18	0	19	1	0	0	0,4 %
44	3000	2,4 %	35	3	33	1	1	0	0,4 %
45	3080	3,0 %	52	3	33	5	0	0	0,5 %
46	3500	5,5 %	126	2	55	6	1	1	0,5 %
47	3725	8,2 %	225	0	65	9	4	1	0,6 %
48	4206	11,2 %	361	2	82	15	2	7	0,7 %
49	5231	18,4 %	787	1	128	23	8	13	1,1 %
50	6248	22,9 %	1170	1	216	20	9	17	1,3 %
51	6772	27,2 %	1522	0	260	38	9	12	1,9 %
52	5286	27,8 %	1120	0	302	26	9	14	3,3 %
1	8017	22,2 %	1427	0	280	50	10	9	3,0 %
2	7420	17,2 %	981	1	242	28	9	18	2,3 %
3	6402	16,5 %	782	1	210	42	7	12	1,9 %
4	6038	16,3 %	765	3	163	35	7	14	1,7 %
5	6059	14,7 %	714	2	129	30	2	12	1,5 %
6	5648	13,6 %	597	1	117	33	10	11	1,3 %
7	4912	14,3 %	502	1	130	43	11	16	1,2 %
8	5102	15,2 %	576	3	121	52	7	19	1,2 %
9	4494	13,4 %	398	1	87	82	7	25	0,9 %
10	4237	11,5 %	269	2	98	85	7	26	0,8 %
11	4024	11,5 %	243	0	87	93	13	27	0,7 %
12	3800	10,9 %	159	3	64	140	10	39	0,6 %
13	3753	10,6 %	115	0	70	177	4	33	0,6 %
14	3477	10,1 %	70	3	47	172	11	48	0,5 %
15	2017	9,8 %	25	1	19	116	4	32	0,4 %
16	2865	8,2 %	28	3	17	152	6	30	0,4 %
17	3090	7,2 %	18	0	7	149	6	41	0,3 %
18	2450	7,7 %	7	1	11	126	5	38	0,3 %
19	2888	10,4 %	19	2	5	235	3	35	0,4 %
20	2807	10,3 %	8	1	6	229	4	41	0,4 %
21	3039	9,2 %	11	3	8	205	4	49	
22	3103	5,5 %	3	0	7	120	1	39	
23	2052	4,0 %*	2	1	3	40	1	35	
24	2034	2,5 %*	2	1	2	25	2	18	
25	1526	2,9 %*	0	1	6	20	2	15	
26	1143	1,7 %*	6	0	1	5	0	8	
27	1097	2,1 %*	6	0	4	7	0	6	
28	1168	1,4 %*	4	0	7	4	0	1	
29	794	1,4 %*	0	0	6	3	0	2	
30	514	1,6 %*	1	0	5	0	0	2	
31	557	1,4 %*	3	1	2	2	0	0	
32	591	1,5 %*	0	2	6	1	0	0	
33	590	1,4 %*	2	2	4	0	0	0	
34	948	0,8 %*	0	2	2	2	2	0	
35	201	0,0 %*	0	0	0	0	0	0	
Total	159990		13174	54	3182	2650	198	766	
UKE/ *week*	Prøver/ *Specimens*	% positive	A(utypet) *not subtyped*	A(H1) pdm09	A(H3)	B ikke genotypet *not lineage typed*	B/ Victoria lineage	B/ Yamagata lineage	
		Type A:	16410		Type B:	3614			

Table 1: Proportion of specimens positive for influenza virus, influenza virus detections per type/subtype/lineage (sentinel plus non-sentinel), and weekly incidence of influenza-like illness, in Norway from week 40/2016 through week 35/2017.
*During the off-season weeks, only laboratories with influenza virus detections submitted weekly reports with number of specimens tested.

Pre-season seroprevalence and age-distribution of viruses detected in 2016-17 season.

In figure 7, the pre-season population immunity within age groups against the different influenza viruses, described in Section 3, is shown together with the in-season occurrence of infections for the corresponding viruses and age groups, displayed as incidence of laboratory verified cases.

Figure 7. Prevalence of protective antibody to various influenza viruses in August 2016 (% seropositive, bars) and the age distribution of the different influenza viruses in the 2016/2017 influenza season (from week 40/2016 through week 20/2017, incidence per 10^4 population, line plot).

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. The age profiles of immunity, as well as of infection, are very different between the different subtypes and lineages.

Particularly in the children and young adults, there is a good correspondence between high pre-season seroprevalence and suppressed incidence of infection for A(H1N1) and A(H3N2). Although the number of laboratory verified H1N1 cases is very low, the profile corresponds well to the incidence age pattern seen last winter. This is the case also for the H3N2, B/Yam and B/Vic viruses (cf. our report for the September 2016 VCM).

For other age segments and for the influenza B lineages, seroprevalence did not predict the relative in-season incidences so well this season.

Surveillance of laboratory-confirmed influenza in hospitalised patients

In the laboratory-based surveillance system of influenza-confirmed hospitalisation, seven microbiological hospital laboratories participate. These laboratories cover approximately 58% of the Norwegian population, and report each week the number of influenza virus detections in hospitalised patients (all wards) according to influenza type (A, B) and age group. From week 40/2016 through week 20/2017 influenza virus was detected in 2968 hospitalised patients. The number hospitalisations increased gradually from week 45, peaked in week 52, decreased from week 1 to week 3 and then decreased slowly (Figure 8). Most patients hospitalised with influenza were 60 years or older (Figure 8). Influenza A virus was the most frequently detected influenza type among the hospitalised patients (86%). This is the third year this surveillance system has been in operation. The

cumulative number of influenza-confirmed hospitalisations this season was somewhat higher compared to the level reported in the 2014/2015 season when also influenza A/H3N2) predominated (n = 2679) (Figure 8).

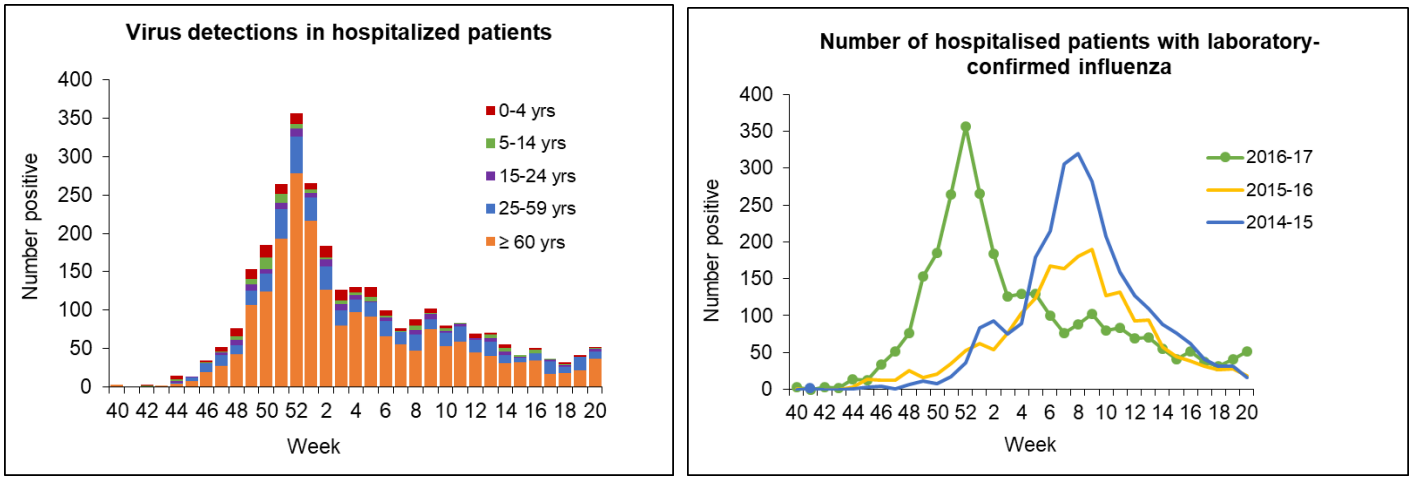


Figure 8. Left hand panel: The number of influenza virus detections in hospitalised patients per week during influenza season 2016/2017, age-distributed. Right hand panel: The number of hospitalised patients with confirmed influenza per week the three last influenza seasons. To be able to compare the seasons, week 1/2016 is the average of the number of patients hospitalised with influenza in week 53/2015 and week 1/2016.

Influenza patients in intensive care units

This season it was piloted whether the Norwegian Intensive Care Registry (NICR) can be used as a data source for a national surveillance of influenza patients in intensive care units (ICUs). Almost all ICUs in Norway report data to NICR. As part of the pilot, NICR asked all ICUs from week 46/2016 through week 20/2017 to report weekly the number of patients in ICUs with laboratory-confirmed influenza (J10), the number of patients in ICUs with clinically suspected influenza (J11) and the number of deaths among patients with confirmed or suspected influenza admitted to ICUs (Table 2). Anonymised data was reported from NICR to the NIPH. Since this is the first season the scheme was operated, it is not possible to compare the results from this season with results from previous seasons.

Table 2. The number of confirmed or suspected influenza ICU admissions and deaths from week 46/2016 through week 20/2017.

Number of patients admitted in ICUs with laboratory-confirmed influenza	256
Number of patients admitted to ICUs with clinically suspected influenza	178
Number of deaths among patients with laboratory-confirmed or clinically suspected influenza admitted to ICUs	26

Excess all-cause mortality

The NIPH has been conducting weekly all-cause mortality surveillance since the 2015/2016 season, using the EuroMOMO algorithm. Historical data are available since 2008. This season, significant excess mortality was observed in Norway in six consecutive weeks (week 50/2016 through week 3/2017) as well as in week 5/2017 and 8/2017 in the elderly (> 65 years). Excess mortality was also observed in week 52/2016 in the age group 15-64 years. The increase in the number of deaths coincided with the weeks in which the influenza activity was highest. The level of excess mortality was higher this season compared to the level observed in 2014/2015. http://www.euromomo.eu/

2: Characterisation of influenza viruses circulating in Norway, 2016-17 season

Influenza A(H3N2)

By week 35, 1550 samples have been PCR-positive for H3 at the NIC Norway, 15% of those have been sequence analysed and a representative selection of these, 44%, have been submitted to GISAID. Strain-based reporting of virus characterisation data was done routinely through TESSy. All H3 viruses belonged to the H3 genetic clade 3C.2a with several subgroups circulating at the same time (see phylogeny and cluster analysis). The most prevalent group of H3 viruses possessed the N121, T131K, R142K, N144K and R261Q substitutions in the HA. Both T131K and R142K are in antigenic site A and have previously been related to antigenic drift. In the south-eastern part of Norway and in mid-Norway H3 cases increased rapidly very early in the season (week 43) and these mutated viruses caused most outbreaks driving this rapid increase. The HA of these viruses grouped directly under the 3C.2a main clade, while the NAs were more like NAs of the H3 subgroup 3C.2a1 viruses. In general, 3C.2a1 subgroup viruses have been reported to dominate in Europe this season. This was not the case in Norway. A small increase of 3C.2a1 viruses was seen during the summer months. The 3C.2a1 viruses in Norway possessed the N121K, N171K, I406V and I140M substitutions. During the summer months, 3C.2a1 viruses possessing the E62G, K92R, R142G, Q311, R201Q substitutions, some also with T135K, were detected.

Other 3C.2a main-clade viruses circulating in Norway this season resembles the A/Cote D'lvoire/697/2016 reference virus with the N121K, N122D and R144K substitutions, some of the Norwegian viruses in addition possessed the F219Y substitution. (see phylogeny sections)

There has been little change in the distribution of H3 viruses with regard to genetic subclades throughout the season. Possibly, there was a slight overweight of 3C.2a1 viruses during the summer months. (Figure 9).

From week 40 to week 35, 89 influenza H3 viruses (6% of H3 viruses received at NIC Norway), both virus isolates and clinical samples, have been shipped to the WHO Collaborating Centre for Reference and Research on Influenza, Crick Worldwide Influenza Centre. Approximately 11% of the H3 viruses received at the NIC have been propagated in cells for further analysis.

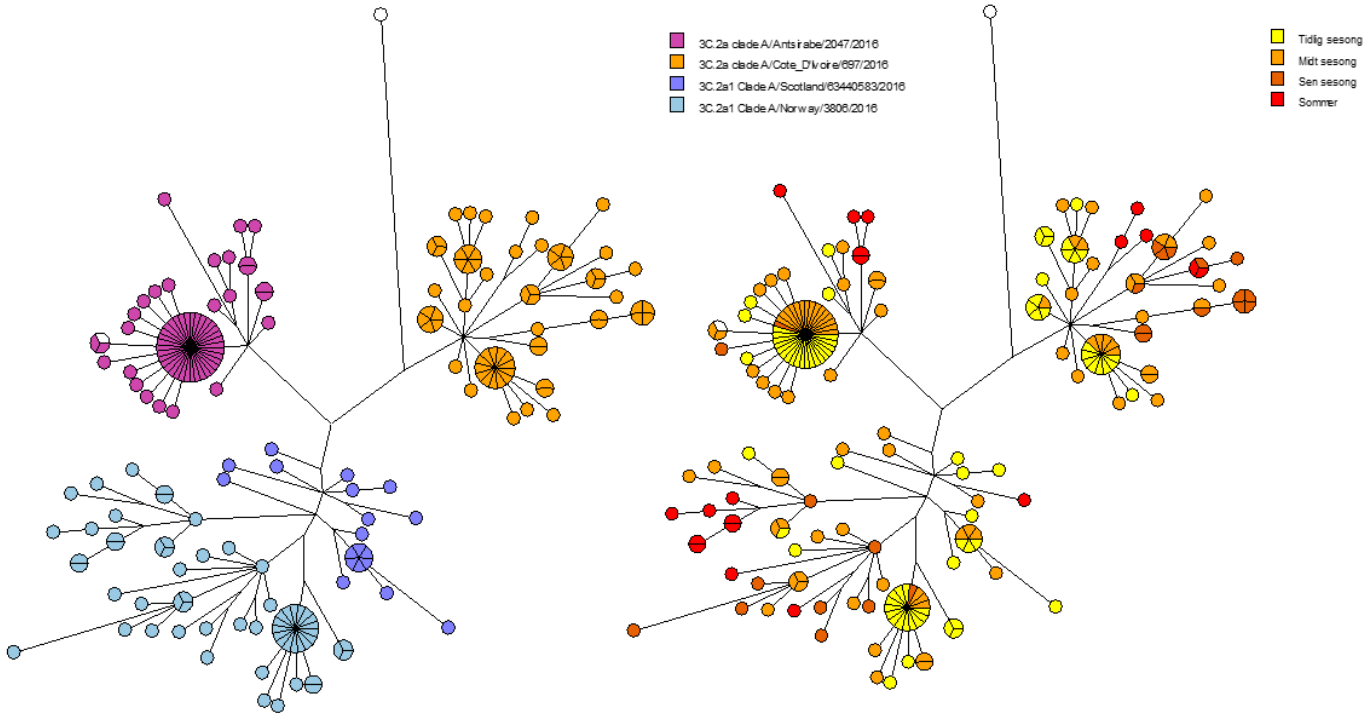


Figure 9: Cluster analysis of HA H3 viruses in Norway compared to the 2016/17 H3 vaccine component A/Hong Kong/4801/2014 (white circle). Maximum parsimony analysis of the first 770 nucleotides of the HA genes. Left figure shows clustering in regard to defined genetic subclades. Right figure shows the distribution of different subclades through the season. Viruses from the beginning of the season (yellow, week40-50), mid season (light orange, week 51-12), late season (dark orange) and summer (red).(Data includes viruses up to week 35)

Neuraminidase activity analysis of the NA genes from the different H3N2 viruses could indicate that the 3C.2a group of viruses had more efficient NA activity than the 3C.2a1 viruses. All H3 viruses react poorly in the HA assay (Table 3).

Table 3: HA and NA activity by different H3 clades; mean dilution to standardise NA activity; and mean HA titre

3C.2a subgroups	Mean dilution for IC50*	Mean HA titre
3C.2a clade A/Antsirabe/2047/2016	43	2,5
3C.2a clade A/Cote_D'Ivoire/697/2016	60	2
3C.2a1 Clade A/Norway/3806/2016	32	3
3C.2a1 Clade A/Scotland/63440583/2016	33	2

*Mean dilution for IC50 value indicates the dilution factor needed to adjust/standardise the neuraminidase activity of the virus to 15500 RFU. Higher value indicates a virus with higher initial neuraminidase activity.
HA titre is a measure of haemagglutinating activity and was for H3N2 viruses measured using guinea pig red blood cells.

Samples from persons vaccinated for the 2016/17 season made up nearly 3% of all samples received to the NIC Norway, compared to 1.4% in the 2014/15 season and 1.2% in the 2015/16 season and a higher proportion of influenza infected vaccinated people was seen in the sentinel samples compared to the non-sentinel. A higher proportion in this group is as expected, but the proportion was higher than usual. The proportion of elderly in sentinel samples is lower than in the non-sentinel group. Most people vaccinated in Norway are elderly and this season the elderly were overrepresented with H3 influenza. Table 4 summarises the percentage of patients vaccinated with lab confirmed influenza.

Table 4: Percentage vaccinated with lab-confirmed influenza

		Proportion vaccinated infected with influenza									Total		
		Outpatients (%)			Hospitalised (%)			Sentinel (%)	Non-sentinel (%)	Vaccinated infected with influenza (%)	Vaccinated intected with influenza (antall)	Influenza positive samples (number)	Samples from vaccinated (%)
Sdeason	Dominating virus in season	H3	H1	B	H3	H1	B						
2014-15	H3/B	1,4	1,6	0,6	1,1	0,0	0,7	4,3	0,7	0,9	22	2511	1,4
2015-16	H1/B	0,6	0,7	0,6	0,0	0,6	0,6	2,8	0,6	0,4	16	3917	1,2
2016-17	H3	2,8	0	0,2	2,0	0,0	0,4	11,1	1,1	1,7	40	2386	2,9

Influenza B

B/Victoria/2/1987 lineage

Out of 199 samples PCR positive for B/Victoria at the NIC Norway, 32% have so far been sequence analysed and a representative proportion of these, 58%, have been submitted to GISAID. One main drifted group of the influenza B/Victoria viruses circulated in Norway, possessing the substitutions R80K and T258P.
Six cases of the B-Victoria deletion variant viruses were detected during April through June, in different parts of Norway. These viruses have been reported from WHO-CC and CDC to be antigenically different from the vaccine strain. The viruses possessed the 162/163 amino acid deletion in HA together with N to S in position -2 of the reading frame of HA (position 14 of the signal peptide) and I180V and R498K substitutions. One virus possessed the ancestral N in position -2 together with N518D. These substitutions were not seen in B-Victoria deletion variants in the USA. The phylogenetic analysis indicated at least two introductions of this variant virus into Norway (Figure 10).

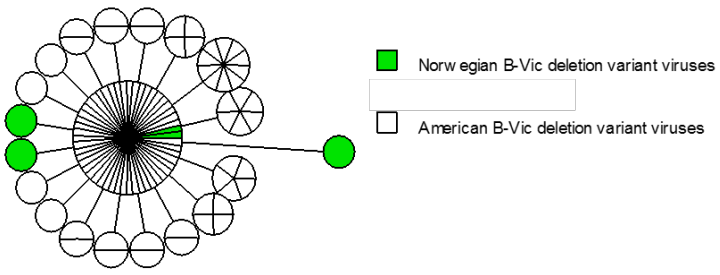


Figure 10: Maximum parsimony cluster analysis of influenza B-Victoria deletion variants in Norway 2016-17 (green) and the USA (white). One additional deletion variant virus from Norway was not included in the analysis due to short sequence obtained. See also the phylogeny section.

Preliminary serology data (not shown) with human sera collected in august 2016 might indicate only a slightly reduced immunity to the influenza B/Victoria HA 162-163 deletion variant compared to MDCK cell isolated cultivars of the current influenza B Victoria vaccine virus Brisbane/60/2008. Further analyses are ongoing to reveal the antibody protection in various age groups against this new variant.

From week 40 through week 35, 23 influenza B/Victoria viruses (12% of B/Victoria viruses received at NIC Norway), both virus isolates and clinical samples, have been shipped to the WHO Collaborating Centre for Reference and Research on Influenza, Crick Worldwide Influenza Centre. Approximately 14% of the B-Victoria viruses received at the NIC have been propagated in cells for further analysis.

B/Yamagata/16/1988 lineage

Out of 818 samples PCR positive for B/Yamagata at the NIC Norway, 12% have so far been sequence analysed and a representative selection, 45%, of these have been submitted to GISAID. All B/Yamagata viruses from this season in Norway belonged to the genetic clade 3. They all possessed the M251V substitution and a minor group possessed D232N in addition. The D232N substitution creates one additional glycosylation site in HA (see phylogeny section).

From week 40 to week 35, 33 influenza B/Yamagata viruses (3% of B/Yamagata viruses received at NIC Norway), both virus isolates and clinical samples, have been shipped to the WHO Collaborating Centre for Reference and Research on Influenza, Crick Worldwide Influenza Centre. Approximately 4% of the B-Yamagata viruses received at the NIC have been propagated in cells for further analysis

Influenza A(H1N1)pdm09

Few H1 viruses have circulated in Norway this season, but have been somewhat more frequent during the late summer months. 34 have been PCR positive for H1N1 at the NIC Norway and 26 of these have been sequence analysed (76%) and a representative selection, 63%, out of these have been submitted to GISAID. Strain-based reporting of virus characterisation data was done routinely through TESSy. The H1 viruses clustered together genetically with the A/Slovenia/2903/2015 6B.1 group of viruses. (see phylogeny section). H1N1 viruses during the summer months possessed the S74R, S164T and I295V substitutions in HA.

From week 40 to week 35, 13 influenza H1N1 viruses (55% of H1N1 viruses received at NIC Norway), both virus isolates and clinical samples, have been shipped to the WHO Collaborating Centre for Reference and Research on Influenza, Crick Worldwide Influenza Centre. Approximately 26% of the H1N1 viruses received at the NIC have been propagated in cells for further analysis.

Antiviral resistance monitoring

Monitoring of antiviral susceptibility has not revealed any resistance in Norwegian viruses this season.

Table 5. Norwegian influenza viruses resistant to M2 blockers (adamantanes) and the neuramidase inhibitors oseltamivir and zanamivir, during the period from week 40/2016 through week 35/2017.

pr. 08/09-17	Oseltamivir (Tamiflu®)		Zanamivir (Relenza®)		Adamantaner (Amantadin, Rimantadin)	
virus	Tested	Oseltamivir resistant viruses	Tested	Zanamivir resistant viruses	Tested	Adamantane resistant viruses
H3	173	0 / (0 %)	161	0 / (0 %)	0	
B	57	0 / (0 %)	57	0 / (0 %)		
H1pdm09	10	0 / (0 %)	9	0 / (0 %)	0	

Two screening tools were used to determine oseltamivir/zanamivir susceptibility: sequence analysis of viral genes or a fluorescence-based neuraminidase inhibition assay.

* we have not tested for adamantane resistance in the 2016/17 season

3: Seroepidemiology Data, August 2016

The National Seroepidemiological Influenza Programme for the year 2016 analysed a total of 2028 serum samples collected during the weeks 31-35 from clinical/microbiological laboratories covering the 18 of 19 counties of Norway. The anonymised convenience sera are aiming to be representative of the Norwegian population geographically and by age composition.
The 2016 serum panel was tested by haemagglutination-inhibition (HI) against the 2016/17 seasonal influenza vaccine strains (trivalent/quadrivalent) (Table 1), i.e. A/California/07/2009(H1N1pdm09, the vaccine virus X-179A was used), A/Hong Kong/5738/14 (a H3N2/A/Hong Kong/4801/14 (3C.2a)-like reference virus), B/Brisbane/60/08 (B/Victoria-lineage 1A-like virus), and B/Phuket/3073/13 (B/Yamagata-lineage 3-like virus). Two additional viruses were also included in the analyses: The recent H1N1 virus isolate A/Slovenia/2903/15 (a H1N1 B/Michigan/45/15 6B.1-like virus, the H1 component of the 2017 southern hemisphere influenza vaccine) and A/Switzerland/9715293/13 (a H3N2 3C.3a-like virus, the H3 component of the 2015/16 season influenza vaccine). HI titres ≥ 40 against the influenza A strains and ≥80 against ether-treated influenza B strains were considered as protective levels and recorded as seropositive in this analysis. The results are shown in Table 6 and Figure 12.

Summary of outcomes

The results from the seroepidemiology study in August 2016 show that population seroprevalence to the H1N1pdm09 vaccine virus is high (46 %, 'All ages') and has increased significantly from August 2015. This is in accordance with the dominant circulation of H1N1pdm09 viruses (about 72 %) the preceding 2015/16 influenza season. The seroprevalence to the H1N1pdm09 virus in August 2016 is the highest observed since the influenza pandemic in 2009.
The previous season A(H3N2) viruses were scarce (about 7 % of circulating viruses), thus a reduced seroprevalence to H3N2 viruses were observed with the highest reduction against the A/H3N2 component of this season's influenza vaccine (A/Hong Kong/5738/14 was used, a A/Hong Kong/4801/14 -like virus, 3C.2a genetic group). A lesser reduction was seen against the A/Switzerland/9715293/13 (3C.3a genetic group, H3 component of the previous season vaccine). The reduction in seroprevalence against A/Hong Kong virus might be due to waning immunity against this H3 variant and thus shorter duration of protective antibodies.
The seroprevalences against influenza B viruses were also reduced in most age groups, both against the B/Victoria- and the B/Yamagata-vaccine strains, B/Brisbane/60/08 and B/Phuket/3073/14 (quadrivalent vaccine only), respectively.

Influenza A(H1N1)pdm09

In August 2016 the prevalence of protective antibodies to A(H1N1)pdm09 was 46 % (All ages), an increase of 7 percentage points from August 2015. This is consistent with the high level of H1pdm09-like viruses circulating the preceding season with the pdm09 being the dominant virus (72 %). A similar pattern was seen for the various age groups (Table 1, Figure 12) with the highest increase (13 percentage points) in the 5-14 year olds. A similar increase was also seen in the other age groups (between 4 to 8 percentage points) except for those 60 year or older with no change in seroprevalence to H1pdm09 from the previous year. The serum panel was also tested against the more recent H1pdm09 reference strain A/Slovenia/2903/2015 (subgroup 6B.1). The seroprevalence to this strain is similar to the pandemic strain for 'All ages', although a somewhat higher prevalence (4 and 6 percentage points) is seen in 0-4 and 15-24 year olds, respectively, while for the 60+ year olds there was a reduced seroprevalence by 3 percentage points.

Normalization/adjustment of HI-titres to A(H1N1)pdm09. In August 2016 and the previous years 2011 to 2015 the serum panels were tested against the reassortant vaccine strain X-179A (A/California/07/09). The resulting HI titres with X-179A vaccine virus have been adjusted to the A/California/07/09 wild type virus using an international standard serum to A(H1N1)pdm09 (IS10/202). The normalized/adjusted results are compared to the HI results from previous years as indicated (Table 1).

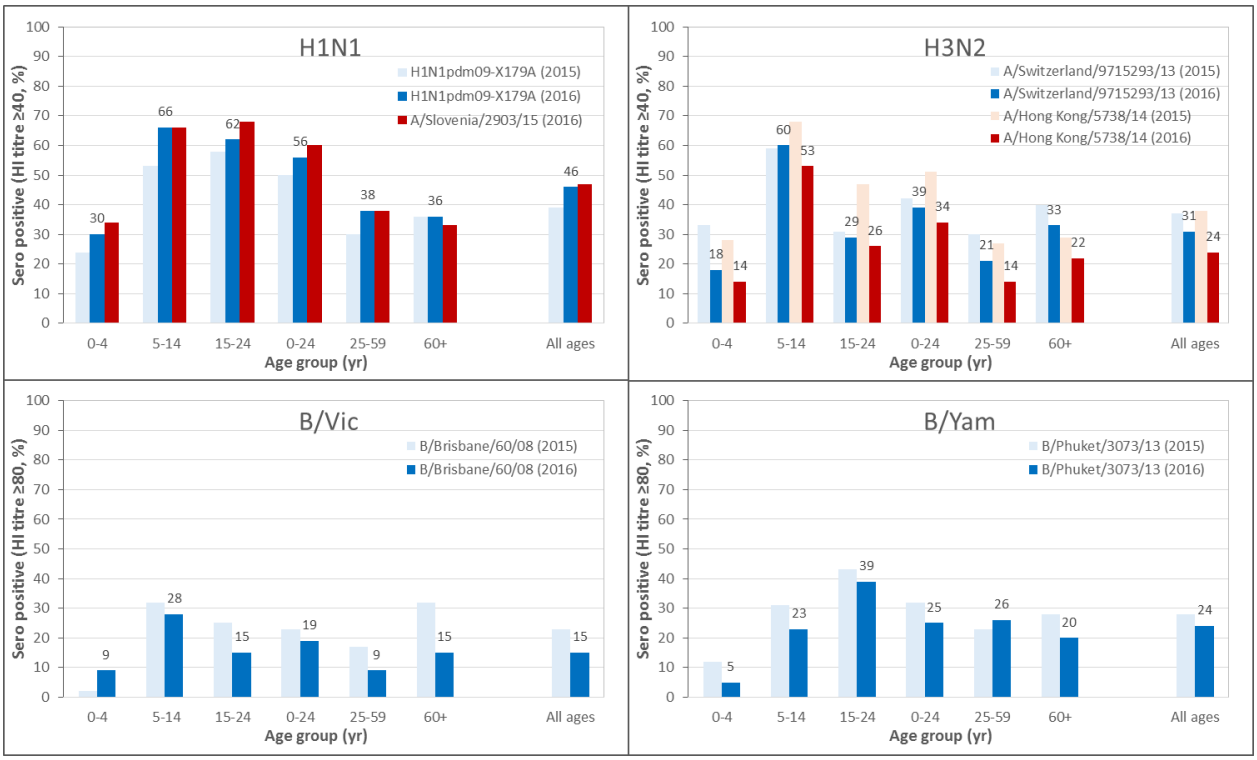


Figure 12. Seroprevalence in August 2016 against current influenza A and B reference and vaccine strains in various age groups. For comparison the seroprevalence against some virus strains in August 2015 are also shown. Columns in dark colour (blue, red) show the seroprevalence in 2016. Columns in light blue and pink colour show the corresponding seroprevalences in 2015 for some strains. Further details are given in the text

Influenza A(H3N2)

The seroprevalence in August 2016 against the current H3N2 vaccine strain (A/Hong Kong/4801/14, 3C.2a genetic group, represented by A/Hong Kong/5738/14), as well as the seroprevalence against the vaccine strain of the 2015/16 season (Switzerland/9715293/2013, 3C.3a genetic group virus), are reduced compared to the previous season, from 38 % to 24 % and from 37 % to 31 % for 'All ages', respectively. A reduced seroprevalence is seen in most age groups, the highest reduction in those 15-24 year old (by 21 percentage points), while a reduced seroprevalence by 13 to 17 percentage points is seen in the other age groups, except for those 60 year and older with less reduced seroprevalence against the H3N2 vaccine virus strain (by 7 percentage points). (Table 6, Figure 12). This is consistent with the low proportion of H3N2 viruses circulating the preceding season, i.e. about 7 % of detected viruses. The seroprevalence in August 2016 was particularly low (14 %) for those below 5 years of age and the 25-59 age group. This reduced seroprevalence against H3N2 viruses might thus have contributed to the high number of H3N2 viruses circulating the current season.

Influenza B

For both influenza B/Victoria and B/Yamagata lineage vaccine strains, a reduced seroprevalence was seen in August 2016, i.e. for 'All ages' a reduction by 8 and 4 percentage points, respectively (Table 6). A similar reduction in seroprevalences are seen also for most age groups for both influenza B lineage viruses except for the 0-4 year olds (B/Victoria viruses) with increased seroprevalence of 7 percentage points and for 25-59 year olds (B/Yamagata viruses) a modest increase of 3 percentage points (Table 6). In particular, for the age group 60 years and above a large reduction in seroprevalence (17 percentage points) to the B/Victoria lineage vaccine virus is observed.

Table 6. Influenza Seroepidemiological results in August 2016 - Comparison between age groups.
For comparison data from studies performed for the preceding seasons 2009-2015 are also included.

Influenza strains (Year[$])	Age groups 0-4	5-14	15-24	0-24	25-59	60+	All ages
H1 California/07/09 (2009)	**0***	**1**	**12**	**5**	**2**	3	3
H1 California/07/09 (2010 Jan)	60	**65**	46	**56**	39	36	45
H1 California/07/09 (2010)	**19**	**39**	**43**	**36**	**21**	**14**	26
H1 X-179A/A(H1N1)pdm09 (2011)	26	**31**	**37**	**33**	**17**	**13**	21
H1 X-179A/A(H1N1)pdm09 (2012)	**14**	**35**	**39**	**32**	**14**	**14**	22
H1 X-179A/A(H1N1)pdm09 (2013)	**26**	**43**	**53**	**43**	**26**	**20**	32
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*
H3 Victoria/361/11 (2013)	27	57	38	43	21	29	32
H3 Texas/50/12 (2013)	28	65	38	45	22	29	34
H3 Texas/50/12 (2014)	**21**	**67**	**48**	**50**	**27**	42	40
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*
B/Vic Brisbane/60/08 (2010)	**3**	**7**	**6**	**6**	11	**18**	10
B/Vic Brisbane/60/08 (2011)	25	**31**	**9**	**21**	**10**	21	17
B/Vic Brisbane/60/08 (2012)	17	**18**	**8**	14	**8**	15	12
B/Vic Brisbane/60/08 (2013)	13	31	15	21	16	23	19
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/Yam Wisconsin/1/10 (2013)	12	22	40	27	20	17	22
B/Yam Massachusetts/2/12 (2013)	17	31	66	42	36	29	37
B/Yam Massachusetts/2/12 (2014)	**14**	35	**60**	**41**	39	38	39
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*
Sera analysed (n): 2013 Aug	202	349	356	907	786	436	2129
Sera analysed (n): 2014 Aug	201	337	354	892	790	429	2111
[1)]Sub-panel (n) of 2014 sera	89	127	109	325	251	138	714
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

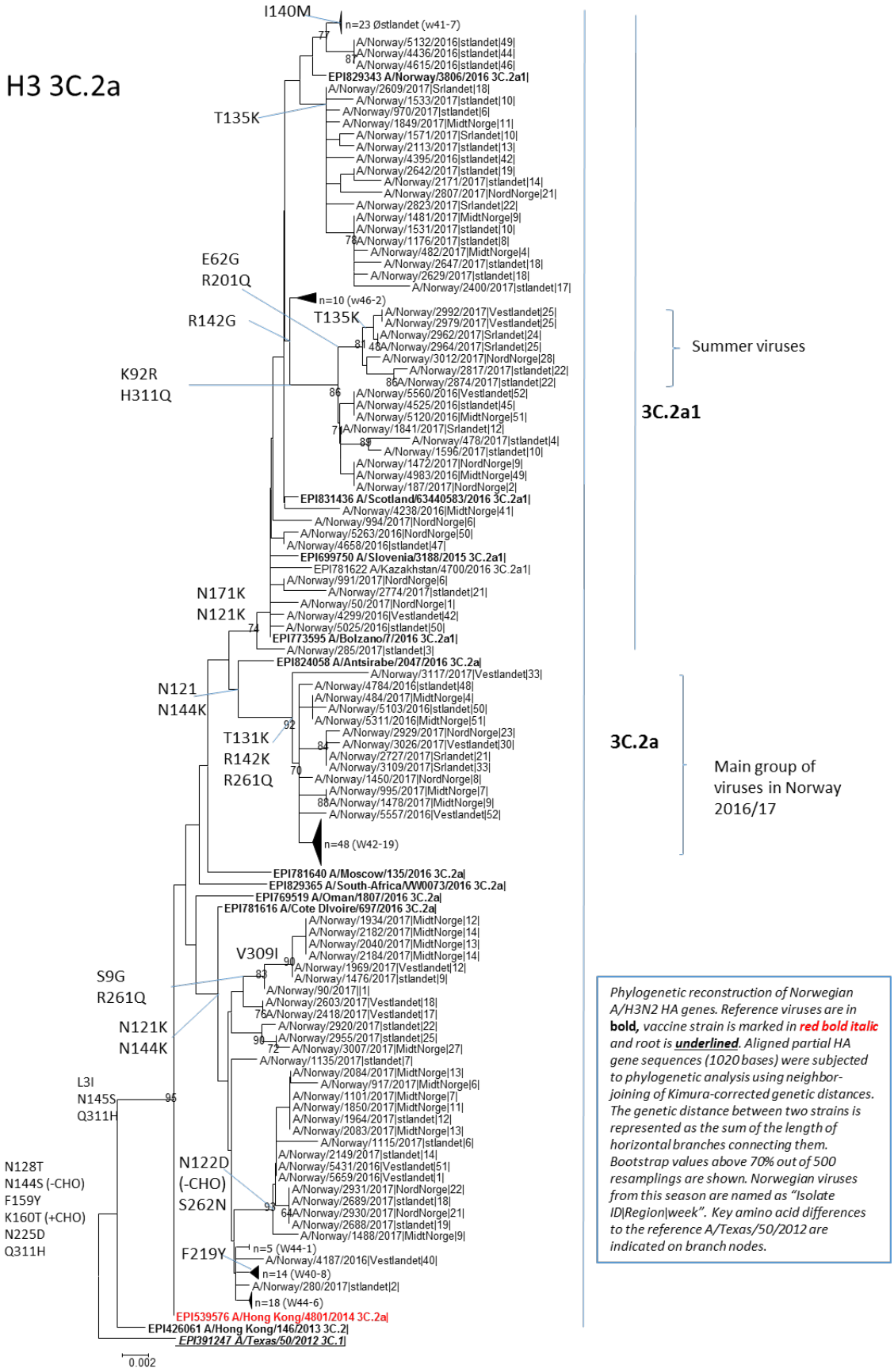
[$]Year of serum collection and HI analysis.

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

**Components of the northern hemisphere influenza vaccine (trivalent/quadrivalent) for the season 2016-2017.

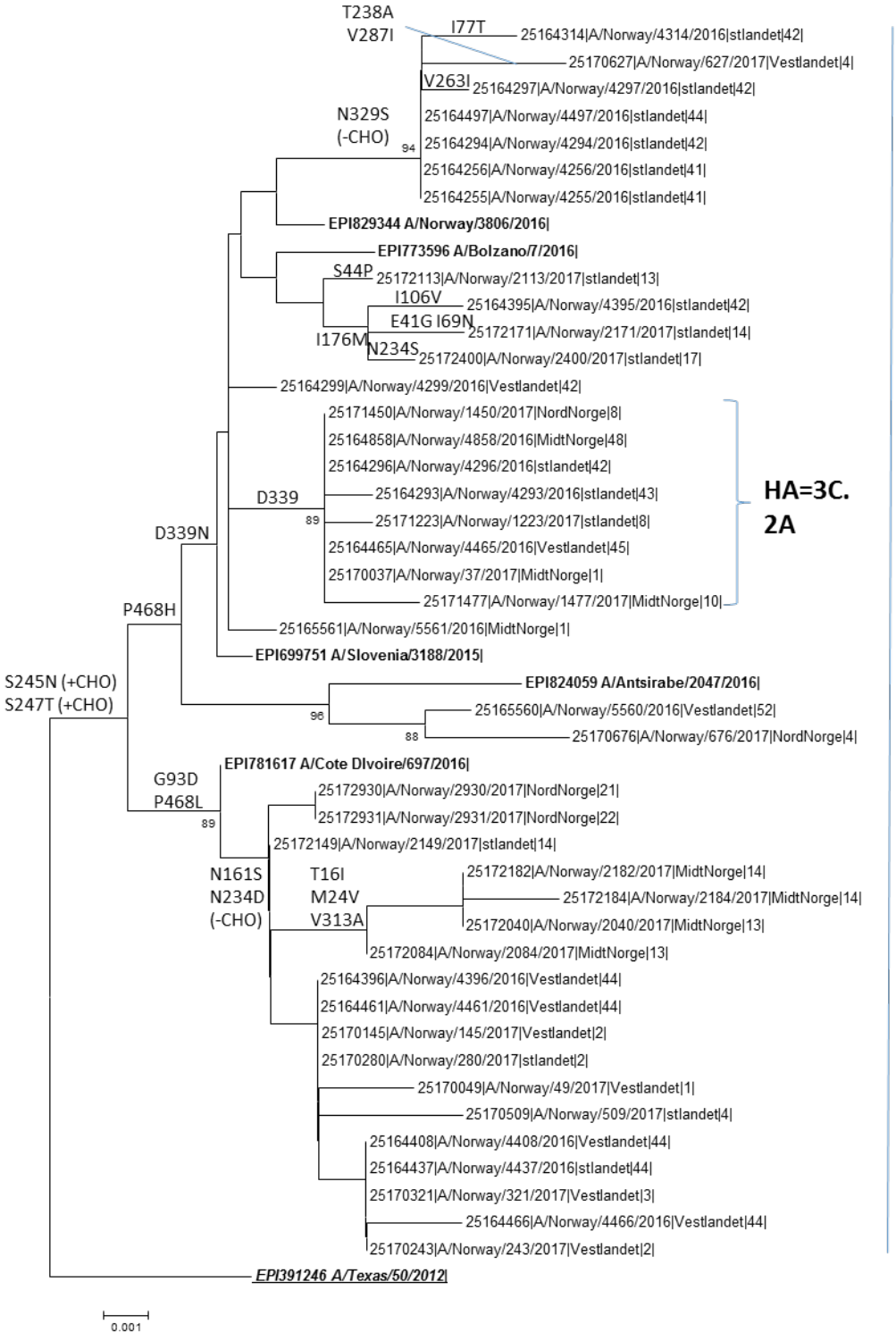
B/Yam: B/Yamagata/16/1988 lineage; **B/Vic**: B/Victoria/2/1987 lineage.

4 Phylogeny: Influenza sequences, Norway 2016-17



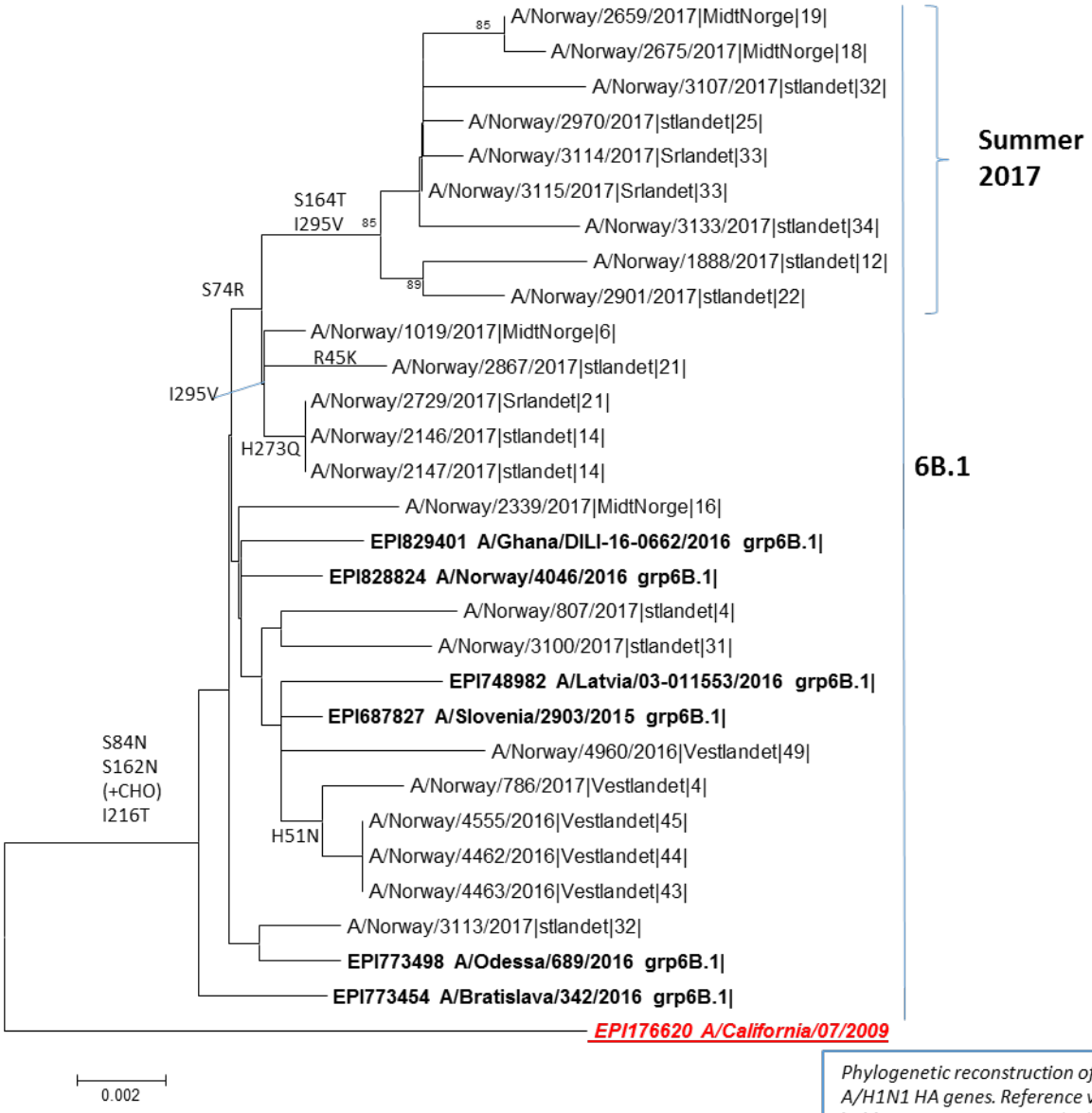
Phylogenetic reconstruction of Norwegian A/H3N2 HA genes. Reference viruses are in **bold,** *vaccine strain is marked in* ***red bold italic*** *and root is* ***underlined****. Aligned partial HA gene sequences (1020 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. The genetic distance between two strains is represented as the sum of the length of horizontal branches connecting them. Bootstrap values above 70% out of 500 resamplings are shown. Norwegian viruses from this season are named as "Isolate ID|Region|week". Key amino acid differences to the reference A/Texas/50/2012 are indicated on branch nodes.*

N2 3C.2a

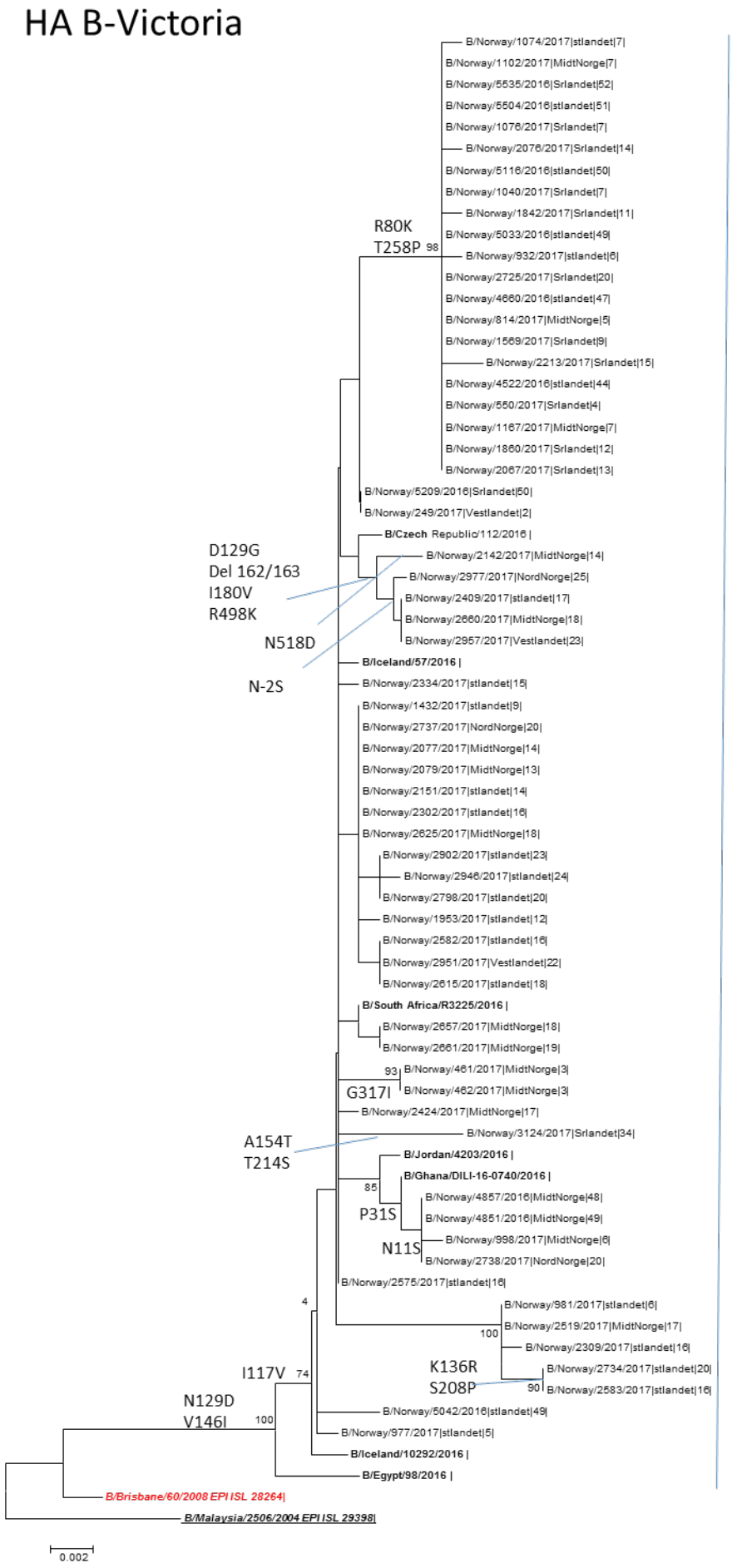


Phylogenetic reconstruction of Norwegian A/H3N2 NA genes. Reference viruses are in **bold,** *and root is* ***underlined****. Aligned partial HA gene sequences (1010 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. The genetic distance between two strains is represented as the sum of the length of horizontal branches connecting them. Bootstrap values above 70% out of 500 resamplings are shown. Norwegian viruses from this season are named as "Isolate ID|Region|week". Key amino acid differences to the reference A/Texas/50/2012 are indicated on branch nodes.*

H1 6B.1

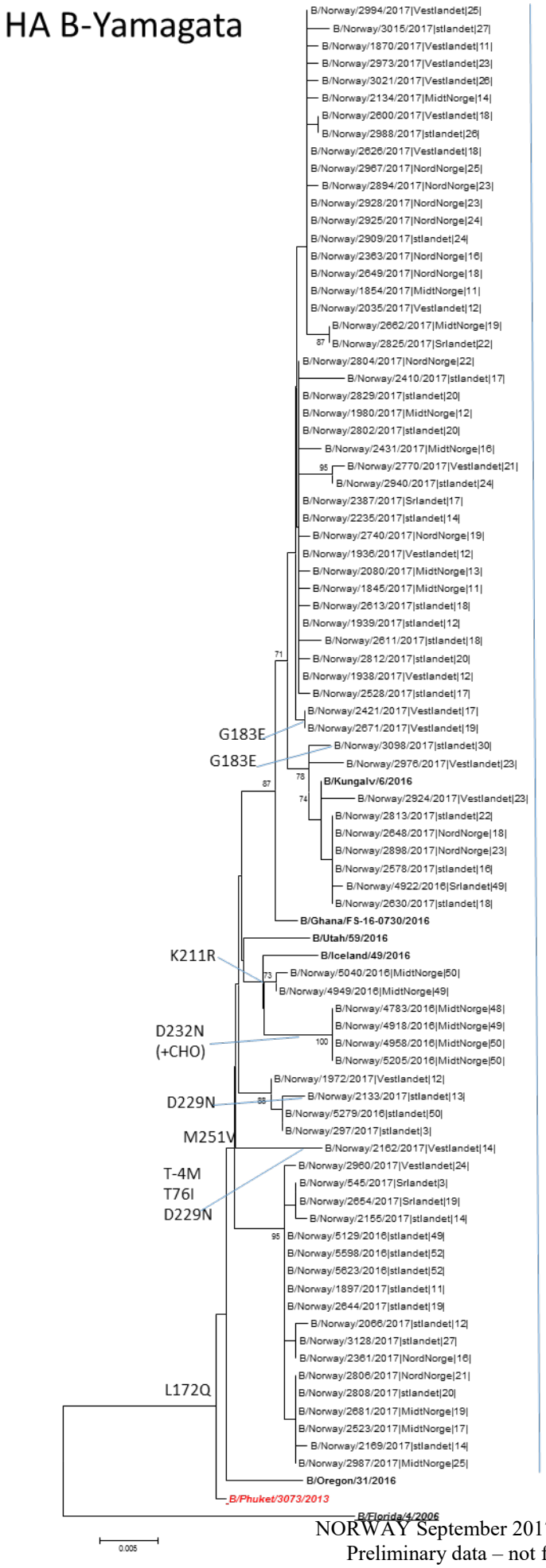


Phylogenetic reconstruction of Norwegian A/H1N1 HA genes. Reference viruses are in **bold,** *vaccine strain is marked in* ***red bold italic*** *and root is* ***underlined****. Aligned partial HA gene sequences (1100 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. The genetic distance between two strains is represented as the sum of the length of horizontal branches connecting them. Bootstrap values above 70% out of 500 resamplings are shown. Norwegian viruses from this season are named as "Isolate ID|Region|week". Key amino acid differences to the reference A/California/07/2009 are indicated on branch nodes.*



Phylogenetic reconstruction of Norwegian B-Victoria HA genes. Reference viruses are in **bold,** *vaccine strain is marked in* ***red bold italic*** *and root is* ***underlined****. Aligned partial HA gene sequences (1055 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. The genetic distance between two strains is represented as the sum of the length of horizontal branches connecting them. Bootstrap values above 70% out of 500 resamplings are shown. Norwegian viruses from this season are named as "Isolate ID|Region|week". Key amino acid differences to the reference A/Brisbane/60/2008 are indicated on branch nodes.*

*One deletion variant virus was left out of the phylogeny due to too short sequence



Phylogenetic reconstruction of Norwegian A/H3N2 HA genes. Reference viruses are in **bold,** *vaccine strain is marked in* ***red bold italic*** *and root is* ***underlined****. Aligned partial HA gene sequences (1046 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. The genetic distance between two strains is represented as the sum of the length of horizontal branches connecting them. Bootstrap values above 70% out of 500 resamplings are shown. Norwegian viruses from this season are named as "Isolate ID|Region|week". Key amino acid differences to the reference B/Florida/4/2006 are indicated on branch nodes.*

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