NIPH
Norwegian Institute of Public Health

REPORT

2018

NORWAY: NATIONAL INFLUENZA CENTRE:

Influenza Epidemiological Information prepared for the WHO Informal Meeting on Strain Composition for Inactivated Influenza Vaccines for use in the Season 2018-19

Atlanta, September 2018

NORWAY: National Influenza Centre

Influenza Epidemiological Information prepared for the WHO Informal Meeting on Strain Composition for Inactivated Influenza Vaccines for use in the Season 2019

Atlanta, September 2018

Department of Influenza

NIPH
Norwegian Institute of Public Health

Published by Norwegian Institute of Public Health
Division of Infection Control and Environmental Health
Department of Influenza
September 2018

Title:
NORWAY: National Influenza Centre – Influenza Epidemiological Information prepared for the WHO Informal Meeting on Strain Composition for Inactivated Influenza Vaccines for use in the Season 2019. Atlanta, September 2018

Authors:
Karoline Bragstad
Kristian Waalen
Ragnhild Tønnessen
Trine Hessevik Paulsen
Torstein Aune
Dagny Haug Dorenberg
Remilyn Ramos-Ocao
Siri Helene Hauge
Olav Hungnes

Graphic design template:
Per Kristian Svendsen

Graphic design cover:
Fete Typer

The report can be downloaded as pdf
www.fhi.no/publ/2018/influenza-epidemiological-information/

ISBN 978-82-8082-919-1 digital

MeSH: influenza, public health surveillance, influenza season 2017-18, infectious diseases

Citation: Bragstad K, Waalen K, Tønnessen R, Paulsen TH, Aune T, Dorenberg DH, Ramos-Ocao R, Hauge SH, Hungnes O. " Norway National Influenza Centre – Influenza Epidemiological Information prepared for the WHO Informal Meeting on Strain Composition for Inactivated Influenza Vaccines for use in the Season 2019. Atlanta, September 2018 ". Oslo: Norwegian Institute of Public Health, 2018.

Norwegian Institute of Public Health
National Influenza Centre, Oslo
Department of Influenza
Norwegian Institute of Public Health
P.O. Box 222 Skøyen
N-0213 Oslo, NORWAY
Tel: (+47) 21 07 65 20
Fax: (+47) 21 07 64 47
e-mail: NIC-Norway@fhi.no
www.fhi.no/influensa

NORWAY:
National Influenza Centre

Influenza Epidemiological Information prepared for the WHO Informal Meeting on Strain Composition for Inactivated Influenza Vaccines for use in the Season 2019 Atlanta, September 2018

Contents

1: The 2017-2018 influenza season, Norway

Summary

- Considerable immunity towards influenza A(H3N2) virus was observed prior to this season, after many infections during the preceding season. There was also strong immunity to A(H1N1)pdm09 virus, but the proportion with immunity to current influenza B viruses was quite low.
- The influenza outbreak of 2017/18 started in mid-December and was unusually prolonged. Although intensity never reached high levels, the cumulative magnitude was larger than in the preceding seasons.
- The influenza season was dominated by influenza B/Yamagata-lineage virus. A lower number of influenza A(H3N2) circulated at the same time. By week 12/2018, influenza B cases had decreased significantly, while the A(H3N2) persisted longer and were 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 flu this season compared to the previous three seasons due to the protracted outbreak.
- A uniform group of B/Phuket/3373/2013-like influenza B/Yamagata-lineage viruses drove the main outbreak, whereas for A(H3N2) virus, several genetic groups co-circulated, with genetic clade 3C.2a2 making up the majority of the H3N2 viruses.
- Despite very few cases of influenza B/Victoria-lineage infection this season, the novel two-amino acid HA deletion variant represented a larger proportion than in the preceding season, and increased during the outbreak. Six out of 17 genetically characterised B/Victoria viruses were of this HA amino acid 162/163 deletion variant.
- The moderate number of H1N1 viruses that circulated belonged to subclade 6B.1.
- The incidence of laboratory-confirmed influenza in hospitalised patients was highest in the elderly.
- Excess mortality was observed in the elderly in week 51/2017 to week 3/2018 and the weeks 6/2018 - 12/2018. Fatal influenza cases were also reported from intensive care units.

A look back at preceding seasons

The preceding 2016/17 season main outbreak peaked unusually early and was strongly dominated by influenza A(H3N2) viruses, belonging to various subclades under the 3C.2a clade. The outbreak, which was of medium intensity, was associated with higher than usual excess mortality, primarily among the elderly. Influenza B viruses, mostly of the Yamagata lineage, predominated toward the end of the season. Influenza B/Victoria-lineages occurred only sporadically, but among the 64 that have been HA sequenced we detected six viruses belonging to a novel variant carrying a two-amino acid deletion in the HA.

Influenza A(H1N1)pdm09 viruses predominated in the 2015/16 season.

Last time there was a major countrywide influenza B/Yamagata lineage outbreak was during the 2012/13 season when it co-dominated with influenza A(H1N1)pdm09 virus. B/Yamagata lineage viruses also predominated in Northern Norway in the 2014/15 season.

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.

The ILI consultation rate began to rise gradually from week 47/2017, crossed the epidemic threshold in week 51 and increased rapidly to medium intensity in week 52 (Fig.1, right). A temporary peak in ILI activity was observed in week 1/2018, but after a slight decline in ILI activity in week 2, the increase resumed and the consultation rate peaked in week 7, not exceeding medium intensity. From that point onwards, there was a gradual decline, bringing activity under the outbreak threshold by week 15.

Although the intensity never reached high levels, the total magnitude was large due to the long duration of activity. Except for the 2009 pandemic, the total number of consultations with an ILI diagnosis was larger this season than any previous season since the beginning of records according to the current scheme for ILI reporting in 2006/2007 (Figure 1). Twenty outbreaks were reported from health care institutions, where ten were caused by influenza A, nine by influenza B and one caused by influenza of unknown type.

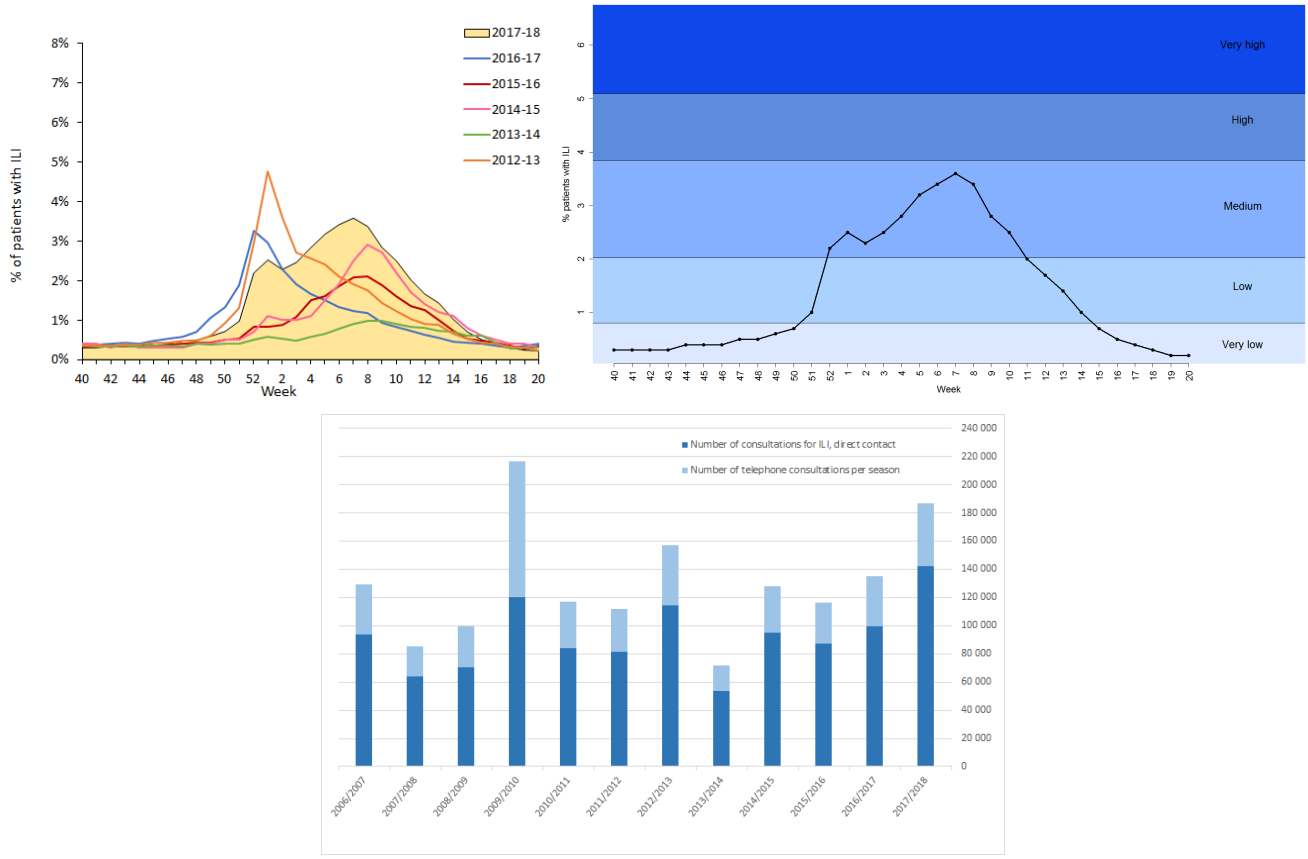


Figure 1: Weekly incidence of ILI, Norway 2017-2018.
Proportion of patients in general practice and emergency clinics presenting with ILI, by calendar week. In the left-hand panel a selection of previous seasons is also shown. In the right-hand panel, the ILI incidence is shown against the present-season MEM intensity thresholds. The lower panel compares season total ILI diagnoses with previous seasons.

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. 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.

Sporadic cases of laboratory verified influenza were recorded weekly throughout the summer and early autumn 2017 (cf. our report for the September 2017 VCM). A clear increase in the numbers was noticed from late November onwards (Figure 2, table 1). The all-laboratories positivity rate exceeded the 10 per cent mark in the week before Christmas (wk 51) and passed 20 per cent the subsequent week. Following a levelling off in early January, the rise resumed in mid-January and peaked in week 7 with 3271 influenza detections and 36 per cent positives. The subsequent decline brought detections below the 10 per cent mark again in week 16. After detections petered out at the end of May, sporadic detections have been made through all summer weeks.

Initially, influenza A(H3N2) were in majority, but the rise from late November was primarily driven by influenza B viruses of the Yamagata lineage. The latter viruses were in majority from week 49/2017 through week 11/2018, after which A(H3N2) viruses again were the most frequent.

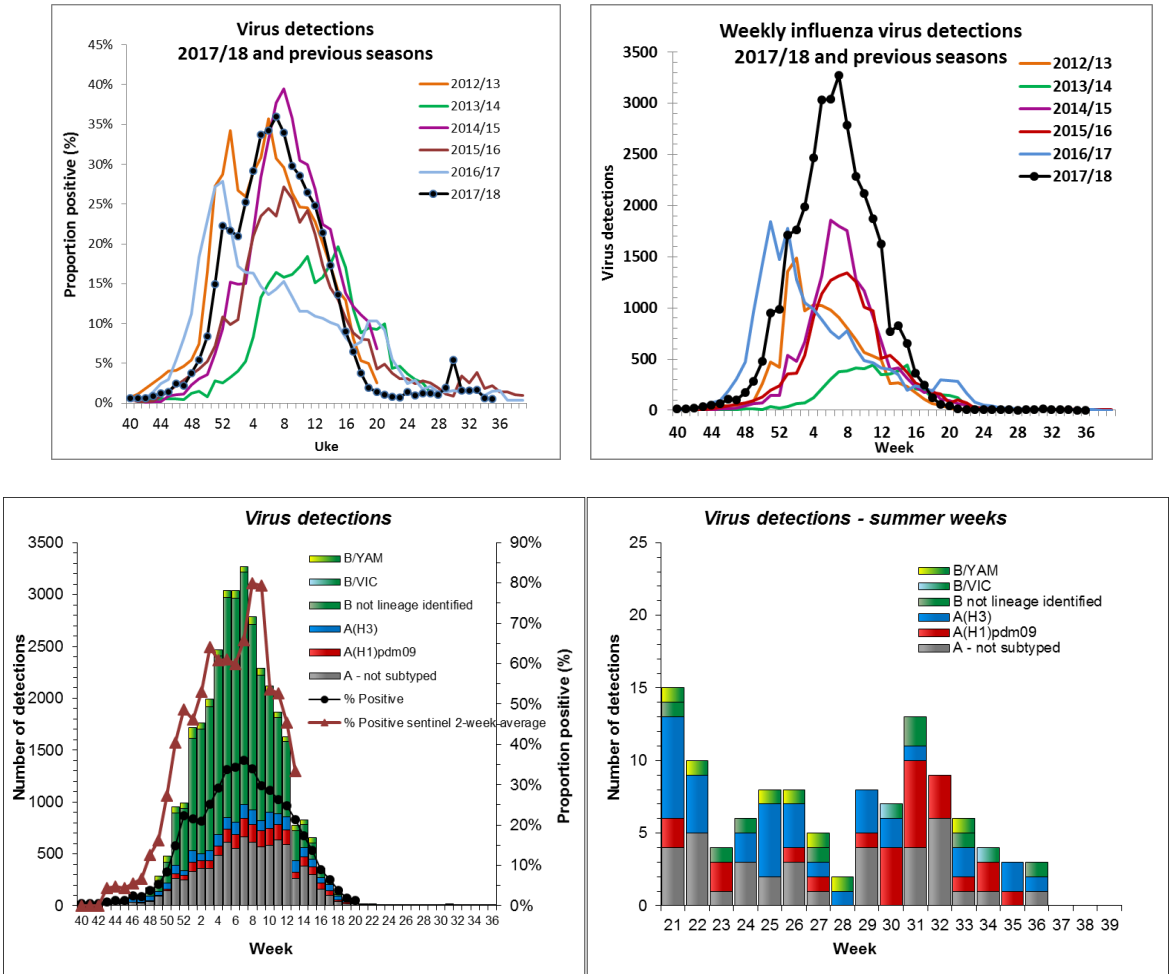


Figure 2: Laboratory detections, Norway 2017-2018. Upper left-hand panel: Weekly proportion of influenza virus positive specimens, with previous season proportions shown for comparison. Upper right-hand panel: Weekly number of influenza virus detections, with previous season numbers shown for comparison.
Lower panels: Weekly number of the different influenza viruses is displayed as stacked bars, while influenza virus positivity rates of sentinel specimens and all lab testing, respectively, are shown as line graphs. For visibility, the summer weeks are displayed on a different scale in the right-hand lower panel.

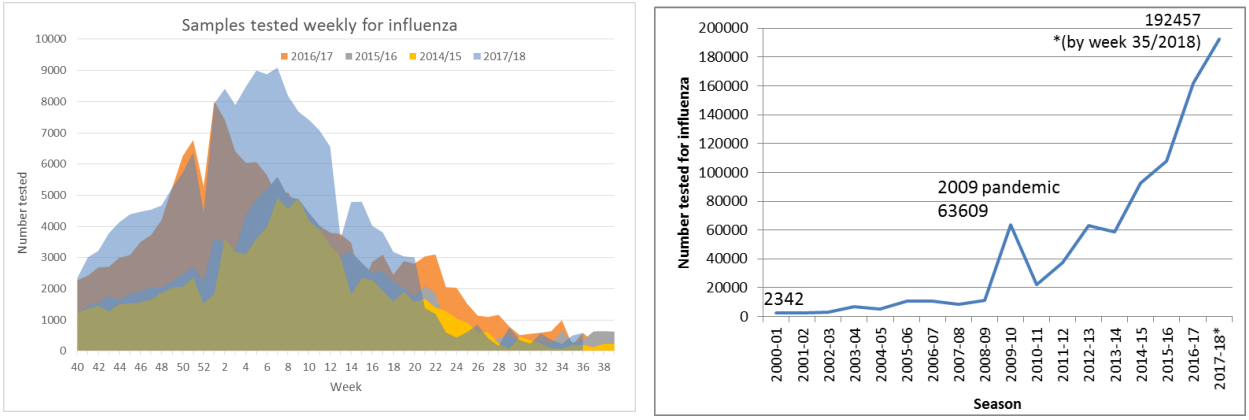


Figure 3. Number of tests for influenza virus carried out in Norwegian medical microbiology laboratories, as recorded in weekly reports to the NIC. Left panel: Number of tests per week, comparison of current season and three preceding seasons. Right panel: Number of tests per season, since reporting of this parameter began in year 2000 (*current-season comprises 48 out of 52 weeks).

By week 36/2018, more than 192 000 specimens have been analysed for influenza virus in Norwegian medical microbiology laboratories this season (Figure 3). This number has been rising continuously through several years, and the number of influenza positives has to be interpreted with this in mind. However, the 19 % rise in tested specimens since the previous season does not in itself explain the increase by 66 % of influenza positives (Figure 2) this season.

Among 34452 reported influenza virus infections, approximately two thirds were type B and one third type A (figure 4). Among genotyped type B viruses, Yamagata/16/88-lineage viruses were strongly predominant (98 %). A(H3N2) constituted the majority of the subtyped type A viruses, making up nearly 80 % of the sentinel type A specimens and 75 % of non-sentinel type A viruses that were tested for both H1 and H3 subtypes. The relative frequencies are generally consistent between the all-laboratories and sentinel data. The somewhat larger proportion of influenza B in sentinel specimens (73 % vs. 63 %) may not be significant, but it may also reflect a truly higher proportion of influenza B in outpatients compared to hospitalised patients. This is supported by the fact that there is a similar difference in type A:B proportions in the data from hospital laboratories that report detection data from outpatients and hospitalised patients separately (data not shown).

Figure 4. Proportions of 2017/18 season influenza virus subtypes and lineages among viruses analysed in Norway, by 13th of September 2018. For comparison, all-laboratories proportions of A/B type, A subtypes and B lineages are shown in the upper row. 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. Sentinel data are not biased in this way but the numbers are more limited.

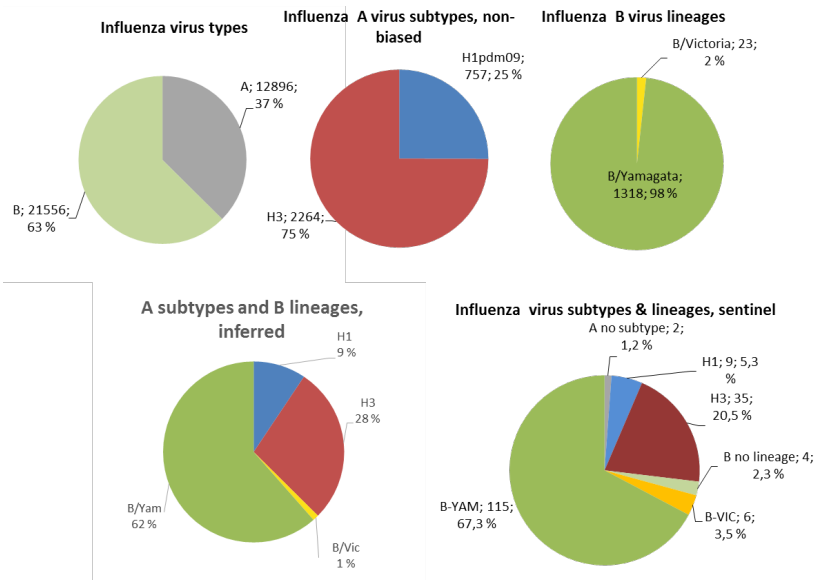


Table 1: Weekly incidence of influenza-like illness (ILI), number of specimens tested for influenza, proportion of specimens positive for influenza virus, and influenza virus detections per type/subtype/lineage (sentinel plus non-sentinel), in Norway from week 40/2017 through week 5/2018.

		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	0,3 %	2349	0,6 %	3	1	1	5	4	0	2
41	0,3 %	3007	0,7 %	5	1	1	4	6	0	2
42	0,3 %	3219	0,9 %	2	3	3	9	5	0	2
43	0,3 %	3782	1,3 %	14	2	1	9	9	0	1
44	0,4 %	4140	1,4 %	19	1	1	18	6	0	8
45	0,4 %	4387	2,5 %	16	10	10	20	10	0	6
46	0,4 %	4472	2,2 %	30	4	4	40	25	0	12
47	0,5 %	4539	3,7 %	26	4	2	32	13	1	24
48	0,5 %	4671	5,4 %	41	5	4	48	38	1	41
49	0,6 %	5235	8,4 %	95	6	5	33	107	0	43
50	0,7 %	5722	14,9 %	147	15	6	55	201	2	59
51	1,0 %	6367	22,3 %	260	45	10	82	504	2	57
52	2,2 %	4438	21,6 %	246	48	15	47	600	0	47
1	2,5 %	7933	20,9 %	331	88	37	111	1083	1	102
2	2,3 %	8417	25,2 %	357	74	28	67	1206	1	56
3	2,5 %	7894	29,1 %	362	71	31	96	1386	4	71
4	2,8 %	8475	33,7 %	486	90	22	114	1715	0	64
5	3,2 %	8998	34,3 %	613	124	29	116	2115	2	66
6	3,4 %	8878	36,0 %	551	137	38	117	2157	1	79
7	3,6 %	9093	34,0 %	662	178	51	135	2239	1	56
8	3,4 %	8190	29,8 %	611	172	56	140	1790	1	70
9	2,8 %	7677	28,5 %	566	156	59	97	1404	0	65
10	2,5 %	7417	26,4 %	579	166	51	153	1143	1	74
11	2,0 %	7073	24,8 %	633	147	43	109	926	0	54
12	1,7 %	6562	21,4 %	587	145	47	126	728	0	40
13	1,4 %	3601	17,3 %	261	60	34	116	284	1	50
14	1,0 %	4783	13,6 %	382	88	35	92	221	1	42
15	0,7 %	4793	9,0 %	298	75	28	74	155	1	51
16	0,5 %	4021	6,5 %	162	58	35	48	60	0	33
17	0,4 %	3808	3,8 %	102	44	21	56	33	0	12
18	0,3 %	3185	2,0 %	39	15	10	37	17	0	13
19	0,2 %	3041	1,4 %	20	10	7	18	6	0	6
20	0,2 %	3012	0,6 %	15	8	7	6	11	0	3
21		1377		4	2	2	7	1	0	1
22		1195		5	0	0	4	0	0	1
23		599		1	2	3	0	1	0	0
24		436		3	0	0	2	1	0	0
25		612		2	0	0	5	0	0	1
26		850		3	1	1	3	0	0	1
27		414		1	1	1	1	1	0	1
28		166		0	0	0	1	0	0	1
29		767		4	1	1	3	0	0	0
30		357		0	4	4	2	0	1	0
31		241		4	6	6	1	2	0	0
32		571		6	3	3	0	0	0	0
33		369		1	1	1	2	1	0	1
34		234		1	2	2	0	0	1	0
35		502		0	1	1	2	0	0	0
36		588		1	0	0	1	1	0	0
Total	Total	192457		8557	2075	757*	2264	20215	23	1318
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:	12896			Type B:	21556		

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

Pre-season seroprevalence and age-distribution of viruses detected in 2017-18 season.

In figure 5, 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.

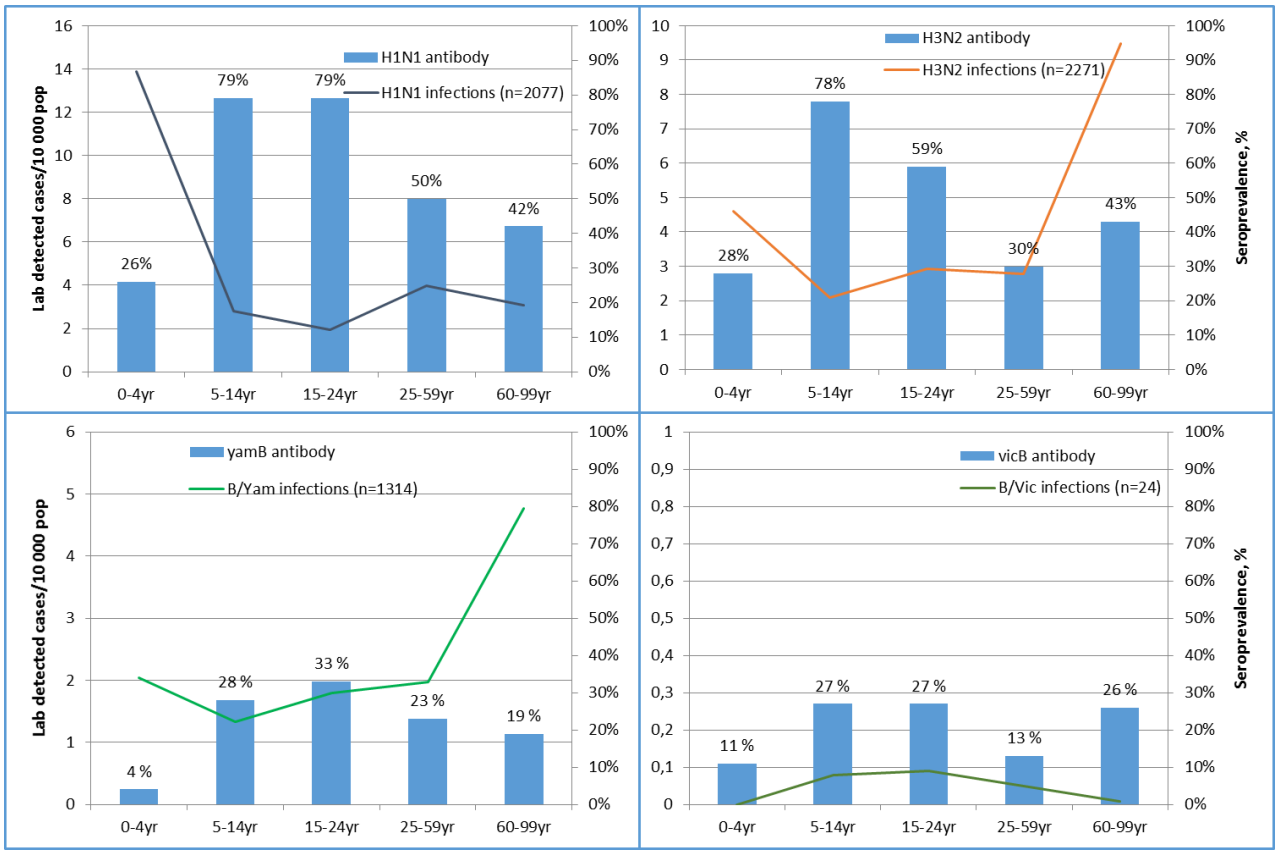


Figure 5. Prevalence of protective antibody to various influenza viruses in August 2017 (% seropositive, bars) and the age distribution of the corresponding influenza viruses in the 2017/2018 influenza season (up to week 5/2018, incidence of subtype/lineage detections per 10^4 population, line plot).

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.

In the school-age children and young adults, there is a good correspondence between high pre-season seroprevalence and suppressed incidence of infection for A(H1N1). The recorded incidence of A(H3N2) infections is also lowest in the school-age children which had the highest pre-season seroprevalence. However, the HI seroprevalence data do not appear to explain why the H1N1pdm09 virus preferentially affects the infants and why A(H3N2), but not A(H1N1)pdm09, preferentially affects the elderly.

For the B/Phuket/3433/2013-like B/Yamagata-lineage viruses, the pre-season seroprevalence was relatively low in the elderly where the incidence is the highest. However, the seroprevalence is considerably lower in the infants, who do not seem to be selectively targeted by the virus.

B/Victoria-lineage viruses circulate only sporadically and too few have been identified to make any meaningful age profile interpretation for these viruses.

Influenza in different age groups

It is well recognised that the elderly are more affected by influenza in seasons with influenza A(H3N2) predominance. Through a number of years a similar pattern has been noted in Norwegian surveillance data for the influenza B/Yamagata lineage, while the B/Victoria lineage and A(H1N1)pdm09 have been skewed more toward younger age groups. These patterns were also clearly apparent during the present season (Figure 6). With B/Yamagata being the most predominant and with A(H3N2) in second place this season, this explains well why the elderly were particularly affected.

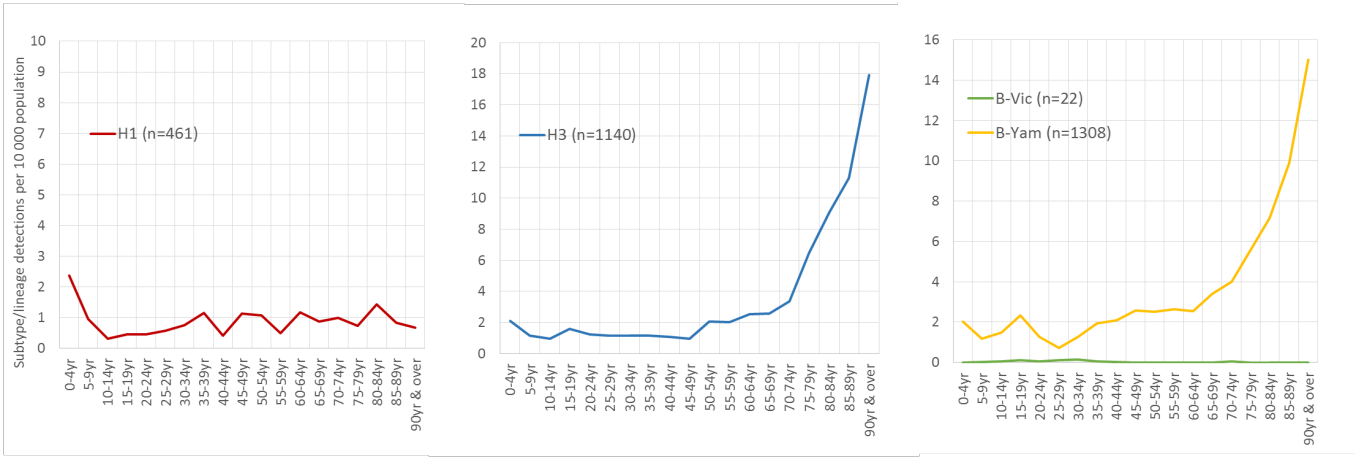


Figure 6. Incidence of subtype/lineage detections by 5-year age group, based on viruses analysed in the Norwegian National Influenza Centre during the 2017/18 influenza season.

Compared to the three preceding seasons, more elderly people were diagnosed with influenza-like illness the last season. (Figur 7). Many elderly were affected also during the seasons 2016/17 and 2014/15 when influenza A(H3N2) predominated.

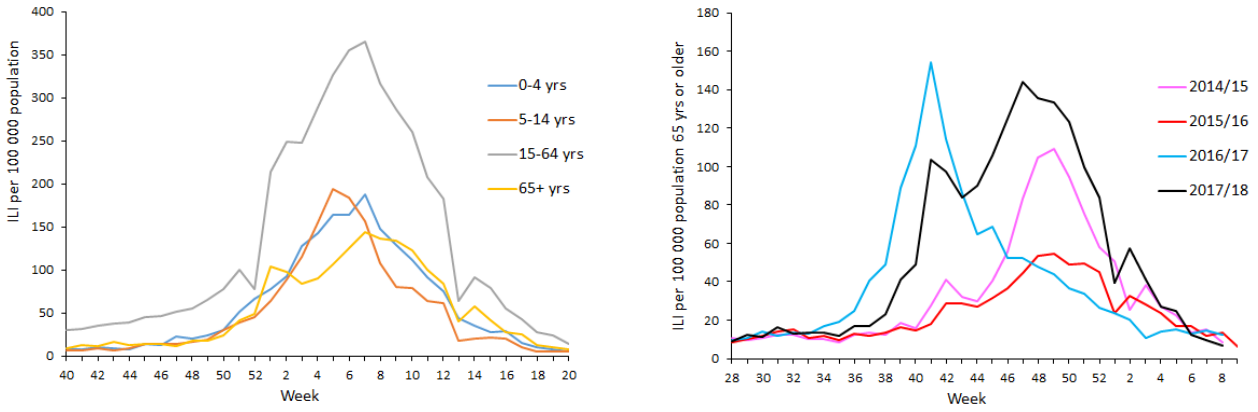


Figure 7. ILI consultations per 100 000 inhabitants, by age group and week during the 2017/2018 season (left), and in elderly above 65 years, per season and week during the last four seasons (right).

This corresponds well with the observation that the elderly predominated among patients hospitalised with influenza (Figure 8), and both influenza B and A (mostly H3N2 when subtyped) were implicated.

Surveillance of laboratory-confirmed influenza in hospitalised patients

Nine medical microbiology laboratories participate in the surveillance of laboratory confirmed influenza in hospitalised patients. These laboratories cover approximately 60% 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 is the fourth year this surveillance system has been in operation. From week 40/2017 to week 20/2018, 5147 hospitalised patients tested positive for influenza virus. The number of detections increased sharply from week 50/2017 to week 1/2018, and after a slight decrease in week 2 and 3/2018 it reached a peak in week 8/2018 (Figure 8) when 470 patients tested positive for influenza. Most patients hospitalised with influenza were 60 years or older (61%). Influenza B virus was the most frequently detected influenza type among the hospitalised patients (56%) whereas a majority of detections during the start and the end of the season were influenza A.

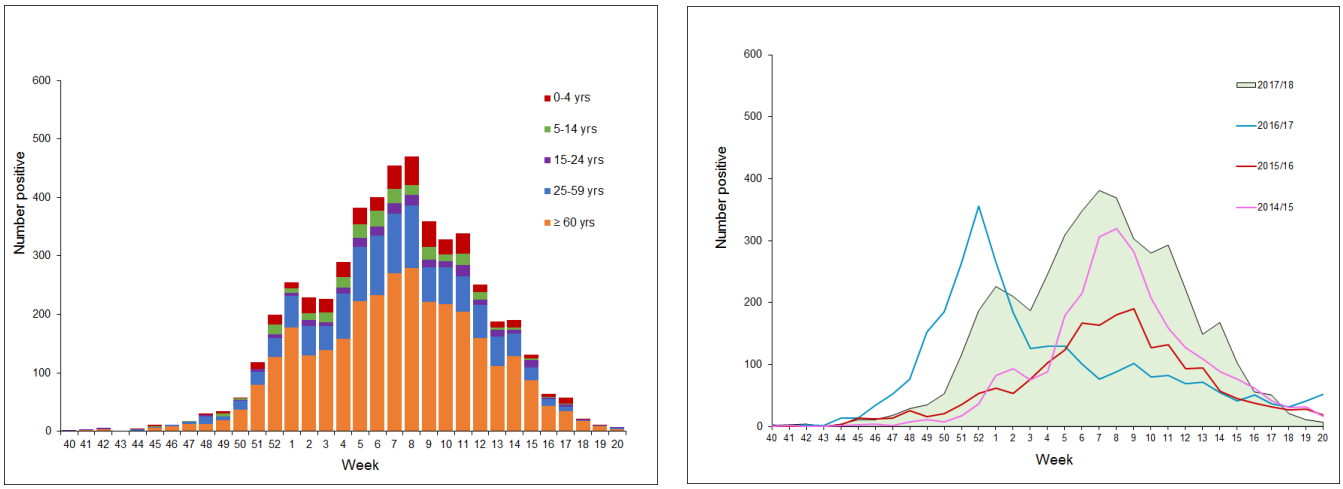


Figure 8. Left hand panel: The number of influenza virus detections in hospitalised patients per week during influenza season 2017/2018, age-distributed, in the eight clinical microbiological laboratories participating from the start of the season. Right hand panel: The number of hospitalised patients with confirmed influenza per week during the previous four influenza seasons in seven of the laboratories participating. 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

From the 2016/17 season, the Norwegian Intensive Care Registry (NICR) and NIPH have carried out a pilot study to see whether national surveillance of influenza patients in intensive care units is feasible. Almost all ICUs in Norway report data to NICR. As part of the pilot, NICR has 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 (Table 2, Figure 9). Anonymised data are reported from NICR to the NIPH. Although the number of patients admitted to ICUs with laboratory confirmed influenza was significantly larger in the 2017-18 season, the numbers of suspected cases and deaths in the ICUs were on the same level as the 2016-17 season.

Category	2017-18	2016-17
Number of patients admitted in ICUs with laboratory-confirmed influenza	379	256
Number of patients admitted to ICUs with clinically suspected influenza	189	178
Number of deaths among patients with laboratory-confirmed or clinically suspected influenza admitted to ICUs	30	26

Table 2. The number of confirmed or suspected influenza ICU admissions and deaths, influenza seasons 2017-18 and 2016-17, week 46 until week 20 .

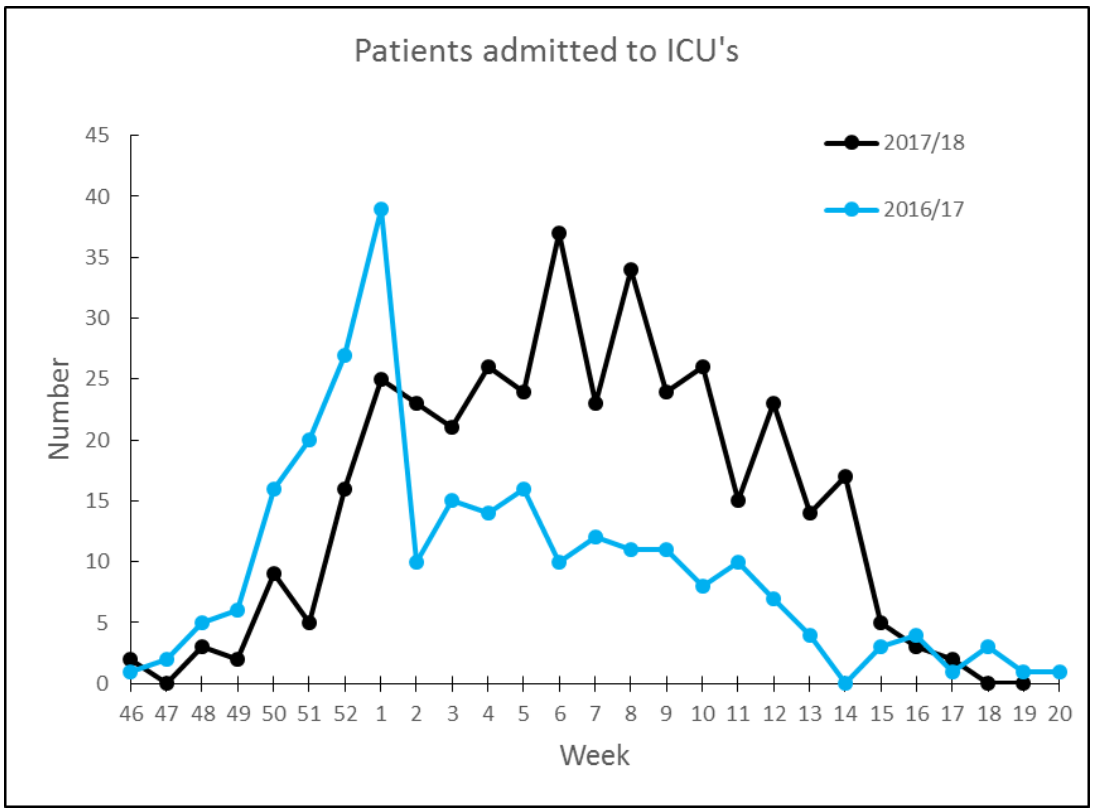


Figure 9. The number of patients admitted to ICU'during weeks 46 to 20 of the influenza seasons 2016/17 and 2017/18.

Excess all-cause mortality

The NIPH has been conducting weekly all-cause mortality surveillance since the 2015/2016 season, using the EuroMOMO algorithm. This season, significant excess mortality has been observed in the elderly (≥65 years) in Norway in the five consecutive weeks 51/2017 - 3/2018, and in the seven consecutive weeks 6/2018 - 12/2018. The level of all-cause excess mortality this winter appears to be at least on par with the two last A(H3N2)-dominated 2014-2015 and 2016/2017 seasons.

Monthly reported non-influenza respiratory viruses

The national monthly reporting scheme for laboratory diagnoses of viruses is based on a voluntary partnership arrangement between medical microbiology laboratories in Norway. The scheme has been running since 1969. The purpose of these reports has been to contribute to the monitoring of communicable infections in the population, especially since many types of infections are not notifiable. Reports from the various microbiology laboratories of positive findings in the current month are collected at the Norwegian Institute of Public Health and then compiled into a summation form for the current year.

Figure 10 shows the monthly reported detections of laboratory confirmed respiratory viruses and mycoplasma in the previous months in Norway. During the autumn of 2017 through November, rhinoviruses were a major cause of respiratory illness. Respiratory syncytial virus (RSV) has played a much lesser role during the last few months after causing a larger outbreak last winter. Human metapneumovirus, on the other hand, was more frequently detected this winter. Respiratory viruses with very low detection frequencies have been omitted. The number of patients tested for the different viruses varies, thus the figures displayed do not accurately portray the actual proportions of infections.

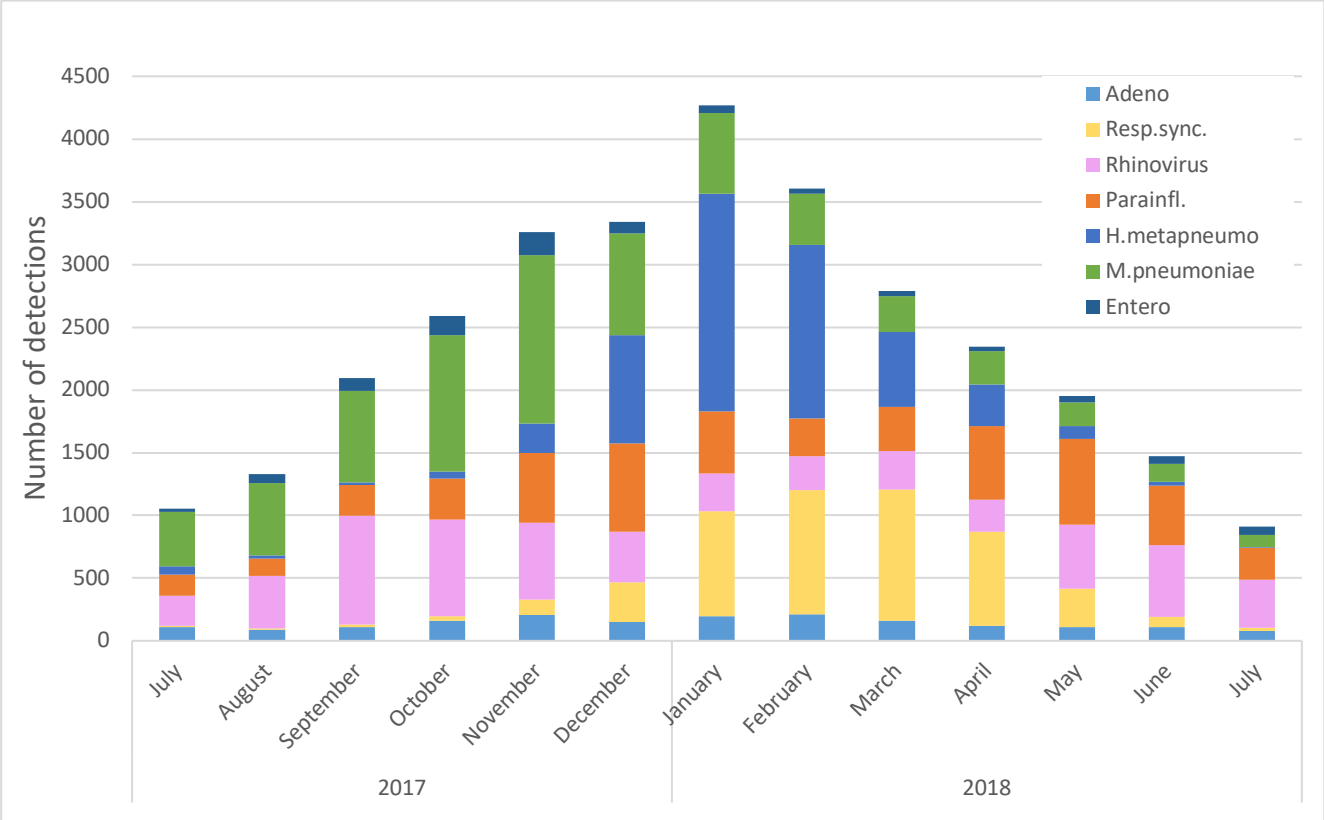


Figure 10: Respiratory virus detections in Norway reported monthly, from July 2017 through July 2018.

2: Characterisation of influenza viruses circulating in Norway, 2017-18 season

B/Yamagata/16/1988 lineage

Out of 1344 samples PCR positive for B/Yamagata in NIC Norway, 6.5 % have been sequence analysed and HA sequences of 4 % of all PCR-positive influenza B viruses have been submitted to GISAID. All B/Yamagata viruses from this season in Norway belonged to the genetic clade 3 and resemble the B/Yamagata viruses from the previous season in Norway. A small group of viruses in the beginning of the season possessed the HA amino acid substitutions Q122K and T181A, otherwise all viruses have had few or none substitutions compared to the vaccine strain (Figure 11; Section 4: Phylogeny). The majority of the NA genes possessed the amino acid substitutions I49M, R65H and I171M.

From week 40, 39 influenza B/Yamagata viruses (3 % of B/Yamagata viruses received in 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. About 2 % have been propagated in cells in the NIC.

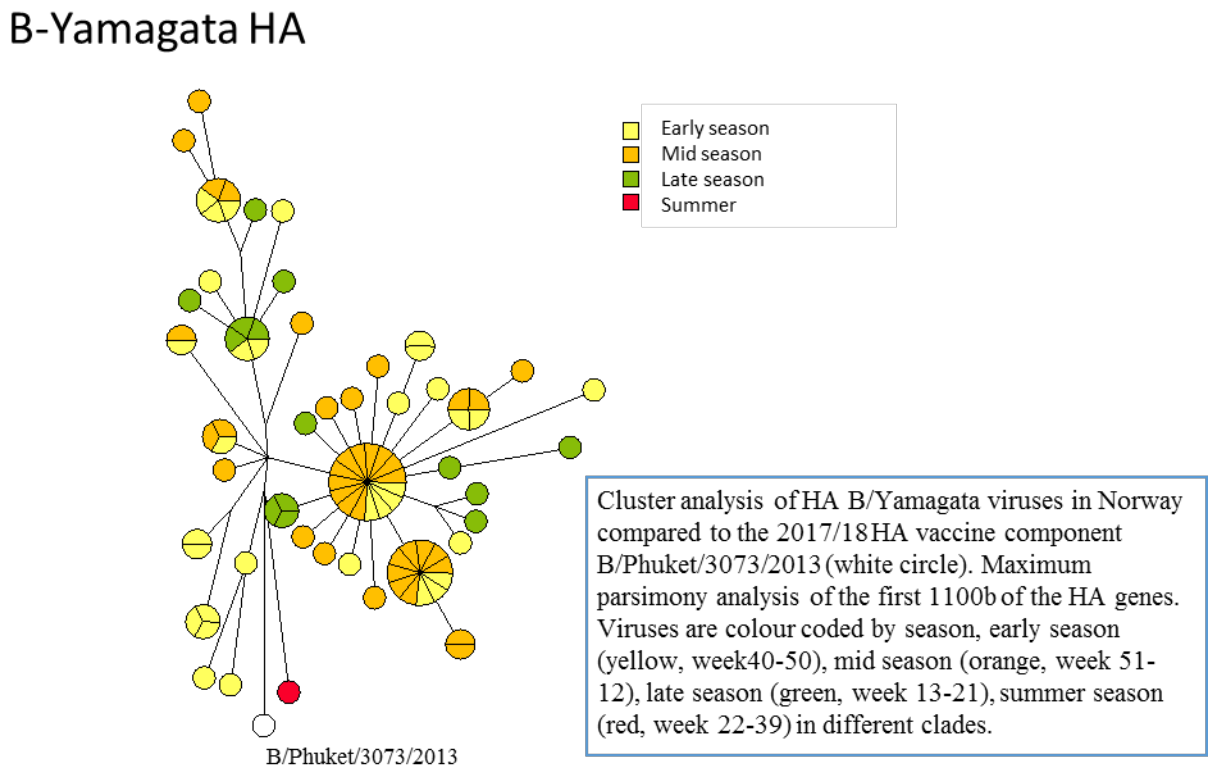


Figure 11: Cluster analysis of B/Yamagata viruses in Norway

Influenza A(H3N2)

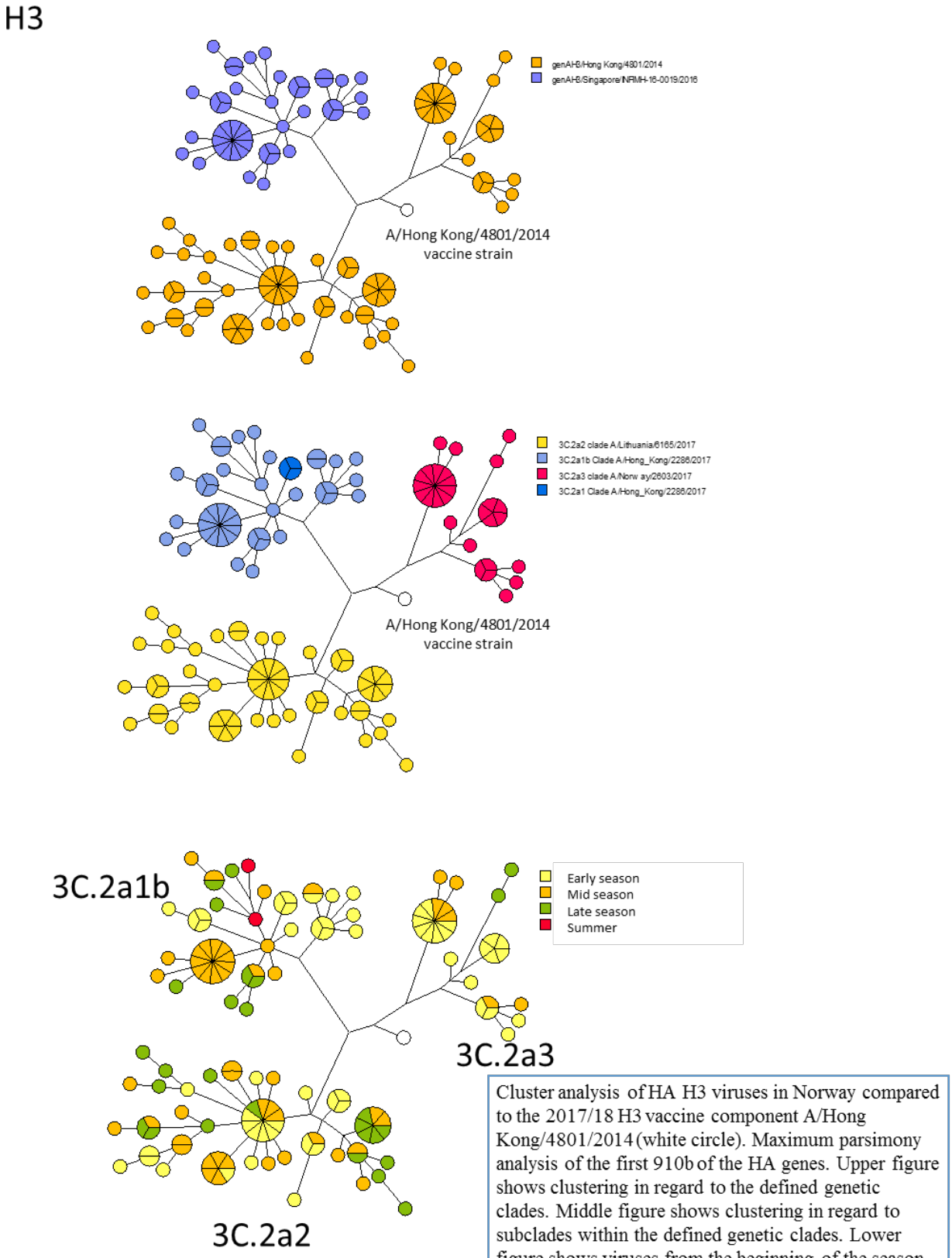
Out of 1157 samples PCR-positive for H3 in NIC Norway, 13 % have been sequence analysed and HA sequences of 7 % of all PCR-positive H3 viruses have been submitted to GISAID. Strain-based reporting of virus characterisation data has been done routinely through TESSy. Both H3 genetic clades 3C.2a and its sub-clade 3C.2a1 have been circulating as during the previous season and the summer months of 2017. The 3C.2a clade has predominated the H3N2 viruses in Norway also this season, the subclade 3C.2a2 viruses slightly outnumbering the other subclades combined. Most of the recent H3N2 viruses also belonged to the 3C.2a2 subclade, but two viruses from the summer months belonged to 3C.2a1b.

The main group of viruses within the genetic 3C.2a2 clade are most closely related to the reference virus A/Lithuania/6165/2017, possessing the T131K, R142K and R261Q substitutions in HA (in reference to A/Texas/50/2012, see phylogeny section). Both T131K and R142K are in antigenic site A and have been related to antigenic drift. These viruses caused the rapid increase in cases in Norway during the previous 2016/17 season. Some recent viruses also possessed P21S and K92R or N144R and A106T substitutions.

The minority of the H3 3C.2a1 viruses from the preceding season, possessing the K92R and H311Q HA substitutions, are the ones that dominated the sub-clade this season. All Norwegian 3C.2a1b viruses now possess K92R and H311Q, and the most recent viruses possess E62G, T135K and R142G in addition, plus T128A in some viruses.

The Norwegian viruses in the 3C.2a2 clade share NA genes with the 3C.2a1 viruses. One could speculate that the 3C.2a1 neuraminidase together with the 3C.2a2 HA improves viral fitness. Most recent Norwegian NA sequences possessed the substitutions I176M, N329S, P126L, I73L and T265I. One sequenced virus from the beginning of the season (A/Norway/3396/2017) possessed several NA amino acid substitutions L140I, V145M, G248E, V303I and S315R (Figure 12; Section 4: Phylogeny section).

From week 40, 60 influenza H3 viruses (5% of H3 viruses received in 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. 5% have been cell-propagated in the NIC.



Cluster analysis of HA H3 viruses in Norway compared to the 2017/18 H3 vaccine component A/Hong Kong/4801/2014 (white circle). Maximum parsimony analysis of the first 910b of the HA genes. Upper figure shows clustering in regard to the defined genetic clades. Middle figure shows clustering in regard to subclades within the defined genetic clades. Lower figure shows viruses from the beginning of the 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 12 Cluster analysis of HA H3N2 viruses in Norway

Influenza A(H1N1)pdm09

Also this season few H1 viruses have circulated in Norway, 487 have been PCR positive for H1N1 at the NIC Norway and 81 of these have been sequence analysed (16.6 %) and HA sequences of 11.5 % of all PCR-positive H1 viruses have been submitted to GISAID. Strain based reporting of virus characterisation data was done routinely through TESSy. These H1 samples belonged to the A/Slovenia/2903/2015 6B.1 group of viruses and grouped phylogenetically with the A/Paris/1289/2017 reference virus, but with the additional amino acid substitutions S74R, S164T and I295V. Some of the recent viruses also possessed T120A (see phylogeny section figure).

Most of the recent H1N1 viruses in Norway possessed T120A plus S180P or I286V plus I372V substitutions in HA. Most of the latest sequenced NA genes possessed the substitutions G77R, V81A, S82P or T72I plus S105N.

From week 40, 27 influenza H1N1 viruses (5,5% of H1N1 viruses received in 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. 6.6% have been propagated in cells in NIC Norway.

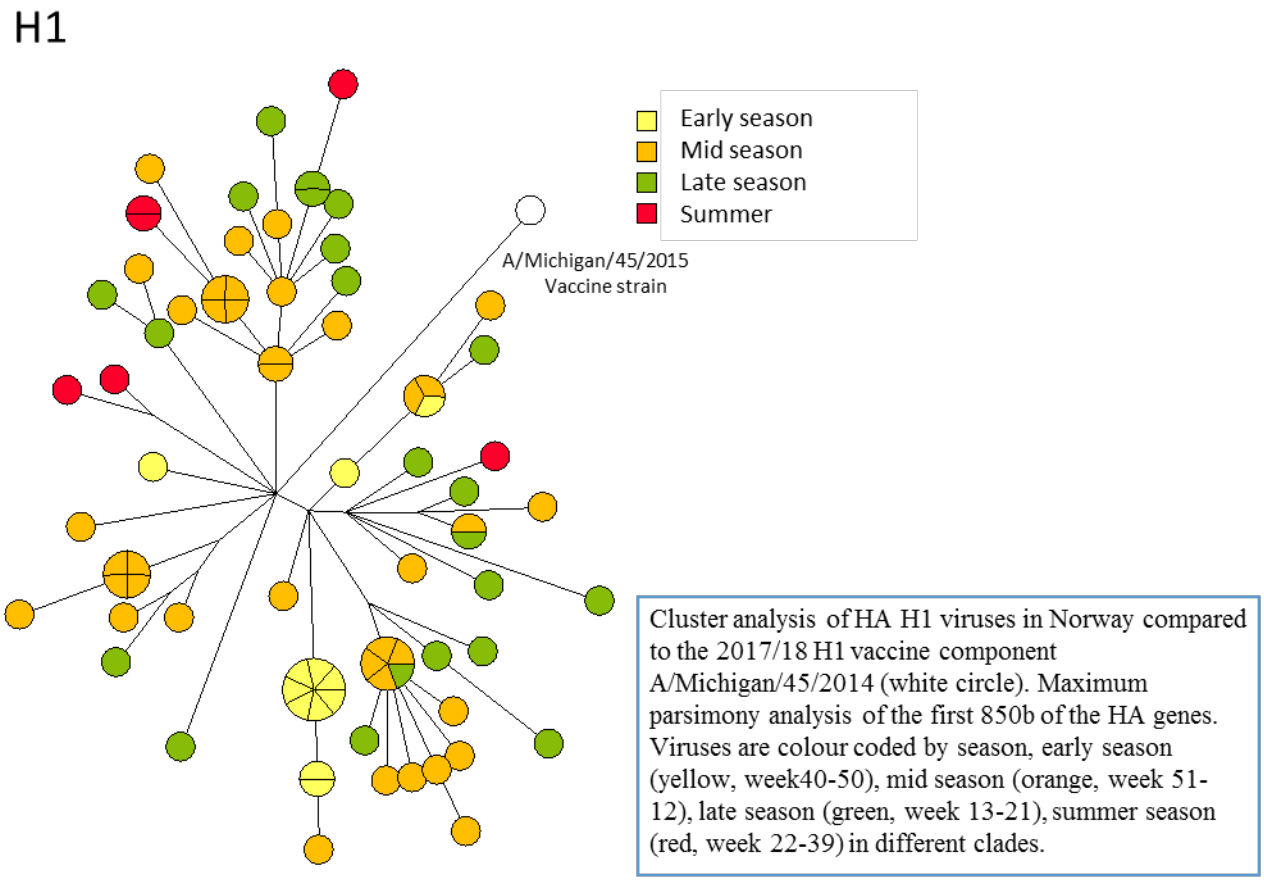
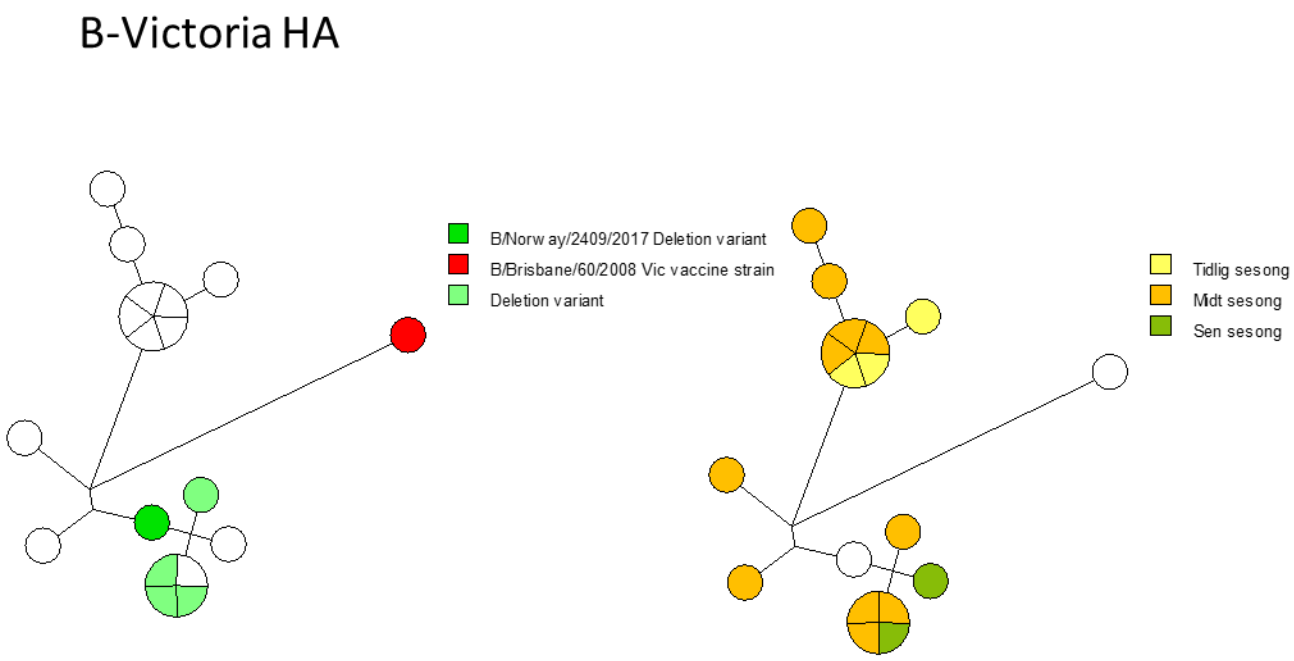


Figure 13: Cluster analysis of HA H1N1 viruses in Norway

B/Victoria/2/1987 lineage

Out of 24 samples PCR positive for B/Victoria-lineage at the NIC Norway, 73% (17) have been sequence analysed. All belong to the clade 1A viruses. HA sequences of 62.5 % of all PCR-positive Victoria viruses have been submitted to GISAID. Most Norwegian B/Victoria-lineage viruses possess the I261L substitution in HA. Six of the B/Victoria-lineage viruses had the HA amino acids 162-163 double deletion of and possessed the D129G and I179V substitutions in addition (see phylogeny section). Most of the recently isolated viruses possessed the same substitutions, but without the two amino acid deletion.
Only five NA genes of B/Victoria have been sequence analysed. Most B/Victoria NA genes possessed the substitutions A62T, I120V and S295R, while one of the NAs of the double-deletion variant possessed F12L, I120V, T211I and S295R.

From week 40 , 13 influenza B/Victoria viruses (54 % of B/Victoria viruses received in 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. 16 % have been propagated in cells in NIC Norway.



Cluster analysis of the HA of B/Victoria-lineage viruses, compared to the 2017/18 vaccine component B/Brisbane/60/2008 and the vaccine representative for the 162-163 deletion variant A/Norway/2409/2017 (red and green circles, respectively, in the left-hand panel). Maximum parsimony analysis of the first 870 nt of the HA gene. In the rightmost panel, viruses are colour coded green for late (summer) season, weeks 22 through 39; orange for mid-season (weeks 51-12), and yellow for early season (weeks 40-50).

Figure 14: Cluster analysis of HA B/Victoria viruses in Norway

Vaccine effectiveness

Out of all samples received for analysis at the NIPH only 2.2% were from vaccinated persons. 13% of the sentinel samples were from vaccinated persons. In the sentinel population a larger proportion of the non-vaccinated was lab confirmed with influenza than in the vaccinated population.
Table 3 summarises the percentage of sentinel patients vaccinated and with lab confirmed influenza.

Virus	Not vaccinated (n=336)	Vaccinated (n=50)
Influenza positive	44,6 %	26 %
B/Yamagata	29,0 %	16 %
A(H3N2)	9,5%	6 %

Table 3. Percentage with confirmed virus infection among sentinel samples from persons vaccinated and not vaccinated. H1N1 and B/Victoria positives were not included because of too few samples.

Antiviral susceptibility monitoring

Monitoring of antiviral susceptibility has not revealed any neuraminidase inhibitor resistance in Norwegian viruses this season. NIC Norway has analysed 8% of viruses received so far for phenotypical resistance. In total 6 % of the H3 viruses, 25 % of the H1 viruses, 3 % of the Yamagata viruses and 29 % of the Victoria viruses have been analysed for antiviral drug resistance either phenotypically or genetically.

Table 4. Norwegian influenza viruses resistant to M2 blockers (adamantanes) and the neuramidase inhibitors oseltamivir and zanamivir, during the period from week 40/2017 through week 35/2018.

per. 11/02-18	Oseltamivir (Tamiflu®)		Zanamivir (Relenza®)		Adamantanes (Amantadin, Rimantadin)	
virus	Number tested	Number Oseltamivir-resistant virus	Number tested	Number Zanamivir-resistant virus	Antall testet	Antall Adamantan-resistant virus
H3	66	0 / (0 %)	54	0 / (0 %)	1	1 / (100 %)
B	41	0 / (0 %)	30	0 / (0 %)		
H1	121	0 / (0 %)	28	0 / (0 %)	1	1 / (100 %)

Two screening tools were used to determine oseltamivir/zanamivir susceptibility: sequence analysis of viral genes or a fluorescence-based neuraminidase inhibition assay.
* we do not test routinely for adamantane resistance, since almost no circulating viruses are susceptible to this class of drug.

3: Seroepidemiology Data, August 2017

The National Seroepidemiological Influenza Programme for the year 2017 analysed a total of 2093 serum samples collected during the weeks 31-35 from clinical/microbiological laboratories covering the 19 counties of Norway. The anonymised convenience sera are aiming to be representative of the Norwegian population geographically and by age composition.
The 2017 serum panel was tested by haemagglutination-inhibition (HI) against the 2017/18 seasonal influenza vaccine strains (trivalent/quadrivalent) (Table 1), i.e. A/Michigan/45/15 (a H1N1pdm09 B.1-like virus), A/Hong Kong/5738/14 (a H3N2/Hong Kong/4801/2014 3C.2a-like virus), B/Brisbane/60/08 (a B/Victoria-lineage 1A-like virus), and B/Phuket/3073/13 (a B/Yamagata-lineage 3-like virus). Two additional viruses were also included in the analyses: H1N1pdm09/California/07/09 (the previous H1N1 vaccine virus X-179A), and A/Norway/3806/2016 (a recent H3N2isolate representing the genetic clade 3C.2a1-like viruses). 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 4 and Figure 15.

The 2017 HI assay: For the year 2017 the HI assay antigens were used with 4 HAU, in agreement with the CONSISE HI assay consensus recommendation. The previous years 8 HAU have been used. The 4 HAU gave somewhat higher HI titres as compared to 8 HAU. The HI results presented for August 2017 have not been corrected for this difference. Studies are in progress to clarify the differences in various age groups for each antigen used.

Summary of outcomes

The population seroprevalence to current influenza A vaccine viruses in August 2017 was relatively high, indicating good protective immunity against the two influenza A vaccine viruses in most age groups. The seroprevalence to A/H1N1pdm09 viruses, including the new H1N1 vaccine strain A/Michigan/45/15, was high (57 %, 'All ages'), an increase of 11 percentage points from the previous year, even though very few H1pdm09 viruses were detected the preceding season. The seroprevalence to the H1pdm09 the last two years are the highest observed since the pandemic in 2009. A/H3N2, the dominant virus the preceding season, constituted about 95 % of circulating viruses in the 2016-2017 season. Thus, high seroprevalence (45 %, 'All ages') was seen in August 2017 to the H3N2 vaccine strain (A/Hong Kong/4801/14-like viruses, a 3C.2a genetic clade virus, represented by A/Hong Kong/5738/14), as well as to genetic subclade 3C.2a1 viruses (represented by the reference strain A/Norway/3806/2016). The seroprevalence to H3N2 ('All ages') is a two-fold increase (21 percentage points) compared to the previous year. However, seroprevalence against the two influenza B vaccine viruses B/Victoria/Brisbane/60/08 and B/Yamagata/Phuket/3073/13 was low to moderate (20 % and 23 %, respectively), and were mainly unchanged for 'All ages' and for most age groups as well, from last year.

Influenza A(H1N1)pdm09

In August 2017 the prevalence of protective antibodies against A(H1N1)pdm09 was 57 % ('All ages'), an increase of 11 percentage points from August 2016. A similar increase was also seen in all age groups (between 10 to 15 percentage points) except for those below 5 years of age with a reduction of 5 percentage points in seroprevalence against H1pdm09 from the previous year. The seroprevalence to the new H1 vaccine strain A/Michigan/45/15 is very similar to the previous vaccine strain X179A (A/California/07/09) both for 'All ages' and in the various age groups.

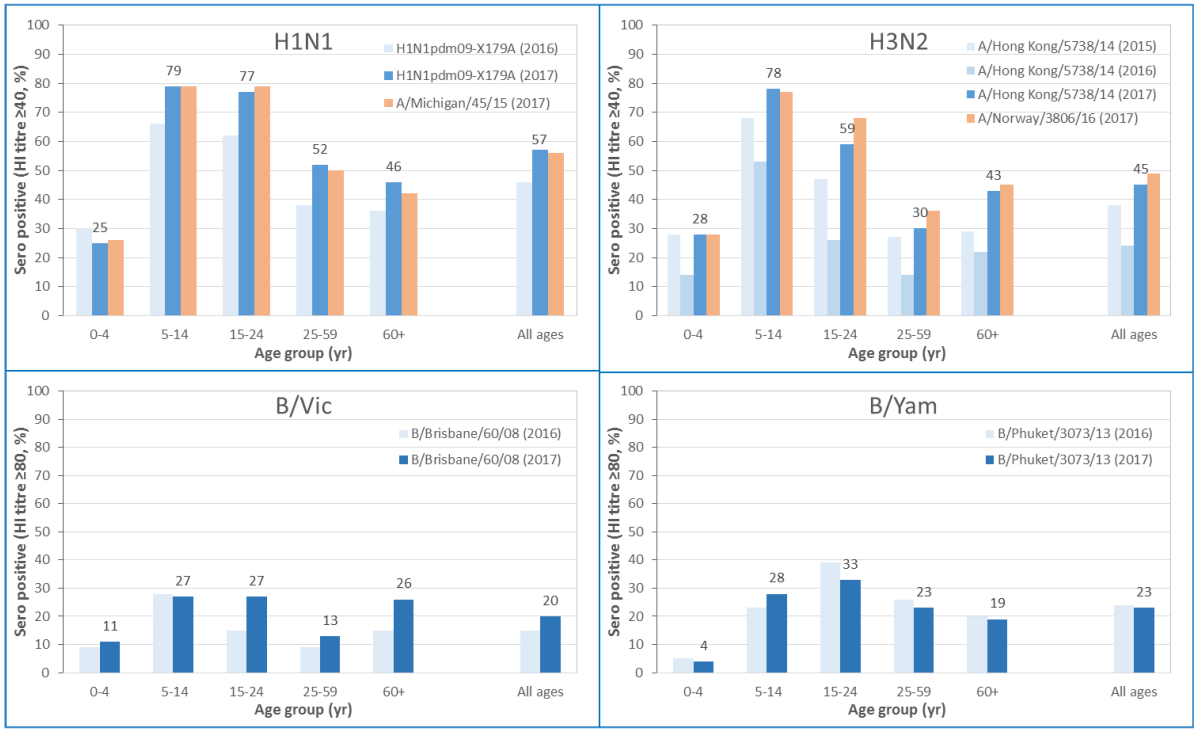


Figure 15. Seroprevalence in August 2017 to current influenza A and B reference and vaccine strains for 'All ages' and in various age groups. For comparison, seroprevalences to some virus strains in August 2015 and 2016 are also shown. Columns in dark colour (blue, red) show the seroprevalence in 2017. Columns in light blue show the corresponding seroprevalences in 2015 and 2016 for some strains. Further details are given in the text.

Influenza A(H3N2)

The seroprevalence in August 2017 to the current H3N2 vaccine strain (A/Hong Kong/4801/14, 3C.2a genetic group, represented by A/Hong Kong/5738/14) had increased significantly compared to the previous year, i.e. from 24 % to 45 % for 'All ages'. This is consistent with the high proportion of H3N2 viruses circulating in the preceding season, about 95 % of detected viruses. Increased seroprevalences were seen in all age groups. The highest increase was in young adults (15-24 year olds) with 33 percentage points, which is a 2.3-fold increase in seroprevalence from last year. A similar increase in seroprevalences (1.5 to 2.1-fold) are also seen in the other age groups to the current H3N2 3C.2a-like vaccine virus. From August 2015 to August 2016 there was a 1.5 to 2 times reduction in seroprevalence to A/Hong Kong (Fig. 10). The reduced pre-season prevalence of protective antibodies in August 2016 might thus have contributed to the dominance of H3N2 viruses circulating the 2016/2017 season. The seroprevalences against genetic clade 3C.2a1 viruses (represented by A/Norway/3806/2016) were nearly the same as for the 3C.2a genetic clade viruses for 'All ages', those below 15 years of age as well as those 60 years and older, while there were somewhat higher seroprevalences (6-9 percentage points) for young adults and adults (25-59 years old).

Influenza B

In August 2017 the prevalence of protective antibodies to influenza B viruses were low to moderate and were mainly unchanged from August 2016 against both B/Victoria- and B/Yamagata-lineage vaccine-like viruses ('All ages'). For most age groups the changes in seroprevalences were less than +/- 5 percentage points. However, for young adults (15-24 year olds) and those 60 years and older an increase of 11 to 12 percentage points in the seroprevalence against the B/Victoria-lineage vaccine-like viruses, represented by B/Brisbane/60/08, were seen (Table 4 and fig 15). Interestingly, relevant to the current flu season with dominance of B/Phuket/3073/13-like B/Yamagata-lineage viruses, the seroprevalence against B/Phuket-like viruses has been decreasing the last two years, after the 2014/2015 season of which B/Phuket-like viruses constituted about 40 % of the circulating viruses. The largest decreases in protective antibodies from August

2015 to August 2017 (8 to 10 percentage points) were seen in those age groups with the highest B/Yamagata virus incidence the current season (Data not shown).

Table 4. Influenza Seroepidemiological results in August 2017 - Comparison between age groups.
For comparison data from studies performed for the preceding years 2014-2016 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*
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*
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/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*
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

[$]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.

**Components of the Northern hemisphere influenza vaccine (trivalent/quadrivalent) for the season 2017-2018.

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

Cross-immunity against the novel B/Victoria-lineage HA deletion variant.

During the preceding 2016/2017 season, a B/Brisbane/60/08 (B/Victoria-lineage) hemagglutinin (HA) double deletion variant was identified in the US and Norway as well as some other countries. Since antigenic characterization using monospecific ferret antisera indicated antigenic drift, there is concern about possible lack of immunity to this variant in the human population. During the 2017/2018 season, the deletion variant was been identified in several other countries as well, but still at low frequency (less than 1 % of circulating influenza viruses, albeit constituting a large and increasing proportion of the Victoria-lineage viruses in some countries). Preliminary HI analysis using pre-2017 human sera from our annual serum collection indicate that sera with antibody against B/Brisbane/60/2008 tended to be reactive also to the deletion variant, suggesting some level of cross-reactive antibodies to the deletion variant virus in the human population (Figure 11). However, there are some indications that the immunity in some age groups might be less cross-reactive (exemplified by sera 1, 2, and 5 in figure 16).

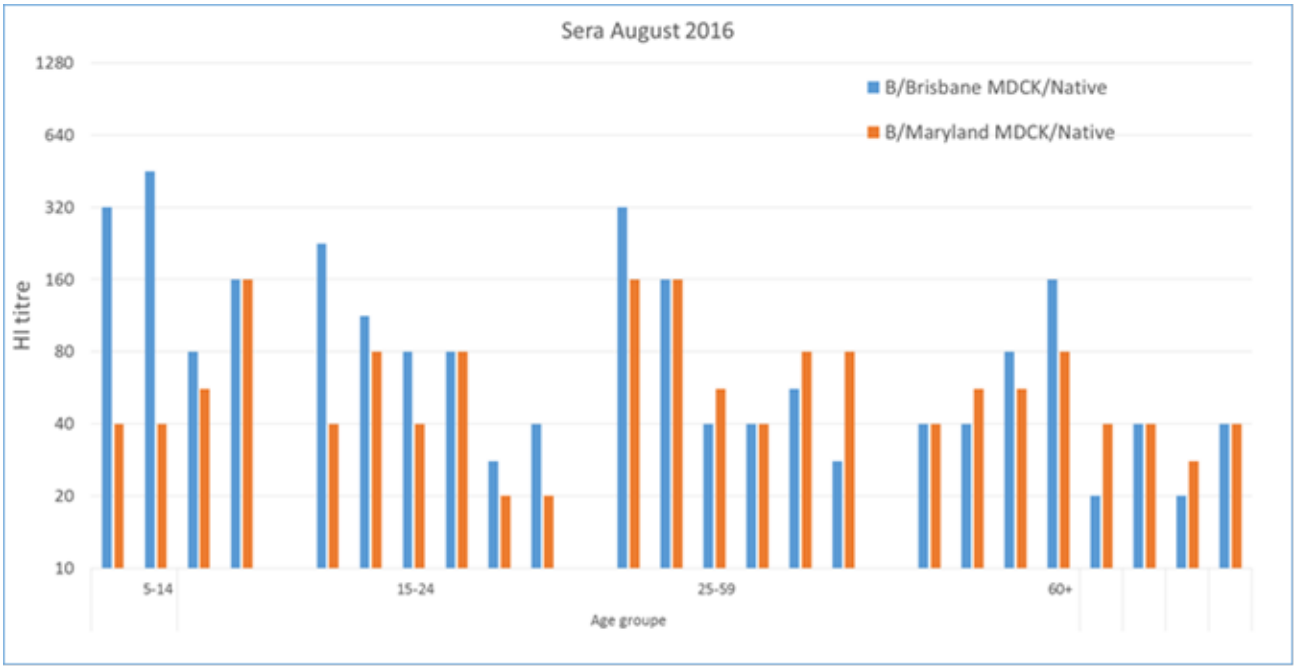
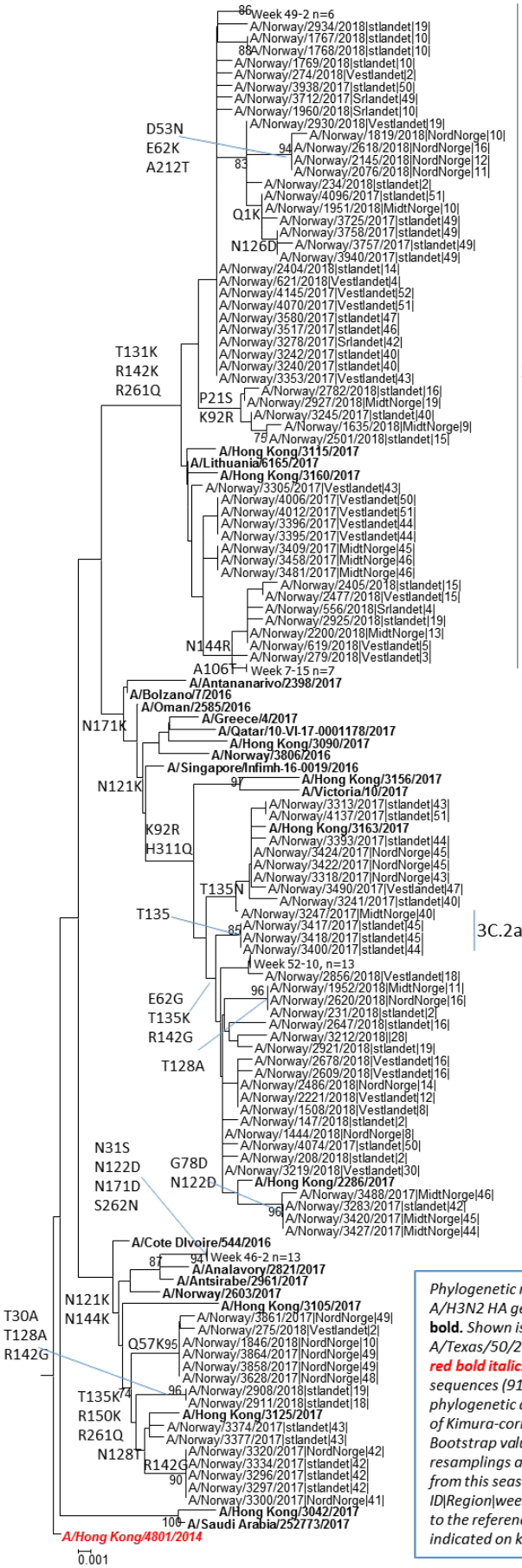


Figure 16. HAI titres in 24 anti-B/Brisbane/60/2008-reactive sera collected in 2016, prior to the deletion variant emergence, against wild-type B/Victoria lineage virus (B/Brisbane/60/2008) and against the novel HA a.a. 162-163 deletion variant, represented by B/Maryland/15/2016. Antigens used were whole-virus MDCK cell isolates.

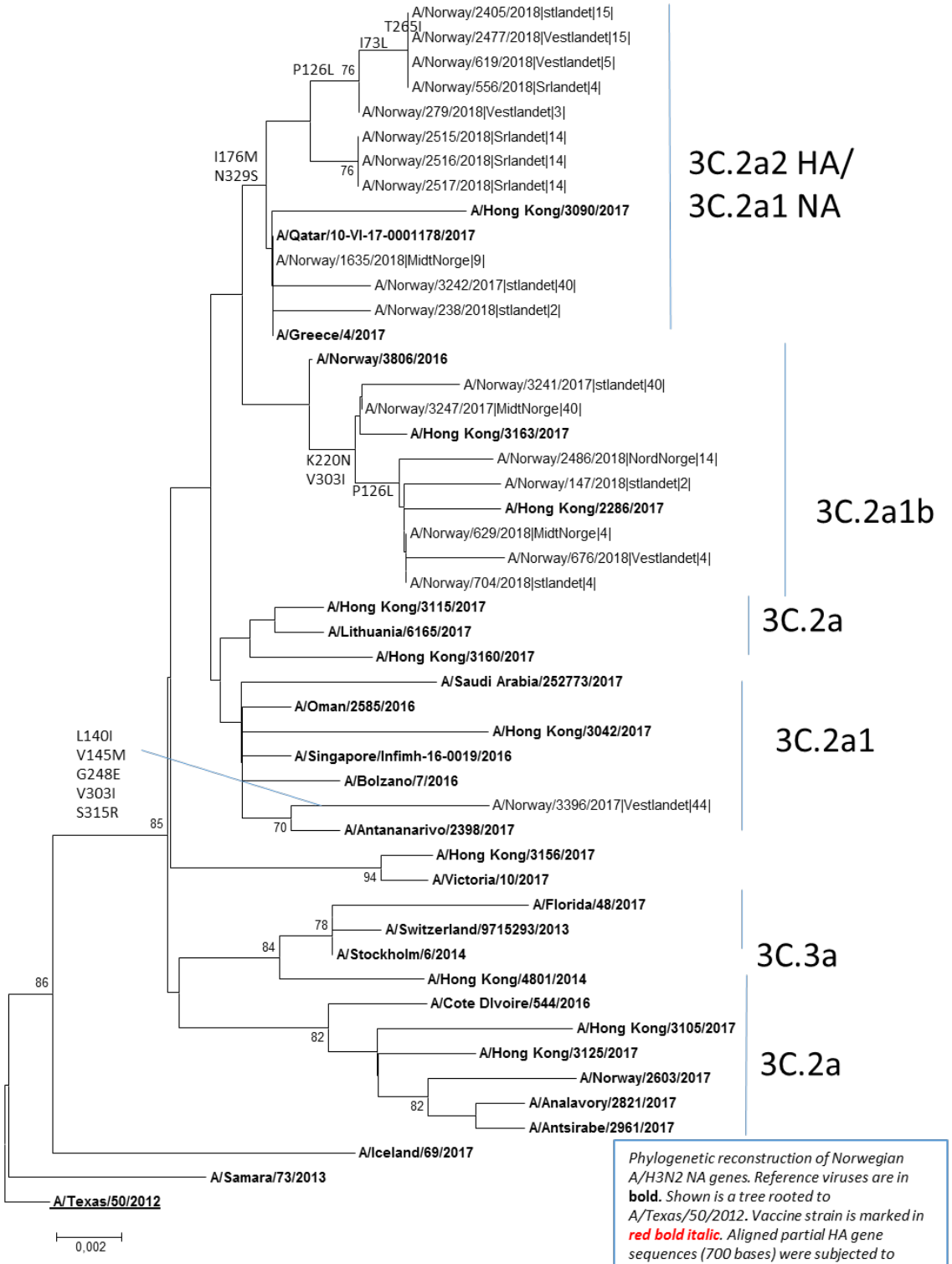
4 Phylogeny: Influenza sequences, Norway 2017-18

HA H3N2

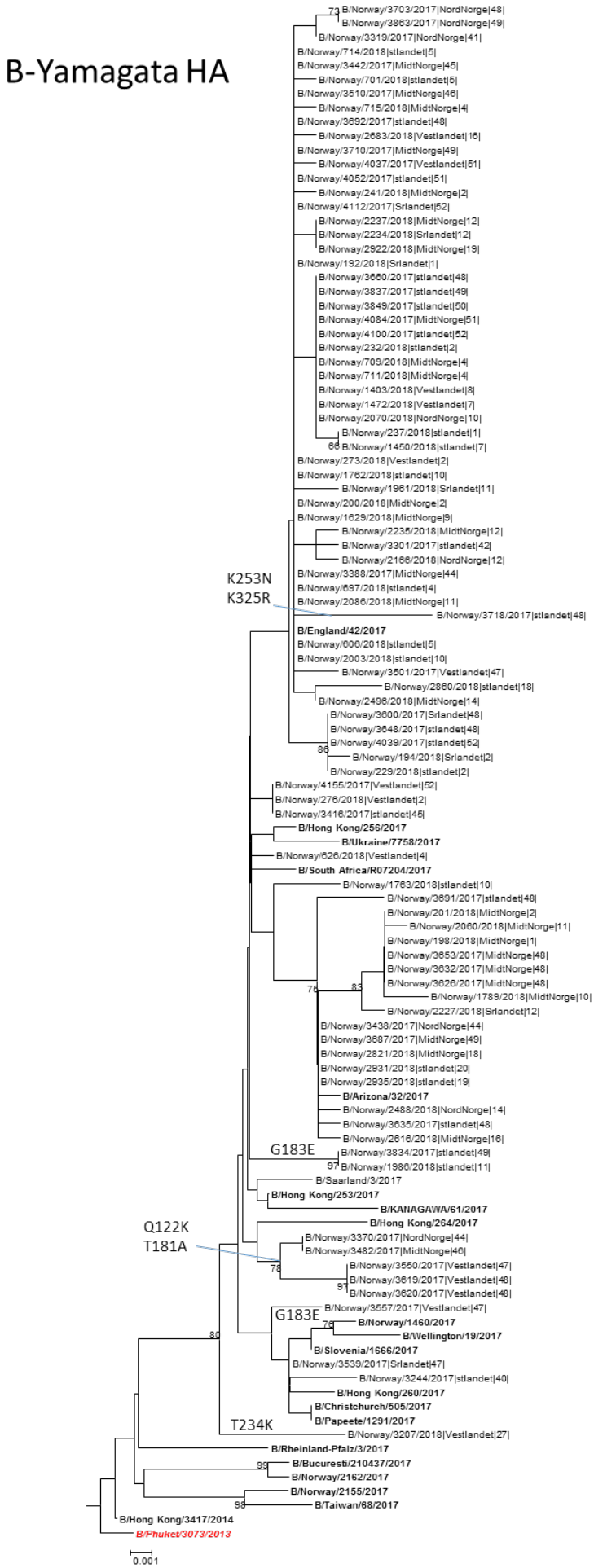


Phylogenetic reconstruction of Norwegian A/H3N2 HA genes. Reference viruses are in **bold.** *Shown is a subtree of a tree rooted to A/Texas/50/2012. Vaccine strain is marked in* ***red bold italic****. Aligned partial HA gene sequences (910 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. 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 key branch nodes.*

NA H3N2

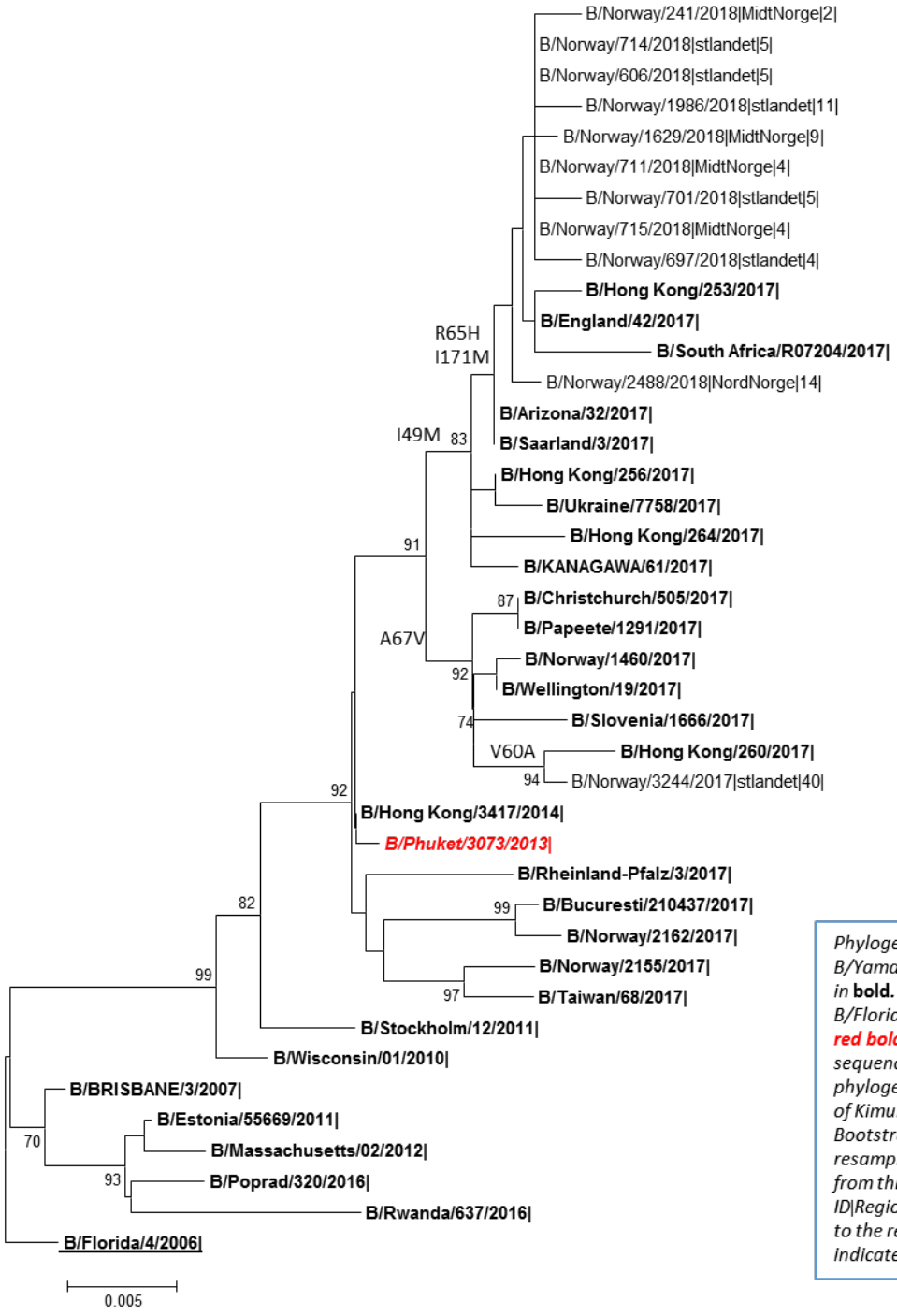


Phylogenetic reconstruction of Norwegian A/H3N2 NA genes. Reference viruses are in **bold**. *Shown is a tree rooted to A/Texas/50/2012. Vaccine strain is marked in* ***red bold italic***. *Aligned partial HA gene sequences (700 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. 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 key branch nodes.*

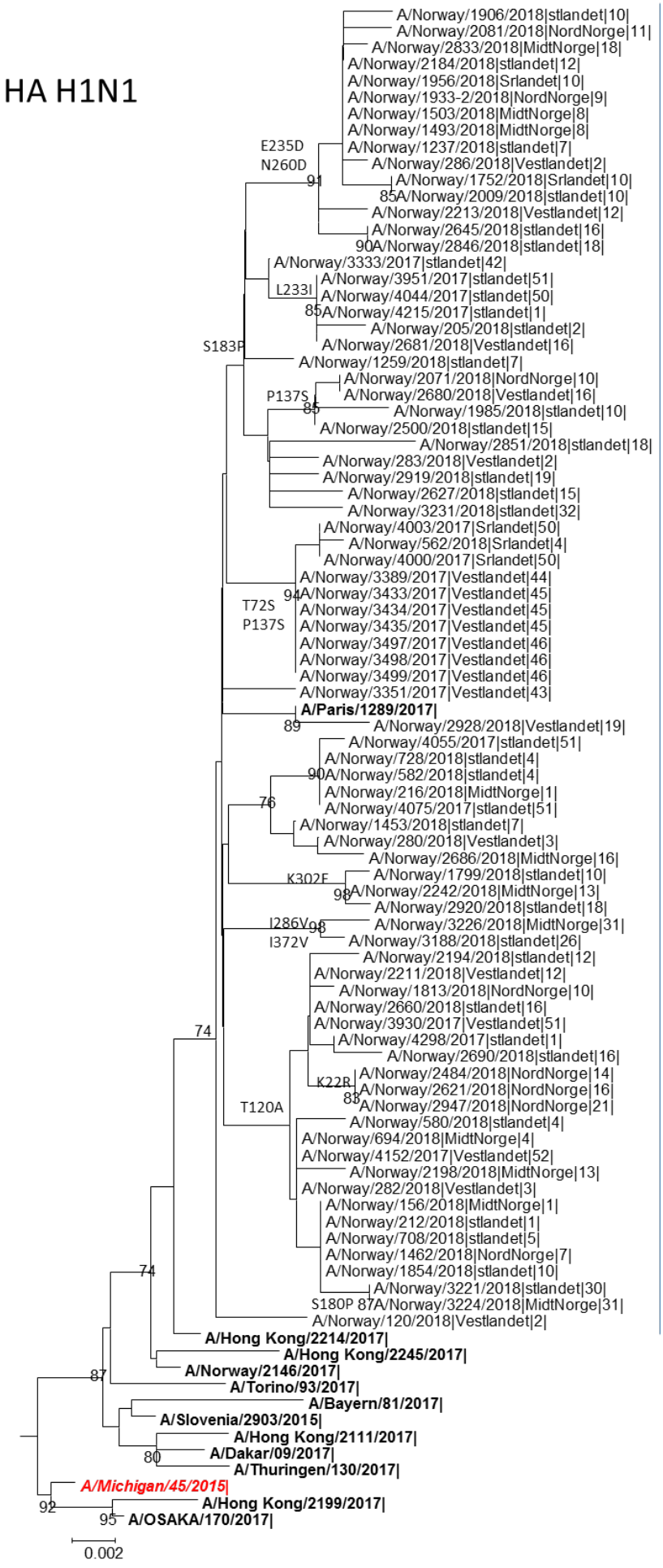


Phylogenetic reconstruction of Norwegian B/Yamagata HA genes. Reference viruses are in **bold.** *Shown is a subtree of a tree rooted to B/Florida/4/2006. Vaccine strain is marked in* ***red bold italic****. Aligned partial HA gene sequences (1020 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. 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/Phuket/3073/2013 are indicated on key branch nodes.*

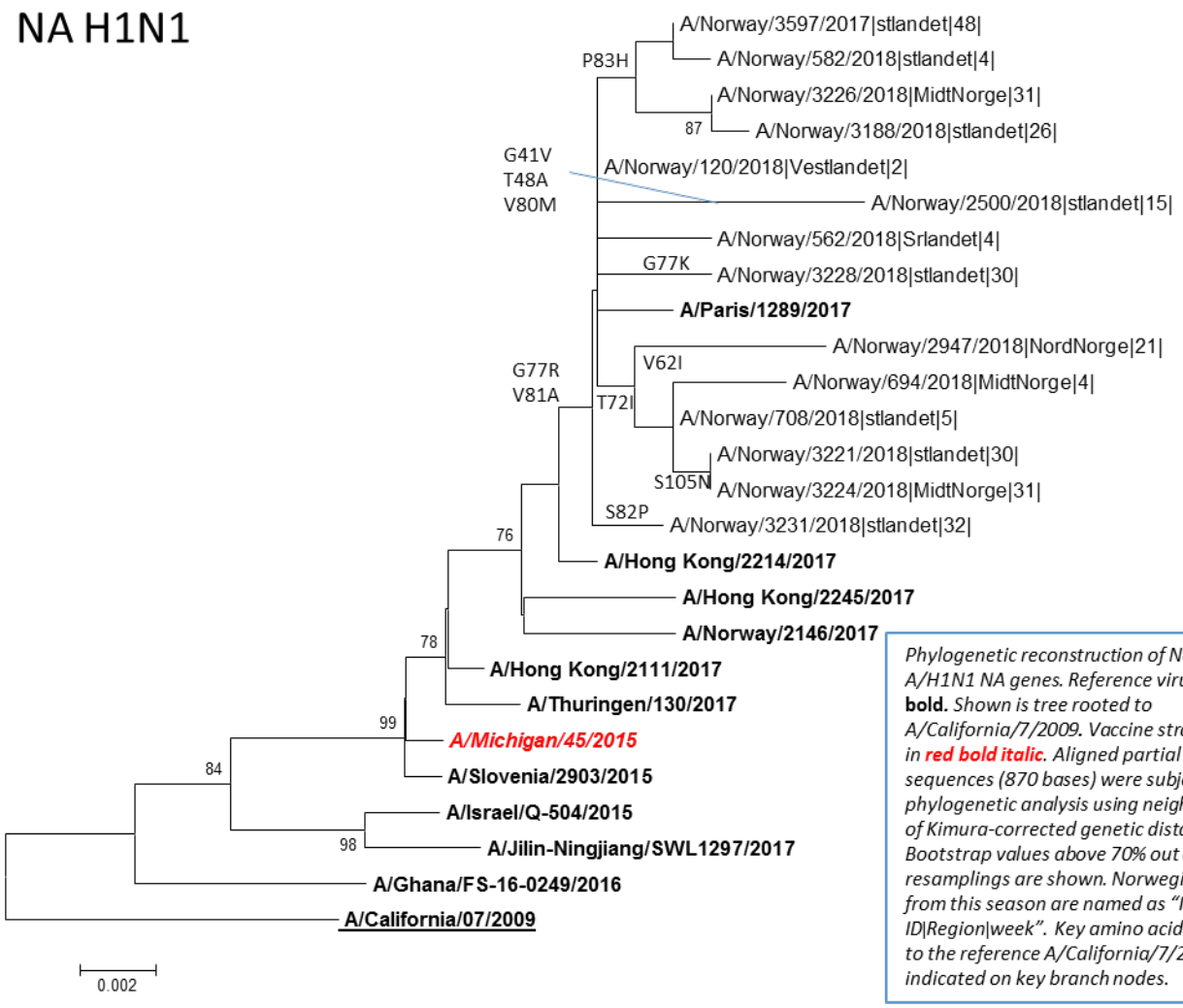
B-Yamagata NA



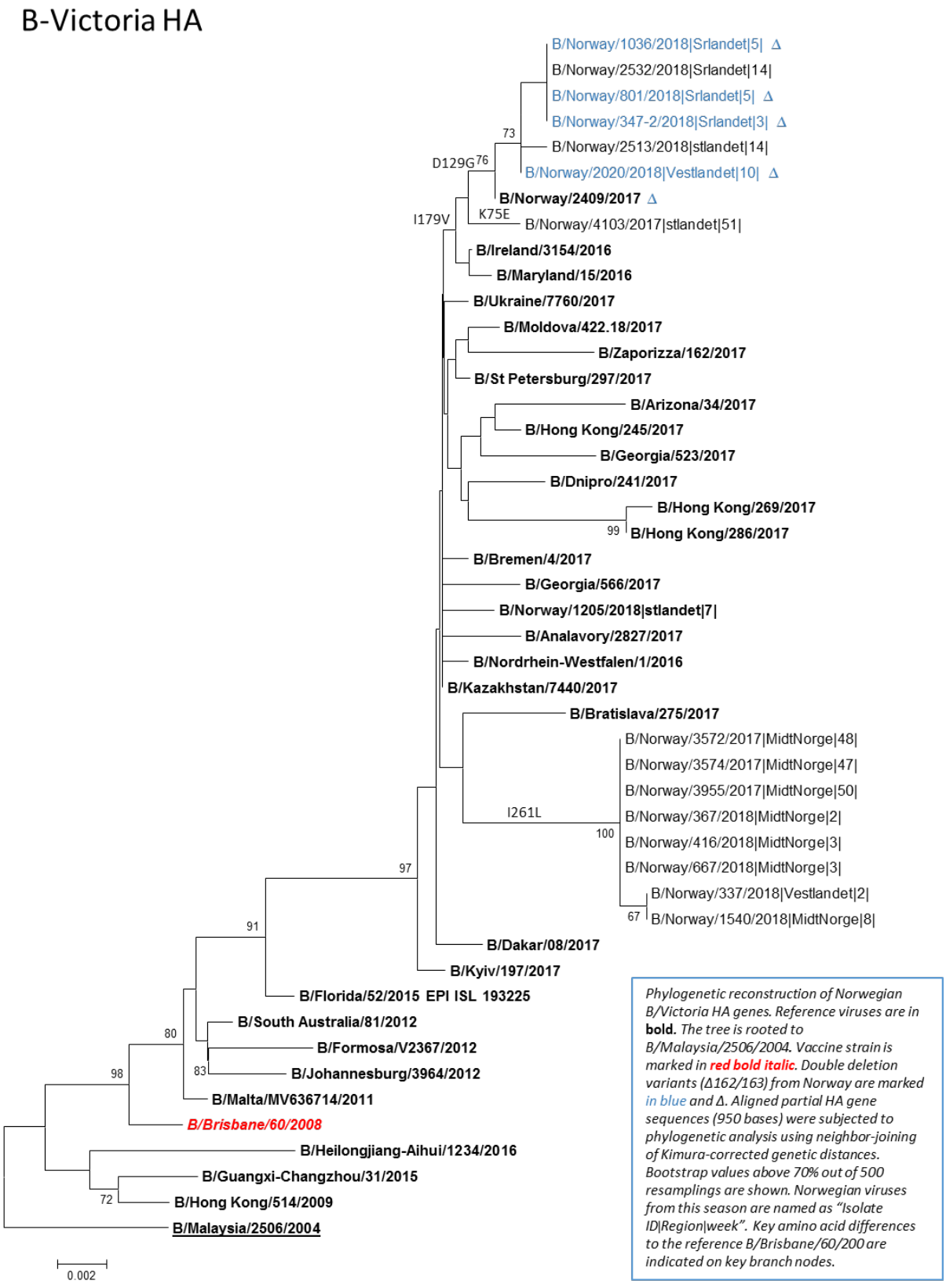
Phylogenetic reconstruction of Norwegian B/Yamagata NA genes. Reference viruses are in **bold**. *Shown is a tree rooted to B/Florida/4/2006. Vaccine strain is marked in* ***red bold italic***. *Aligned partial HA gene sequences (850 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. 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/Phuket/3073/2013 are indicated on key branch nodes.*



Phylogenetic reconstruction of Norwegian A/H1N1 HA genes. Reference viruses are in **bold.** *Shown is a subtree of a tree rooted to A/California/7/2009. Vaccine strain is marked in* ***red bold italic****. Aligned partial HA gene sequences (870 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. 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/7/2009 are indicated on key branch nodes.*



Phylogenetic reconstruction of Norwegian A/H1N1 NA genes. Reference viruses are in **bold.** *Shown is tree rooted to A/California/7/2009. Vaccine strain is marked in* ***red bold italic****. Aligned partial HA gene sequences (870 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. 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/7/2009 are indicated on key branch nodes.*



Phylogenetic reconstruction of Norwegian B/Victoria HA genes. Reference viruses are in **bold.** *The tree is rooted to B/Malaysia/2506/2004. Vaccine strain is marked in* ***red bold italic****. Double deletion variants (Δ162/163) from Norway are marked in blue and Δ. Aligned partial HA gene sequences (950 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. 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/Brisbane/60/200 are indicated on key branch nodes.*

Acknowledgements.

The work presented relies heavily on the essential contributions by the sentinel physicians, Norwegian medical microbiology laboratories, 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, and data on influenza patients in intensive care are provided by the Norwegian Intensive Care Registry. The serology antigen B/Maryland/15/2016 was generously provided by the US CDC, Atlanta, Georgia, USA.

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, and Marianne Morken.

With best regards,

Karoline Bragstad, Kristian Waalen, Ragnhild Tønnessen, Trine Hessevik Paulsen, Torstein Aune, Dagny Haug Dorenberg, Remilyn Ramos-Ocao, Siri Helene Hauge,and Olav Hungnes

National Influenza Centre/Department of Influenza,
Divison for Infection Control and Environmental Health,
Norwegian Institute of Public Health, Oslo, Norway

14 September 2018

Published by the Norwegian Institute of Public Health
September 2018
P.O.B 4404 Nydalen
NO-0403 Oslo
Telefon: + 47-21 07 70 00
The report can be downloaded as pdf
at www.fhi.no/en/publ/