NIPH
Norwegian Institute of Public Health

REPORT

2019

EARLY RISK ASSESSMENT:

What to expect of the 2018/19 influenza season in Norway

Karoline Bragstad
Kristian Waalen
Trine Hessevik Paulsen
Torstein Aune
Brigitte Klüwer
Kjersti Rydland
Olav Hungnes

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Division of Infection Control and Environmental Health;

Department of Influenza

FHI
Folkehelseinstituttet

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

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Authors:
Karoline Bragstad
Kristian Waalen
Trine Hessevik Paulsen
Torstein Aune
Birgitte Klüwer
Kjersti Rydland
Olav Hungnes

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

Graphic design template:
Per Kristian Svendsen

Graphic design cover:
Fete Typer

ISBN digital 978-82-8082-988-7.

Citation: Bragstad K, Waalen K, Paulsen TH, Aune T, Klüwer B, Rydland KM, Hungnes O. " Early risk assessment: What to expect from the 2018/19 influenza season in Norway". [Utsikter for influensasesongen 2018/2019] Report 2018. Oslo: Norwegian Institute of Public Health, 2018.

Content

Early risk assessment

What to expect from the 2018/19 influenza season in Norway

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Scope

This brief report presents the assessment by the Norwegian Institute of Public Health (NIPH) on the influenza situation early in the 2018/2019 season, and possible characteristics of the upcoming influenza outbreak in Norway. The report is based on data from a late-summer serosurvey, early-season surveillance data, and vaccine distribution data. The report is meant to support capacity planning in the health services, provide background information to infection control and other health-care and public health personnel, as well as to provide early in-depth information on the influenza outbreak in general. At this point, as the 2018-2019 outbreak is beginning to unfold, it is of particular interest to assess the different circulating influenza viruses, their eventual spread, and how this will influence the extent of illness, severe illness and mortality in various risk and age groups.

Summary early observations and prospects for the 2017/18 season

- Influenza viruses are on the increase in Norway, but still at a low level as the Christmas/New Year holidays are approaching.
- Comparing with historical data, the weekly developments of clinical and laboratory verified influenza is following a course that in previous years have led to outbreaks peaking in late February or March.
- Influenza A(H1N1) viruses are becoming increasingly predominant. Influenza B viruses are unusually rare.
- Seroepidemiology data from August 2018 indicate that immunity in Norway against circulating influenza A(H1N1) and A(H3N2) viruses is quite strong. Also for the B/Yamagata-lineage virus that caused last winter's influenza outbreak, there was a marked increase in people with antibody at protective levels.
- Added to this comes the immunity due to the subsequent influenza vaccination campaign in the autumn. Rates of vaccination were raised considerably this year.
- The A(H1N1) viruses are clade 6B.1 A/Michigan/45/2015 and group together with the A/Switzerland/3330/2017 reference strain, but with the additional substitutions N129D, S185I and N260D in the haemagglutinin HA1 subunit.
- We have at this point no indication that these changes in the HA1 cause significant antigenic drift from the vaccine strain and recently circulating A(H1N1) viruses [1].
- Provided that there is no significant antigenic drift, and given that immunity against the A(H1N1) virus is strong, there is a good possibility that population immunity will limit the extent of the developing influenza outbreak.
- Nonetheless, experience from previous seasons indicate that outbreaks with A(H1N1) viruses that emerged with the 2009 pandemic in some instances cause severe disease that requires intensive care among the non-elderly.
  While the great majority of cases are mild, and the upcoming outbreak may possibly be of limited extent, such severe cases must be expected also this season.
- No resistant viruses have been found among the 74 influenza viruses hitherto tested for susceptibility to antiviral drugs.

The 2018/19 season thus far

Influenza-like illness (ILI) in primary health care

The ILI-rates have been at baseline levels from week 40 throughout week 50. The ILI proportion has been stable at 0.3 % from week 41 to 46 before rising to 0.5 % in week 48 and 49, still not exceeding the epidemic threshold. Compared with historical data (Figure 1), seasons with a similar development have had influenza outbreaks that culminated in late February or March.

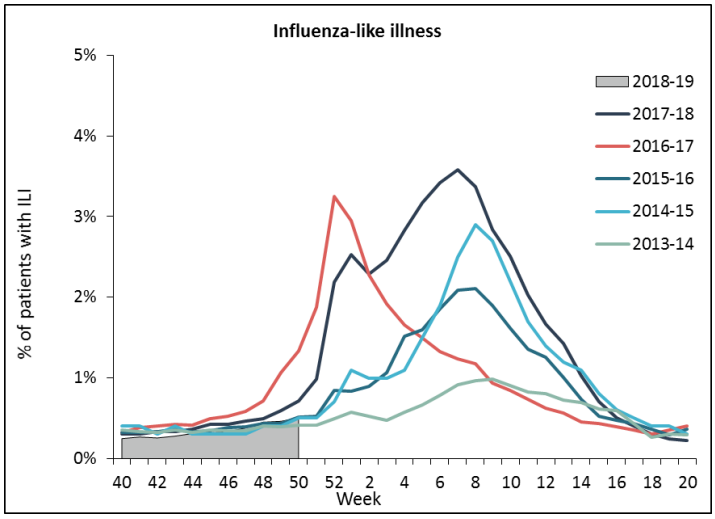


Figure 1: Weekly incidence of ILI, Norway 2018-2019 season. The graph shows the proportion of patients in general practice and emergency clinics presenting with ILI, by calendar week. A selection of previous seasons is also shown.

Severe influenza: laboratory confirmed hospitalised cases

The number of laboratory confirmed influenza cases among hospitalised patients was low during the start of the season, but the increase in the number of cases picked up speed in the weeks 49 and 50, particularly in the 60+ age group. All of the cases have been Influenza A. The number of cases are lower than they were at the same time during the two preceding seasons.

In week 44, higher than expected all-cause mortality was observed in people 65 years or older.

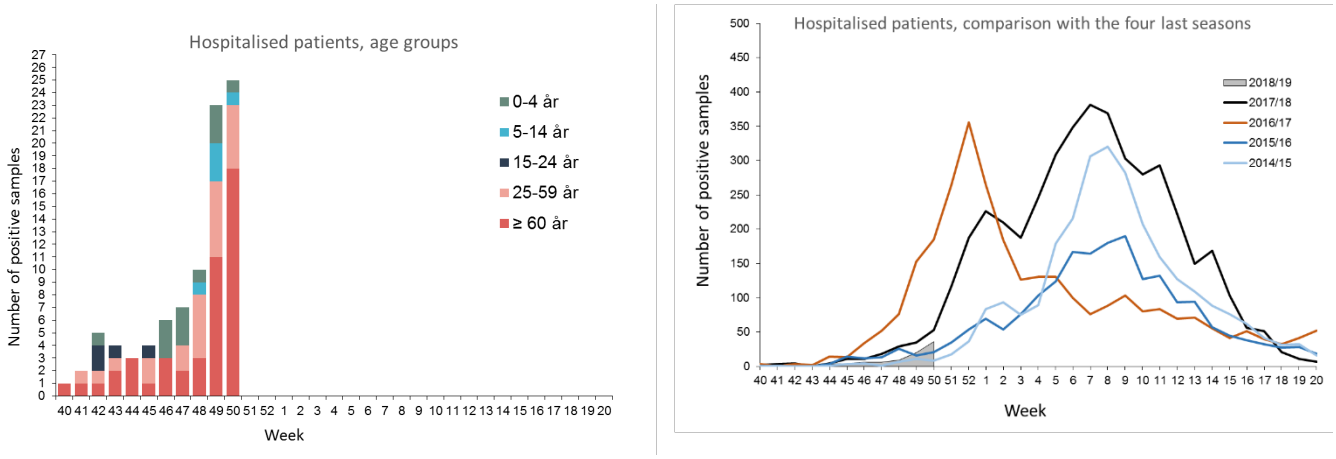


Figure 2: Left hand panel: The number of influenza virus detections in hospitalised patients per week during influenza season 2018/2019, age-distributed, in the nine participating medical microbiology laboratories. Right hand panel: The number of hospitalised patients with confirmed influenza per week compared to the previous four 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.

Laboratory confirmed influenza

There has been a gradual increase in the detections of influenza viruses in Norway since the beginning of October, with a more marked increase in weeks 49 and 50. The weekly total and the proportion of positives is still comparably low (Figure 3). Historically, seasons with a corresponding development of proportion positives have had outbreaks peaking in late February or March (e.g., 2011/2012; 2014/2015; 2015/2016).

During the first few weeks, there was a slight majority of A(H3N2) viruses. This has, however, increasingly shifted toward A(H1N1) predominance in most parts of the country. Interestingly, in the western Norway county of Sogn & Fjordane, a marked increase in influenza A detections during the last two weeks appear to be caused by A(H3N2) viruses. This may possibly be due to a local "founder effect".

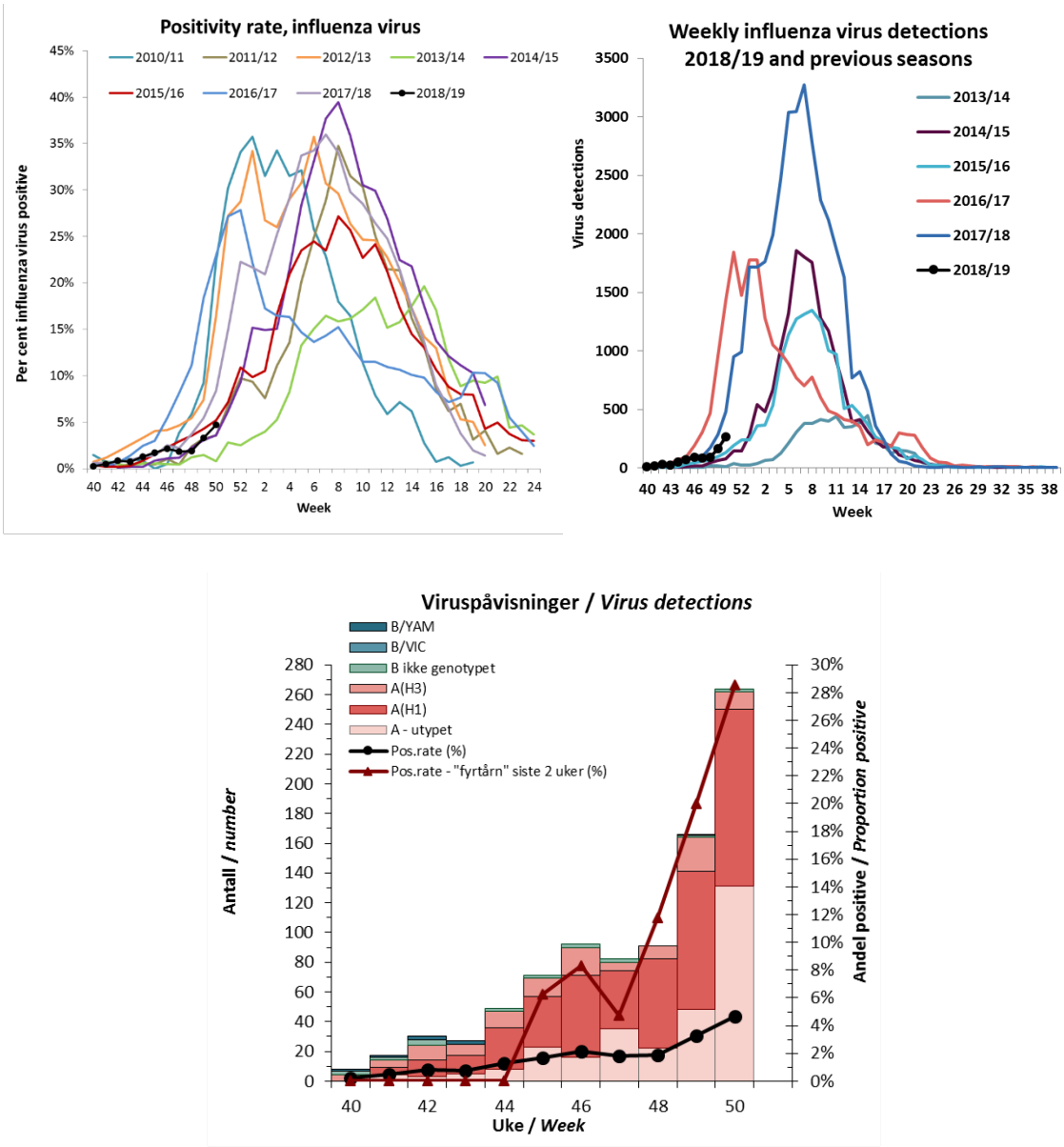


Figure 3: Laboratory detections, Norway 2018-2019. Upper left-hand panel: Weekly proportion of influenza virus positive specimens, with previous season proportions shown for comparison. Upper right-hand panel: Weekly number of influenza virus detections, with previous season numbers shown for comparison.

Lower panel: Weekly number of the different influenza viruses is displayed as stacked bars, while influenza virus positivity rates of sentinel specimens ("fyrtårn", 2-wk average) and all lab testing, respectively, are shown as line graphs.

Altogether, 46476 patients have been tested for influenza during weeks 40-50, resulting in 870 detections of influenza A and 27 detections of influenza B. Among the influenza A virus detections, there is a clear and increasing predominance of subtype H1 (Figure 3, 4).

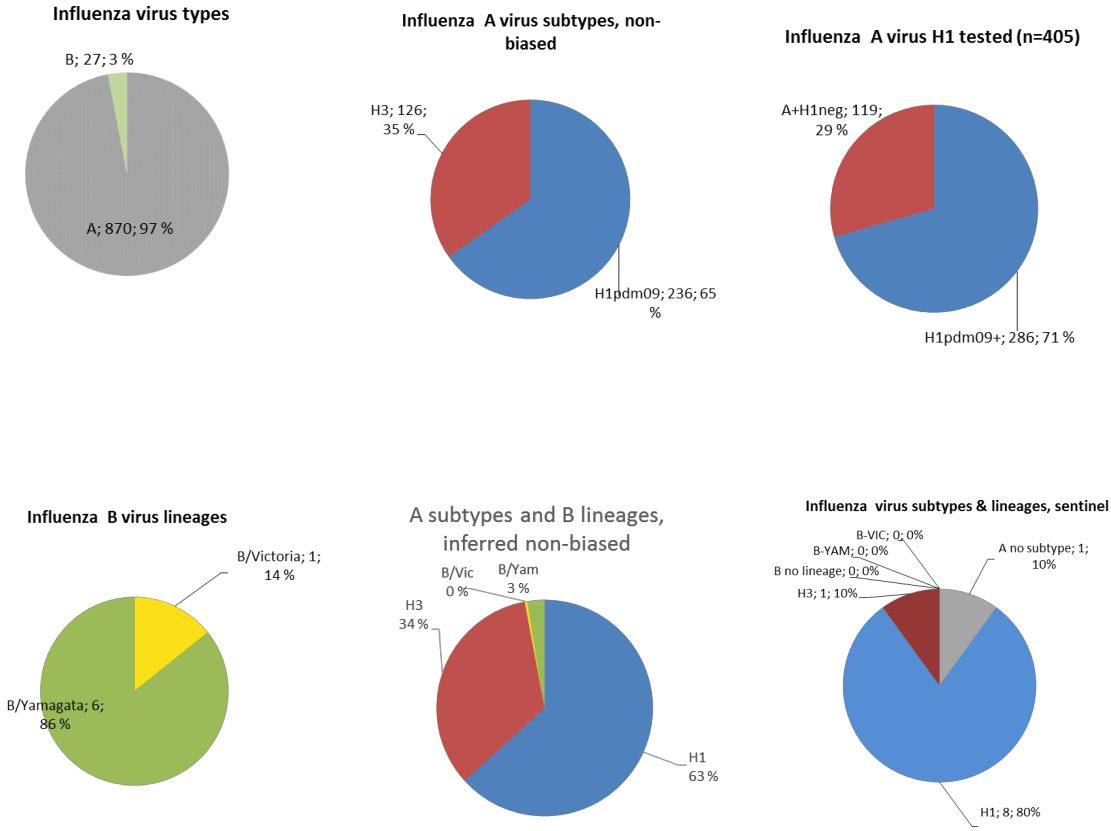


Figure 4. Proportions of 2018/19 season influenza virus subtypes and lineages among viruses analysed in Norway, by 19th December 2018. All-laboratories proportions of A/B type, A subtypes and B lineages are shown in the first four diagrams. The subtype and lineage frequencies are superimposed on type distributions in the lower middle panel, for comparison with the distribution among sentinel specimen data (lower right panel).

To limit the subtype testing bias in the all-laboratories data (nearly three times more viruses have been tested for H1 than for H3), only H1 positives that have also been tested for H3 are counted in the top-middle diagram. A similar proportion is obtained through an alternative approach that uses data from a higher number of laboratories that test all A positives for H1 but not H3, shown in the top-right diagram, where A positives testing negative for H1 serve as a proxy for H3. The sentinel data are not subtype biased in this way but the numbers are very limited at this point.

If the predominance of A(H1N1) indeed remains through this winter's main outbreak, this will represent a continuation of a pattern of H1N1 predominance every third season since the virus emerged with the 2009 pandemic (figure 5). This subtype also predominated during the 2013-14 season but that was a very small outbreak.

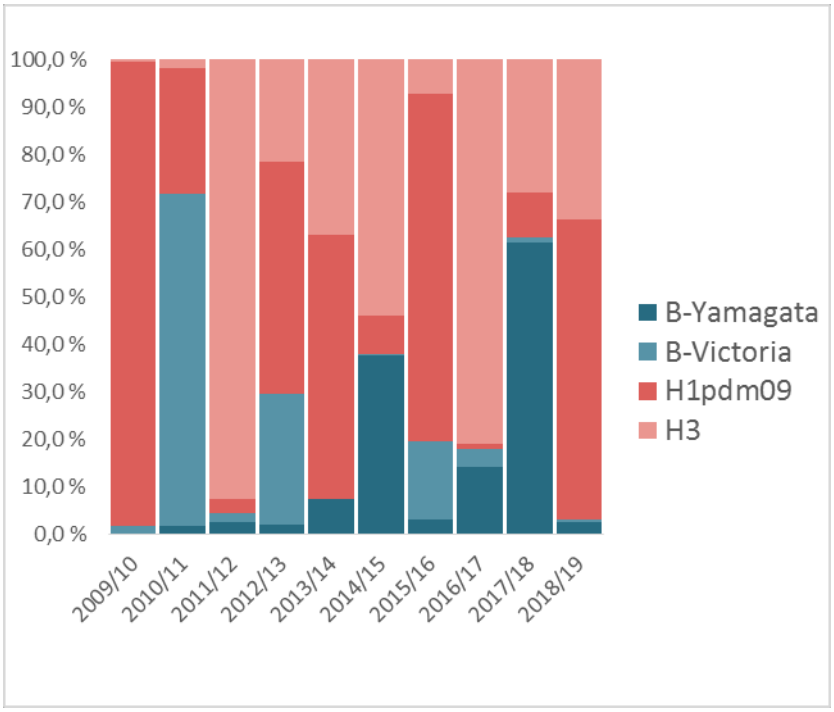


Figure 5: Predominance of influenza viruses in Norway, 2009-2018.

Age distribution of the different viruses

Preliminary age profiles for the A(H1N1) and A(H3N2) viruses indicate that the age patterns this season do not differ from recent seasons (Figure 6). Infants are strongly represented among cases with A(H1N1) infection, and persons 60 years and older are strongly represented among cases with A(H3N2) infection. Age profiles for influenza B/Yamagata and B/Victoria are not available due to the very low number of viruses analysed.

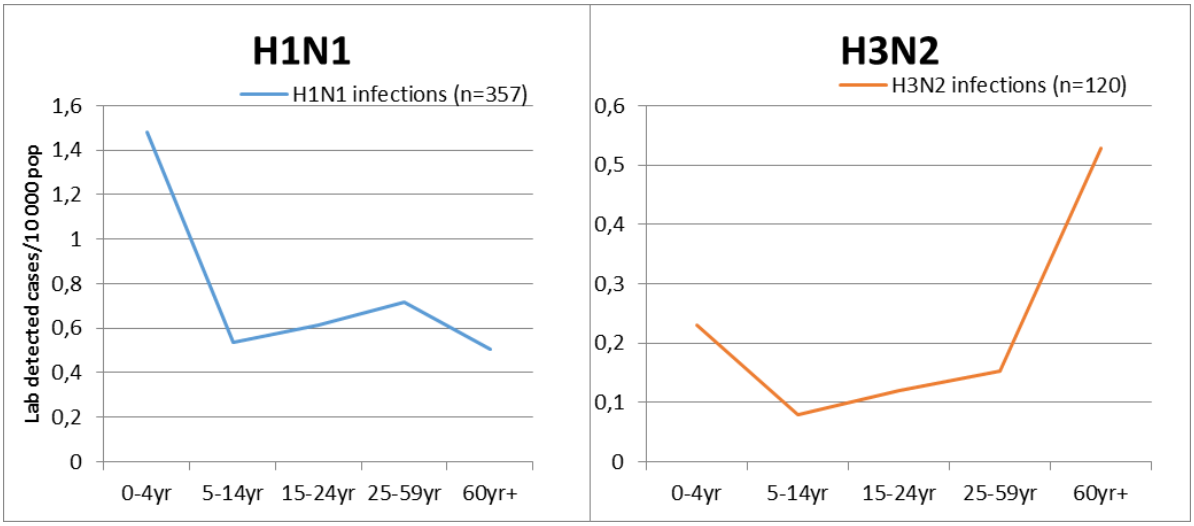


Figure 6. Cumulative incidence per 10 000 population of subtype/lineage detections by age group, based on viruses analysed in the Norwegian National Influenza Centre early in the 2018/19 influenza season.

Genetic characterizations of the viruses in circulation

The analysed H1N1 viruses are all characterised as clade 6B.1 A/Michigan/45/2015 viruses and the major group of H1 viruses currently possesses the following substitutions: S74R, N129D, S183P, S185I, R223Q and N260D and group phylogenetically together with the A/Switzerland/3330/2017, or even closer to the A/Ukraine/7993/2018 reference strain (see phylogenetic tree at the end of the report). There is also a smaller group of H1 viruses circulating possessing the key substitutions I404M and N496S, grouping together with clade A/Paris/1289/2017 reference strain.

The N1 gene of the A/Switzerland/330/2017-like viruses possessed the key amino acid substitutions: Q50K, V67I, F74S and S95N for the same phylogenetic clustering as the HA genes. The closest relative is the A/Ukraine/7992/2018 reference strain.

The characterised H3N2 viruses are all 3C.2a1b A/Alsace/1746/2018 viruses, however these divide into two equally prevalent subgroups; the clade A/Iceland/78/2018 subgroup with the A106V and T131K key substitutions and the clade A/LaRioja/2202/2018 subgroup with the I48R, T128A, T135K (see phylogenetic tree at the end of the report).

The N2 gene of the A/Iceland/78/2018-like viruses possessed the key amino acid substitutions: P136L and S315R.

Influenza B-Yamagata viruses characterised this far seem to be the same as previous season, all clade 3 viruses.

Antiviral susceptibility

No resistance towards neuraminidase inhibitors like oseltamivir and zanamivir has so far been detected, out of 23 H3 viruses, 50 H1 viruses and 1 influenza B virus analysed.

Vaccine

Vaccine match

The H1 viruses circulating is of the same genetic group 6.B1 as the H1 component in the vaccine. Although some few mutations have been found that could influence on the vaccine-match, it is expected that the vaccine to a satisfactory degree will cover the H1 viruses, as it did last season. Both N129D and S85I substitutions characterising the most prevalent H1 group of viruses in Norway at present are positioned in antibody recognition sites A and E, respectively. In addition, all Norwegian viruses possess the R223Q substitution that is associated with antigenic drift. This substitution was however also present in the H1 viruses from last season and still the vaccine showed satisfactory effectiveness. So far, we have received 19 samples from vaccinated persons and none had lab confirmed influenza. At the same time last season we had received 16 samples from vaccinated persons and four were influenza positives (1 H1, 2 H3, 1 B/Yamagata). For influenza A H3N2 viruses we expect the same poor vaccine effectiveness as previous season. It is expected that the vaccines will induce good protection against influenza B viruses. The trivalent vaccine contains the influenza B-Victoria deletion variant, but some cross protection against B-Yamagata viruses, as well as non-deletion B-Victoria viruses, is also anticipated.

Vaccine distribution and coverage

A total of 870 000 influenza vaccine doses have been distributed so far this season; 712 000 of these were specifically meant for persons in medical risk groups and health care personnel involved in direct patient care. These numbers represent an increase in distributed doses of 55-60 % over the last two years (Figure 7).

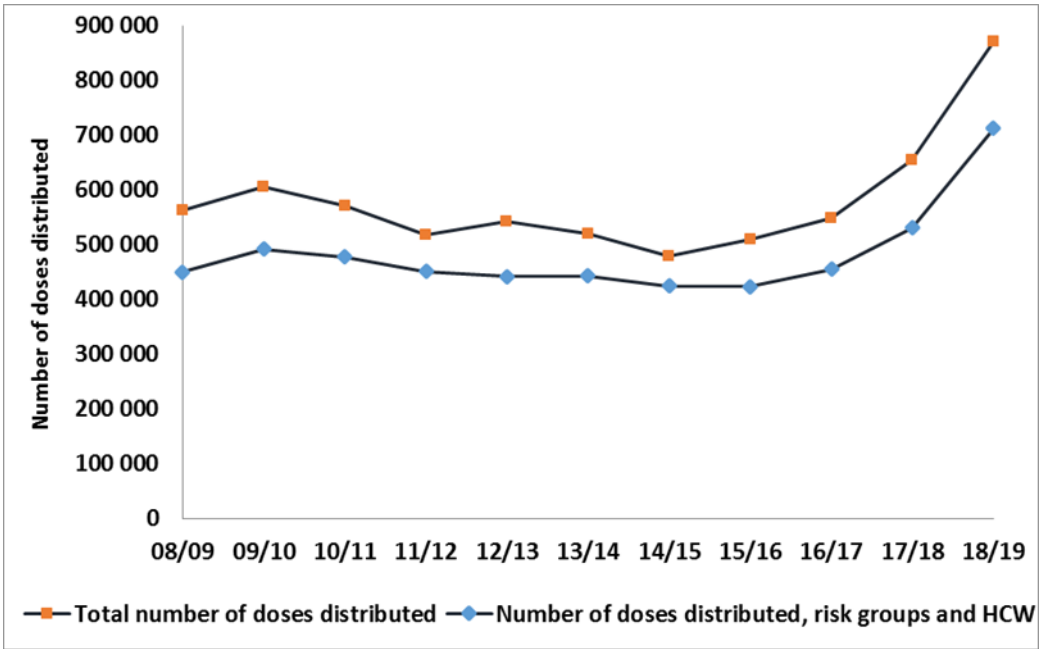


Figure 7: Influenza vaccine doses (seasonal) distributed in Norway, 2008 through 2018 as per 19th December. HCW = Health Care Workers.

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

Population immunity against recent influenza viruses, August 2018

The National Influenza Seroepidemiology Programme annually in August collects about 2000 anonymised convenience sera from clinical/microbiological laboratories across Norway. The sera, aimed to be representative of the Norwegian population geographically and by age composition, are tested by the haemagglutination-inhibition (HI) test to determine the antibody immunity against relevant circulating influenza viruses. As an austerity measure, only a subset of 1178 sera were analysed this year.

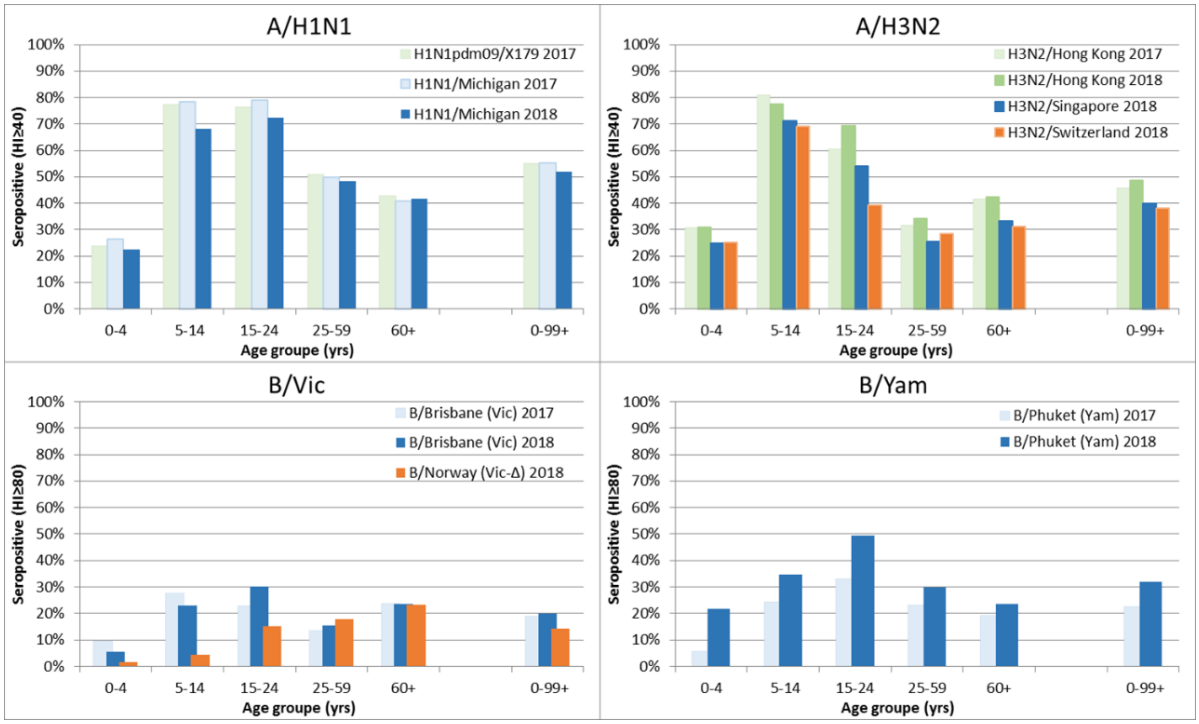


Fig 8. Seroprevalence in August 2018 to current influenza A and B reference and vaccine strains for 'All ages' (0-99+) and in various age groups. For comparison, seroprevalences to some virus strains in August 2017 are also shown. X179A= A/California/07/2009 (H1N1)pdm09; Michigan= A/Michigan/45/2015 (H1N1)pdm09 clade 6B.1; Hong Kong = A/Hong Kong/5738/2014 (H3N2) clade 3C.2a; Singapore= A/Singapore/INFIMH-16-0019/2016 (H3N2) clade 3C.2a1 ; Switzerland= A/Switzerland/8060/2017 (H3N2) clade 3C.2a2; B/Brisbane= B/Brisbane/60/2008 (Victoria lineage); B/Norway= B/Norway/2409/2017 (Victoria lineage, amino acid 162-163 deletion variant); B/Phuket= B/Phuket/3073/2013 (Yamagata lineage).

The main findings are shown in figure 8 and summarised as follows:

For A(H1N1) viruses, the comparatively strong population immunity that has been accumulated in recent years had been maintained in most age groups, even though circulation of this virus was limited during the previous season.

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

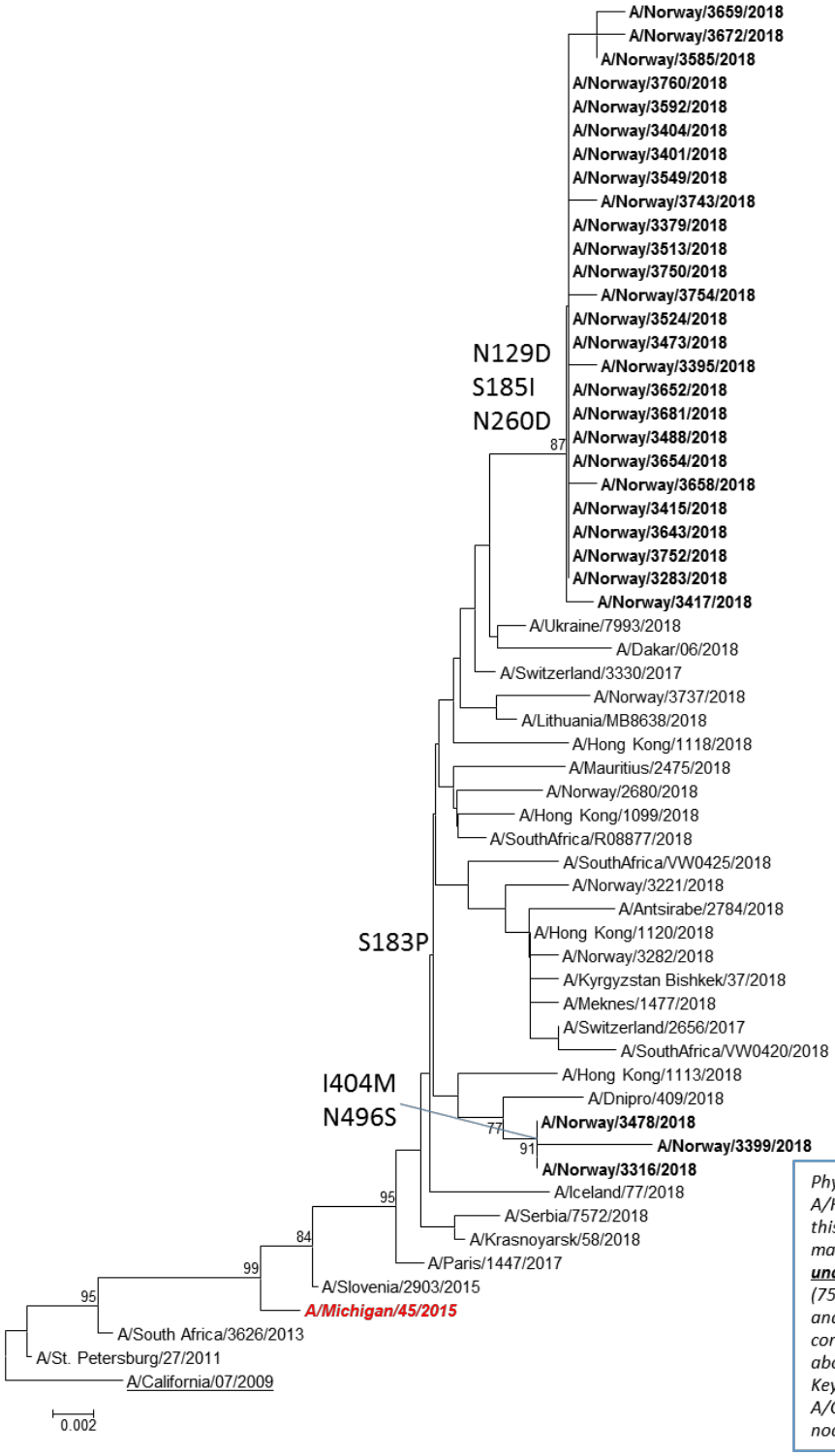
The seroprevalence against B/Victoria-lineage viruses remained low with overall seroprevalence of 20 % against the previous B/Victoria vaccine component B/Brisbane/60/2008.

Interestingly, the seroprevalence against a newly emerged “double deletion” variant, represented by B/Norway/2409/2017 in our analysis, shows a different and reduced pattern for those below 25 years old, and particularly those younger than 15 years. For those 25 years and older the seroprevalence against the two virus variants was similar. The deletion variant virus is now for the first time included in the current influenza vaccine.

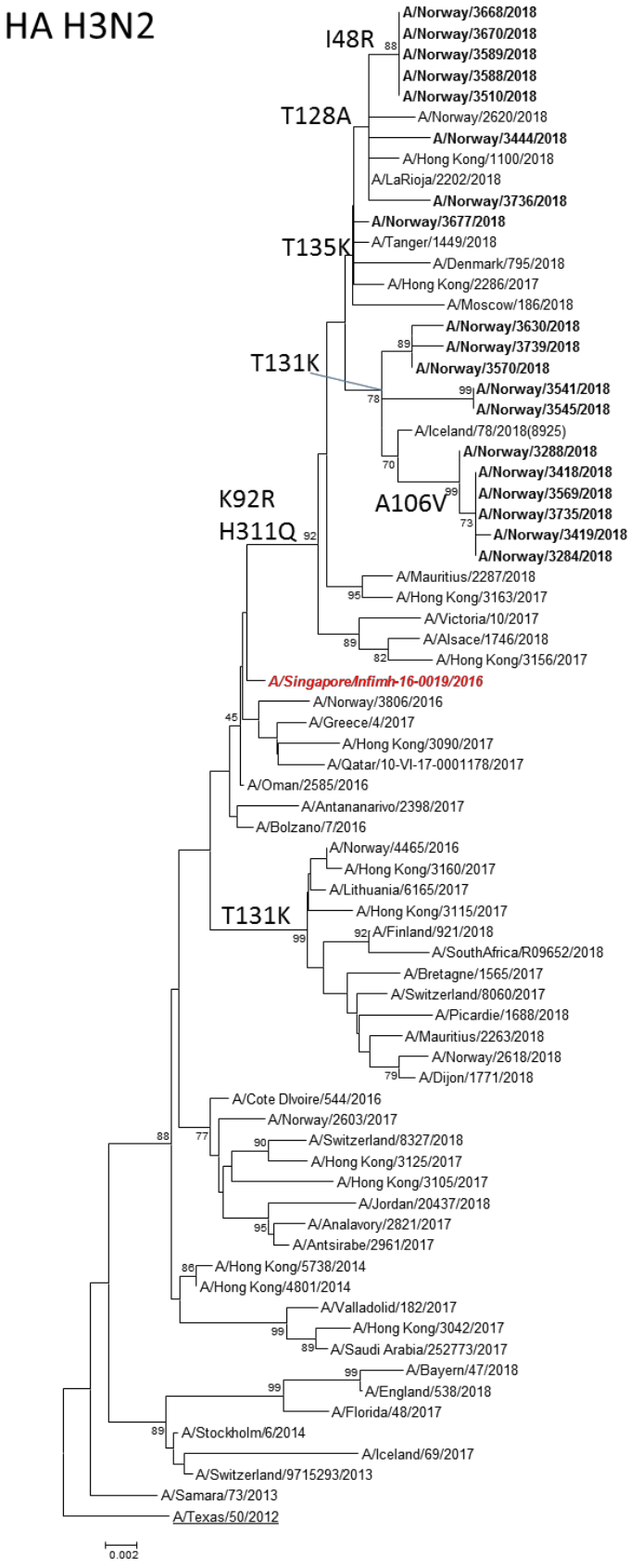
B/Yamagata-lineage viruses predominated last winter, and the seroprevalence against the current variant B/Phuket/3070/2013 increased since 2017 in all age groups. The largest increase occurred in people younger than 25 years, with more modest increases in other age groups.

Phylogeny

HA H1N1



Phylogenetic reconstruction of Norwegian A/H1N1 HA genes. Norwegian viruses from this season are in **bold,** *vaccine strain is marked in* ***red bold italic*** *and root is* ***underlined****. Aligned partial HA gene sequences (750 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. Bootstrap values above 70% out of 500 resamplings are shown. Key amino acid differences to the reference A/California/07/2009 are indicated on branch nodes.*



Phylogenetic reconstruction of Norwegian A/H3N2 HA genes. Norwegian viruses from this season are in **bold,** *vaccine strain is marked in* ***red bold italic*** *and root is* ***underlined****. Aligned partial HA gene sequences (1040 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. Bootstrap values above 70% out of 500 resamplings are shown. Key amino acid differences to the reference A/Texas/50/2012 are indicated on key branch nodes.*

References

1 European Centre for Disease Prevention and Control (ECDC): Influenza virus characterisation, Summary Europe, November 2018 https://ecdc.europa.eu/en/publications-data/influenza-virus-characterisation-summary-europe-november-2018

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.

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

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

With best regards,

Karoline Bragstad, Kristian Waalen, Trine Hessevik Paulsen, Torstein Aune,
Birgitte Klüwer, Kjersti Rydland, and Olav Hungnes

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

28 December 2018

Appendices

Methods

Influenza-like illness

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

Virological surveillance.

A network of volunteer sentinel physicians throughout the country collects specimens from patients with ILI for analysis at the National Influenza Centre.
In addition, medical microbiology laboratories that perform influenza diagnostics weekly report the number of positives and the number of specimens tested, according to virus type/subtype, detection method and patient age group. These laboratories also contribute influenza positive specimens to the NIC for further characterisation. Even though most of these laboratories are affiliated to hospitals, a large proportion of specimens tested for influenza virus are from outpatients visiting general practitioners.

Surveillance of laboratory-confirmed influenza in hospitalised patients

As an extension to the basic weekly reporting of influenza diagnostic testing outcomes, nine medical microbiology laboratories stratify their report into hospitalised patients and outpatients. Together, 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 extended reporting constitutes the basis for the surveillance of laboratory confirmed influenza in hospitalised patients. This is the fifth year this surveillance system is in operation.

Influenza seroepidemiology

The National Influenza Seroepidemiology Programme annually in August solicits about 2000 serum samples collected during the weeks 31-35 from clinical/microbiological laboratories covering the 19 counties of Norway. These anonymised convenience sera are aimed to be representative of the Norwegian population geographically and by age composition. The sera are tested by the haemagglutination-inhibition (HI) test to determine the antibody immunity to relevant circulating influenza viruses. HI titres ≥40 against the influenza A strains and ≥80 against ether-treated influenza B strains are considered as protective levels and recorded as seropositive in the analysis.

Published by the Norwegian Institute of Public Health
January 2019
P.O.Box 222- Skøyen
NO-0213 Oslo
Tel: + 47-21 07 70 00
The report can be downloaded as pdf
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