Folkhälsomyndigheten
PUBLIC HEALTH AGENCY OF SWEDEN

Influenza in Sweden

2014–2015 Season

Influenza in Sweden

2014–2015 Season

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Preface

This report describes the monitoring systems for influenza in use during the winter season of 2014–2015 and the results of both epidemiological and virological surveillance. Data are also compared to previous influenza seasons.

The report is prepared for the World Health Organization (WHO) as part of the Public Health Agency of Sweden's function as a National Influenza Centre (NIC).

Annual reports in English about the influenza seasons in Sweden have been available since 2000 and can be found on the Public Health Agency's website.[1]

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[1] Folkhälsomyndigheten. http://www.folkhalsomyndigheten.se/publicerat-material/publikationer/. Suggested search query: "Influenza in Sweden".

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Summary

The influenza season of 2014–2015 was long and intense. However, despite genetic drift among the circulating influenza A(H3N2) strains, the season was no more severe than previous intense seasons.

The influenza epidemic peaked during weeks 8–10 of 2015. This peak was dominated by influenza A(H3N2) and was followed by a prolonged wave of influenza B. This mirrors the change in dominant type seen throughout Europe.

A total of 10,389 laboratory-confirmed cases of influenza were reported during the 2014–2015 season (Figure 5), which is higher than all previous seasons (except for the 2009 pandemic), including the intense season of 2012–2013. The number of analysed samples was the highest since the 2009 pandemic. However, the peak percentage positive among analysed samples has remained similar among recent intense seasons, indicating that the clinical case definition for laboratory verification remains unchanged. The increased number of samples analysed indicates that more people, likely the elderly, sought care for influenza this season, probably due to the dominance of influenza A(H3N2).

The incidence of all influenza types was the highest among individuals 65 years or older. The highest incidence of influenza A(H3N2) was also seen among adults 65 years or older, and this strain accounted for 62% of the cases.

Only 663 cases of influenza A(H1N1)pdm09 were reported during the season. Hospitalization was reported for 250 (42.4%) of these, of which 31 individuals were placed in intensive care. Most of those requiring intensive care belonged to a risk group (74%), and this highlights the severity of influenza infection for these groups.

Viral characterization showed that some of the circulating A(H3N2) strains had drifted from the vaccine strain, while the A(H1N1) and B/Yamagata lineage were similar to the respective vaccine strains. Only a few samples were detected with B/Victoria lineage. All tested samples were sensitive to the antivirals currently recommended (oseltamivir and zanamivir) except for one (A(H1N1)pdm09 sample that was resistant to oseltamivir.

Vaccination coverage among medical risk groups below 65 years of age was low (~2%). However, vaccination coverage among the elderly (65 years or older) increased modestly compared to last season, continuing the upward trend seen during the previous season.

Sammanfattning

Influensasäsongen 2014–2015 var lång och intensiv. Trots den genetiska driften bland cirkulerande influensa A(H3N2)-stammar var säsongen dock inte allvarligare än tidigare intensiva säsonger. Toppen nåddes 2015 under veckorna 8–10 och dominerades av influensa A (H3N2). Därefter följde en förlängd våg av influensa B (totalt sett stod A(H3N2) för 69 procent av fallen och influensa B för 23 procent). Detta speglar influensasäsongen i övriga Europa.

Totalt sett rapporterades 10 389 laboratorieverifierade influensafall under säsongen 2014–2015, vilket är fler än tidigare säsonger (med undantag för pandemin 2009) inklusive den intensiva säsongen 2012–2013. Antalet analyserade prover var också det högsta sedan pandemin 2009. Andelen positiva analyserade prover var jämförbar med de senaste intensiva säsongerna, vilket visar att den kliniska falldefinitionen inte förändrats. Det ökade antalet analyserade prover tyder på att fler, troligen främst äldre, sökte vård för influensa under säsongen, förmodligen på grund av att influensa A(H3N2) dominerade. Incidensen av samtliga typer av influensa var högst bland personer 65 år eller äldre, särskilt för influensa A(H3N2) där äldre stod för 62 procent av fallen.

Få fall av influensa A(H1N1)pdm09 rapporterades under säsongen – totalt 663 fall. Sjukhusvård rapporterades för 250 av dessa patienter (42,4 procent), varav 31 intensivvårdades. De flesta av dem som krävde intensivvård tillhörde en medicinsk riskgrupp (74 procent).

Viruskaraktärisering visade att en del av de cirkulerande influensa A(H3N2)-stammarna hade förändrats jämfört med vaccinstammen, medan influensa A(H1N1)pdm09 och B/Yamagata liknade respektive vaccinstam. B/Viktoria påvisades endast i ett fåtal prover. Alla virus som analyserats var känsliga för de rekommenderade antivirala medlen (oseltamivir och zanamivir), förutom ett influensa A(H1N1)pdm09-virus som var resistent mot oseltamivir.

Vaccinationstäckningen bland medicinska riskgrupper under 65 år är låg (cirka 2 procent). Täckningen bland de äldre (65 år eller äldre) ökade måttligt jämfört med förra säsongen (från 45,8 till 49,7 procent), och fortsätter den uppåtgående trend som startade under säsongen 2013–2014.

Background

Each winter, influenza epidemics of varying magnitude occur in Sweden. People and society are affected in different ways depending on the characteristics of the circulating viruses and the immunity towards them in different age groups.

New influenza strains, particularly those different enough to cause a pandemic, can be very aggressive and cause severe illness, and these can cause great strain on intensive care units as well as deaths in all age groups. None of these effects are detectable through a single reporting system. In order to get an overall picture of ongoing influenza activity and to remain prepared in case of a pandemic, the Public Health Agency of Sweden (*Folkhälsomyndigheten*) has a number of different epidemiological reporting systems for influenza ranging from the collection of data from different healthcare providers to the analysis of web searches.

Virological surveillance is as important as epidemiological reporting systems. Viruses are typed as influenza A or B by regional laboratories in real time during the influenza season, and some laboratories also determine the subtype for influenza A. Throughout the season, viruses from around the country are characterized by the Public Health Agency with regard to subtype and lineage, vaccine similarity, sensitivity to antiviral drugs, and other factors that might affect the severity of the infections they cause. Viruses are also isolated and sent to the WHO Collaborating Centre (WHO CC) in Mill Hill, London, for further characterisation and to provide a basis for vaccine strain selection. When new strains of influenza virus emerge, reference methods for diagnostics are established at the Public Health Agency and shared with all microbiological laboratories in Sweden.

Surveillance systems

The pyramid below illustrates the different ways that influenza affects those who are infected (Figure 1). Most infected people do not suffer any symptoms, while others fall ill but simply stay home or continue with their daily activities. Of those who are ill, a portion seek healthcare, and a portion of these are so ill that they are hospitalised. Some of these hospitalized patients are so ill that they require intensive care, and a small portion of these die as a result of the influenza infection.

Table 1 describes the data collection systems that were used to monitor influenza activity at the various levels of the influenza pyramid in Sweden during the 2014–2015 season. Each system is described in detail below the table.

Figure 1. The "influenza pyramid" showing possible outcomes of an influenza infection.

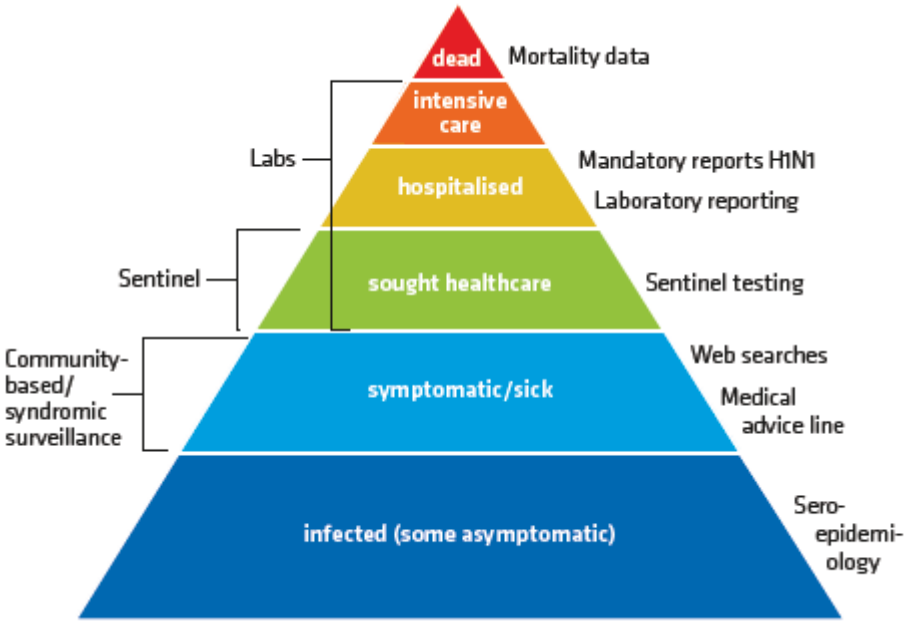


Table 1. Description of all systems used to monitor influenza activity during the 2014–2015 season. The data refer to the period between week 40, 2014, and week 20, 2015, if no other dates are given.

Reporting system/ method	Implementation	What does the system/ method show?	Results (2014–2015)
1. "Webbsök" (Web Search)	An automated system that uses search data from the national medical advice site 1177.se. The number of searches on influenza and influenza symptoms are entered into a statistical model that estimates the proportion of patients with influenza-like illness (ILI).	Estimates the proportion of patients with ILI.	Between week 27, 2014, and week 26, 2015, almost 140,000 queries related to influenza were entered, which was 1.3% of the total number of queries on the webpage.
2. Telephone Advice Line (1177 Vårdguiden)	Weekly aggregated data on the primary reason for contacting the medical advice line (phone number 1177) and the age group of the person concerned are manually reported to the Public Health Agency. Data are collected from 17 of Sweden's 21 county councils.	Primary reason for calling by age group (adults and children).	Approximately 310,000 calls regarding one of the following symptoms: breathing difficulties, fever, sore throat, or coughing. Fever in children accounted for 3.9% of all calls to 1177 during the year.
3. Voluntary laboratory reporting of laboratory-confirmed influenza cases and denominator data	Voluntary weekly reports from laboratories to the Public Health Agency on the number of samples analysed for influenza and the number of positive cases of influenza A (non-A(H1N1)pdm09) and influenza B.	Number of laboratory-confirmed cases of influenza types other than A(H1N1)pdm09 together with the patients' ages and gender distribution. Proportion of samples tested that are positive for an influenza virus.	42,668 samples analysed of which 10,389 (24.3%) tested positive: 663 (6.4%) for A(H1N1)pdm09, 6,008 (57.8%) for non-A(H1N1)pdm09 influenza A, and 3,718 (35.8%) for influenza B.
4a. Statutory laboratory reporting of cases of influenza A(H1N1)pdm09	Legal obligation for all laboratories to report influenza diagnoses along with full patient identity in the web-based reporting system, SmiNet, in accordance with the Communicable Diseases Act.	Number of laboratory-confirmed cases of influenza A(H1N1)pdm09 together with age, gender, and geographical distribution.	663 laboratory-confirmed cases of influenza A(H1N1)pdm09.
4b. Statutory clinical reporting of hospitalised cases of influenza A(H1N1)pdm09	Legal obligation for all hospitalised cases to be reported by the treating physician, in accordance with the Communicable Diseases Act.	Number of hospitalised cases of A(H1N1)pdm09, including risk group, vaccination status, and level of care [hospitalised, intensive care, ventilator, extracorporeal membrane oxygenation (ECMO)].	281 laboratory-confirmed cases of A(H1N1)pdm09 were reported to have been hospitalised. Of those, 31 were reported to be in either intensive care, on a ventilator, or receiving ECMO, and 18 of the 281 cases were also reported through the Swedish Intensive Care Registry (SIR).

Reporting system/ method	Implementation	What does the system/ method show?	Results (2014–2015)
5. Voluntary clinical reporting of laboratory-confirmed influenza cases (all types) in intensive care	Collaboration with the SIR. Treating physicians in intensive care units are asked to report clinical information about patients with laboratory-confirmed influenza.	Severity of infections with different influenza subtypes and impact on the intensive care units.	176 laboratory-confirmed cases of influenza were reported from the SIR. Of those, 18 were reported as A(H1N1)pdm09, 33 were A(H3N2), 70 were influenza A of unknown subtype, and 55 were influenza B.
6. Sentinel sampling	Samples from some patients who present to enrolled general practitioners with ILI, as well as some patients with acute respiratory illness (ARI), are analysed by the Public Health Agency for influenza.	The proportion of sentinel patients with ILI or ARI who have an influenza infection (see also virus characterisation, below).	1,399 samples were analysed of which 373 (26,7%) tested positive for influenza: - 8.6% A(H1N1)pdm09 - 37.3% B/Yamagata-like - 50.1% A(H3N2) - 0.5% B/Victoria-like *3.5% of the influenza A-positive samples could not be subtyped.*
7. Virus characterisation	Continual genotypic and phenotypic assays of laboratory and sentinel samples that tested positive for influenza.	Viruses' vaccine similarity and possible resistance to antiviral drugs and subtyping of influenza A if not performed regionally.	Genetic characterisation with respect to vaccine similarity: - 18/64 A(H3N2) viruses similar to vaccine strain - 36/36 A(H1N1)pdm09 viruses similar to vaccine strain - 34/34 B/Yamagata viruses in genetic clade less well-recognised by vaccine strain - 2/2 B/Victoria viruses in genetic clade of quadrivalent vaccine strain Analysis for mutations associated with resistance to neuraminidase inhibitors: - 141 viruses analysed - Only one resistant to oseltamivir: an A(H1N1)pdm09 virus Phenotypical analysis for resistance to oseltamivir and zanamivir: - 28 viruses analysed - Similar results as the genotypic analyses
8. Crude excess mortality	Weekly data on the aggregated number of deaths in Sweden, by age group, is sent from the Swedish Tax Agency to the Public Health Agency and analysed with statistical models.	All-cause mortality (i.e. not influenza-specific).	During the influenza season, 60,155 persons died in Sweden. Significant excess mortality was seen among persons above 65 years old between weeks 7 and 10, 2015, with the highest numbers reaching 4 standard deviations above the mean during weeks 8 and 9.
9. Vaccination coverage	Periodic collection of coverage data from county councils.	Vaccination coverage per age group.	49.7% among 65 years or older ~2% among risk groups under 65

Webbsök

Webbsök ("Web search") is an automated system established in 2008 that uses a statistical model and completely anonymous data from a medical advice website to estimate the development of sentinel ILI incidence. Data are received daily and collated weekly. The results are published on the web every Monday during the influenza season in the form of a graph, which is three days ahead of the publication of the weekly influenza bulletin.

Telephone advice line

In collaboration with the telephone advice service 1177 Vårdguiden, the Public Health Agency receives aggregated weekly data on calls. The age and reason for calling are registered for all callers. Only one reason for contact can be stated per call; if a caller describes multiple symptoms, the most important one is registered as the reason for contact. Anonymised data on reasons for calling that might indicate an upper respiratory infection are manually transferred to the Public Health Agency each week. The reported data include number of calls related to cough (adults, children), fever (adults, children), and sore throat (all ages combined). The proportion of calls related to fever among children has been found to be a good indicator of influenza activity in the community.

Voluntary reporting of laboratory-confirmed influenza cases

In 1993, the Swedish Institute for Communicable Disease Control (*Smittskyddsinstitutet*, SMI) started gathering information about laboratory-confirmed cases of influenza from the laboratories in Sweden. Since then, the laboratories have voluntarily reported the year of birth, sex, and influenza type (A or B) of each diagnosed case to SmiNet, either manually or through an automated transfer from their laboratory information system. Denominator data (the total number of samples analysed) is also reported via SmiNet or e-mail.

Statutory reporting of influenza A(H1N1)pdm09

When influenza A(H1N1)pdm09 was identified in 2009, statutory reporting in accordance with the Communicable Diseases Act was approved by the Swedish Parliament. Since then, the microbiological laboratories have been required to report all laboratory-confirmed cases. All influenza A-positive samples are analysed for influenza A(H1N1)pdm09.

An additional clinical report is mandatory for patients with laboratory-confirmed infections who have been admitted to the hospital. The reporting is done through the SmiNet system. In addition to patient identity, age, and diagnosis, it is possible to add information regarding date of disease onset, risk group, level of care (hospitalisation, intensive care, ventilator treatment, or ECMO), and vaccination status to the clinical report form. In addition, it is possible to add the date of death

(if applicable) to the case report in SmiNet. Unfortunately, this voluntary information is often left incomplete.

Voluntary reporting of influenza cases in intensive care

Through a collaboration with the Swedish Intensive Care Registry, the Public Health Agency receives data on influenza patients in intensive care daily from this registry. A special influenza module has been added to the registry through which the treating physician at an intensive care unit can report the age, sex, underlying medical conditions, complications, antiviral treatment, vaccination status, and influenza type for patients under treatment.

Sentinel sampling

Only a minority of cases of influenza-like illness (ILI) is caused by influenza. As such, other epidemics that lead to ILI are sometimes misconstrued as influenza epidemics. In order to estimate what proportion of the patients seeking care for ILI actually has influenza, sentinel physicians are encouraged to collect nasal samples from patients with ILI. The Public Health Agency carries out laboratory analyses for influenza free of charge for these samples. Representative positive samples are also used to characterize the circulating strains of influenza.

Virological analysis of sentinel samples contributes to national and international surveillance of circulating influenza viruses. Patient characteristics, including age, sex, risk factors, syndrome (ILI vs. acute respiratory illness (ARI)), and vaccination status, are analysed with respect to the types of influenza that are circulating.

Virus characterisation

Subtyping and lineage typing

All regional laboratories perform subtyping by real-time PCR for influenza A(H1N1)pdm09. Four of these laboratories also perform subtyping for A(H3N2), but none perform influenza B lineage typing. The Public Health Agency of Sweden performs subtyping and lineage typing by real-time PCR for a selection of samples sent in to the agency from the laboratories.

Selection of samples for further characterisation

Influenza-positive samples are collected from laboratories and from the sentinel surveillance program. Samples representing different geographical locations, collection time periods, and types/subtypes are selected for further characterisation. In addition, laboratories are asked to send influenza-positive samples from severely ill or deceased patients, patients with vaccine failure, and patients who do not respond to antiviral treatment. Because isolation of influenza virus on cell cultures in Sweden is only performed by the Public Health Agency of Sweden, and because phenotypic analyses such as the neuraminidase inhibition (NAI) and hemagglutinin

inhibition (HAI) assays need grown virus, Swedish laboratories are continuously asked to provide a representative selection of specimens that can be isolated on cell culture.

Characterisation methods

Characterisation of influenza viruses at the Public Health Agency of Sweden is mainly performed by sequence analysis. This season, the majority of the sequencing was full-genome sequencing performed with NGS (Next Generation Sequencing) on an Ion Torrent platform using direct material (i.e. not virus isolates). This method allows subtyping of all known influenza A subtypes.

Through NGS, the hemagglutinin (HA) gene was characterised with respect to vaccine similarity and changes in receptor affinity (lung receptors versus upper respiratory tract receptors). In addition, the HA target sequences for the subtype/lineage-specific real-time PCR systems used for detection of influenza in clinical samples were analysed for sequence mismatches compared to the real-time PCR primers and probes. The neuraminidase (NA) gene was analysed with respect to amino acid substitutions known to result in reduced or highly reduced inhibition to NA inhibitors according to guidelines from the WHO. Two aspects of the matrix protein (M) gene were analysed by sequencing: the M2 gene of influenza A was analysed for amino acid substitutions resulting in resistance to amantadine, and the M target sequences of both influenza A and B of the real-time PCR systems was analysed for sequence mismatches. The genes for non-structural protein 1 (NS1) and polymerase basic protein 2 (PB2) were analysed for mutations known to be associated with changes in virulence.

Some genetic characterisations were also performed by real-time PCR, including influenza B lineage typing and H275Y mutation analysis of influenza A(H1N1)pdm09 viruses. Phenotypic analysis of sensitivity to NA inhibitors is performed with the NAI assay, which needs viruses isolated on cell culture. This analysis generates IC_{50} values (half maximal inhibitory concentration) for oseltamivir (Tamiflu®) and zanamivir (Relenza®) from which sensitivity of the influenza virus to these inhibitors is calculated and interpreted according to criteria given by the WHO.

A representative selection of the isolated virus samples is sent to the WHO CC in London for antigenic characterization of HA by HAI assay and for phenotypic analysis of sensitivity to NA inhibitors by NAI assay.

Crude excess mortality

In order to identify any excess mortality, the aggregate number of deaths is transferred from the Swedish Tax Agency each week and analysed by the Public Health Agency in a generalised linear model of the Poisson family as part of the European monitoring of excess mortality for public health action (Euro-MOMO) collaboration. Analyses are made for the whole country, by age group, and regionally for the northern, eastern, and southern parts of Sweden.

Additional monitoring activities

Deaths 30 days after influenza infection

The Public Health Agency has access to data on individual deceased persons through the Swedish Tax Agency. A search in this registry is done intermittently to identify which influenza patients are deceased. This can only be done for cases where the personal identification number is known – that is, for influenza A(H1N1)pdm09 cases – and this complements the information added to the case reports in SmiNet.

Vaccination coverage

For the past twelve years, data on vaccination coverage among persons 65 years old and older have been gathered by Sweden's 21 county medical officers for their respective county councils.[2] Various methods for estimation have been used in different counties, including the use of vaccination registries, the number of vaccine doses given or distributed, sentinel reports on vaccination coverage, surveys among GPs, or patient record data. Although the methods vary between counties, the methods have been roughly the same within the counties for the last four years.The data from the 21 county councils have been collated yearly after the influenza season to monitor changes in vaccine acceptance and the progress toward the WHO and EU target of 75% vaccination coverage in this age group. The analysis provides a rough estimate of the proportion of those over 65 years old who were vaccinated against influenza each season. During the 2014–2015 season, an estimate of the vaccination coverage in medical risk groups under the age of 65 was also completed using data from 12 county councils.

Ad hoc reporting

The county medical officers report anything noteworthy regarding influenza that has come to their attention within their counties. Informal information regarding outbreaks from the health care sector and the public is also followed up.

International events

Foreign epidemiology and virology is monitored through the websites of the WHO and the European Centre for Disease Prevention and Control (ECDC) as well as other national and regional websites and media sources. International reporting on influenza-related research, outbreaks, and other events in the media is also monitored.

[2] Between 2003 and 2014, one of the county medical officers or their staff collated the vaccination coverage data. In 2014, this task was transferred to the Public Health Agency.

Reporting

National reporting

During the influenza season, the Public Health Agency condenses national and international data into a detailed weekly bulletin that is published on the agency's website.[3] A preliminary summary of the season is included in the week 21 bulletin.[4] The bulletin provides timely analysis of the current situation in Sweden and abroad and has a wide readership. In fact, the influenza bulletin webpage was the most visited page (excluding the entrance pages) of the agency's website during the season, with 148,758 viewings.

Where necessary, the county medical officers, microbiological laboratories, the National Board of Health and Welfare, and other concerned authorities are informed of exceptional events.

The media have access to updated influenza data through the bulletins on the Public Health Agency's website. During seasonal epidemics, the Public Health Agency is normally contacted by the national media and participates in TV and radio interviews and answers questions for online and print media.

International reporting

The Public Health Agency is the WHO National Influenza Centre for Sweden and is part of the EISN, the ECDC's network dedicated to the monitoring of influenza. As such, the Public Health Agency has an important commitment to report epidemiological influenza data weekly to the ECDC database TESSy, which then forwards the data to the WHO database FluNet.

A representative selection of the influenza-positive samples collected through the sentinel surveillance system and directly from regional laboratories is isolated and sent to the WHO CC in London for further characterisation, as mentioned above.

Characterisation data, including NAI results from the WHO CC, are reported to TESSy and to the Global Initiative on Sharing All Influenza Data (GISAID).

Following the end of the season, a detailed annual report (which you are reading) is sent to the WHO and the ECDC and is published on the Public Health Agency's webpage.

[3] http://www.folkhalsomyndigheten.se/amnesomraden/statistik-och-undersokningar/sjukdomsstatistik/influensa-veckorapporter/aktuell-influensarapport/

[4] http://www.folkhalsomyndigheten.se/documents/statistik-uppfoljning/smittsamma-sjukdomar/Veckorapporter-influensa/2014/_Influensarapport_v20-2014.pdf

Epidemiological data

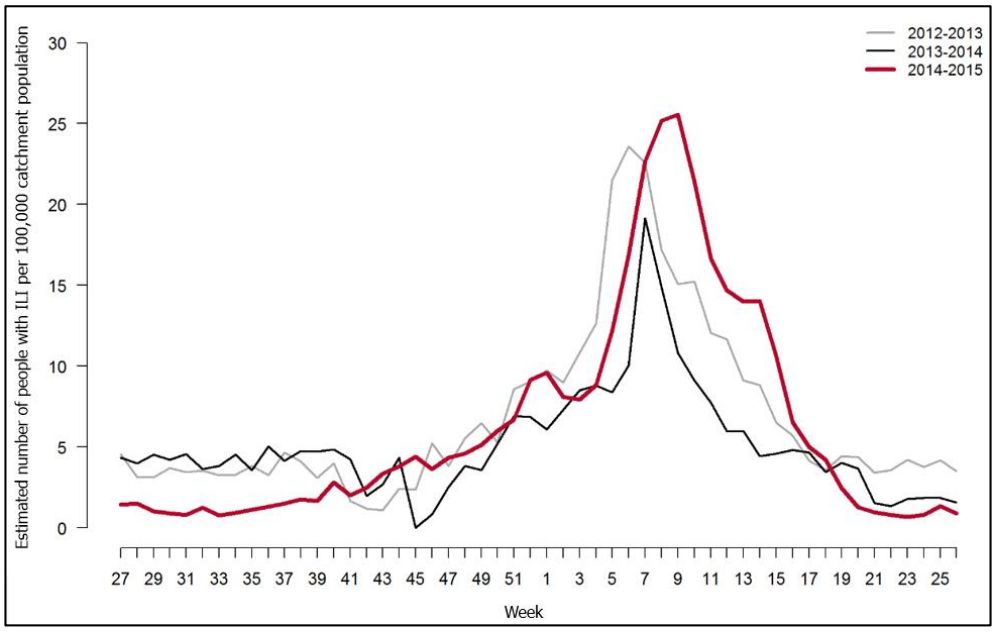
Webbsök

From week 27, 2014, to week 26, 2015, almost 140,000 queries related to *influenza* were submitted to the 1177.se search engine. This is 76,000 more searches than during the previous season, probably due to the addition of new counties to the web service.

According to Webbsök, the influenza season of 2014–2015 lasted for 19 weeks, from week 50, 2014, to week 16, 2015 (Figure 2). During four of these weeks (weeks 7–10), Webbsök showed a high level of influenza activity. During the previous season (2013–2014), influenza activity lasted for 15 weeks, never reached a high level[5], and was only moderately elevated for two weeks. The seasonal pattern corresponds largely to that seen in laboratory-based surveillance.

Webbsök again proved to be a reliable indicator of epidemic development (Figure 3). By providing data on Monday mornings, it was almost three working days ahead of the results from other systems, which were available on Wednesday afternoons at the earliest.

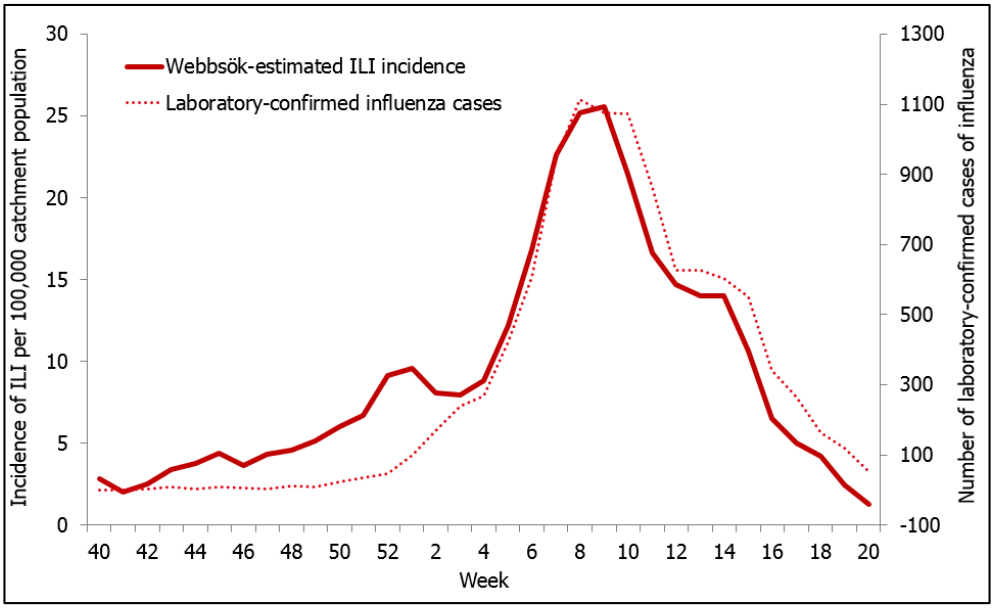
Figure 2. Webbsök's estimated proportion of the population with ILI per week, 2012–2015.



Webbsök's ILI estimate was above the epidemic threshold during weeks 48-16 during the 2012-2013 season, weeks 51-13 during the 2013-2014 season, and during weeks 50-16 during the 2014-2015 season.

[5] The Webbsök threshold for a high level is 22 per 100,000 population.

Figure 3. Webbsök's estimated proportion of persons with ILI and the number of laboratory-confirmed cases, 2014–2015. *The axes have been adjusted to highlight the matching trends reported through the two systems.*



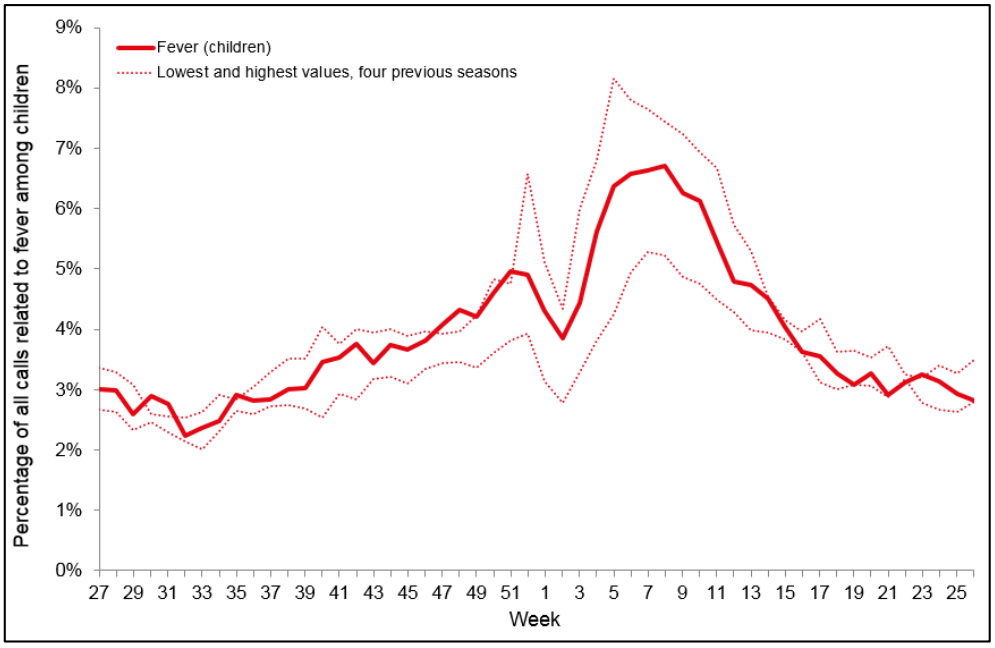
Telephone advice line

As described earlier, the Public Health Agency receives information each week from the medical telephone advice line 1177 Vårdguiden concerning the callers' main reasons for contact. As previously noted, fever among children has been found to be the best indicator of influenza activity in the community.

The number of calls regarding fever among children exceeded the epidemic threshold in week 47, 2014, and was 20% higher than during season 2013–2014, which reflects the intensity of the 2014–2015 season. An average of 4.6% of the calls throughout the season were regarding children with fever (Figure 4). The highest number of calls (4,344) and percentage (6.7%) was registered during week 8, 2015. The peak weeks corresponded with the peak of influenza A(H3N2), and these were followed by an extended period of elevated activity corresponding to the wave of influenza B seen in the laboratory-based surveillance data.

A noticeable peak in calls is seen around the Christmas holidays every year, followed by a drop. The reason for this pattern might be decreased access to face-to-face health care services during the holidays leading to an increase in telephone consultations.

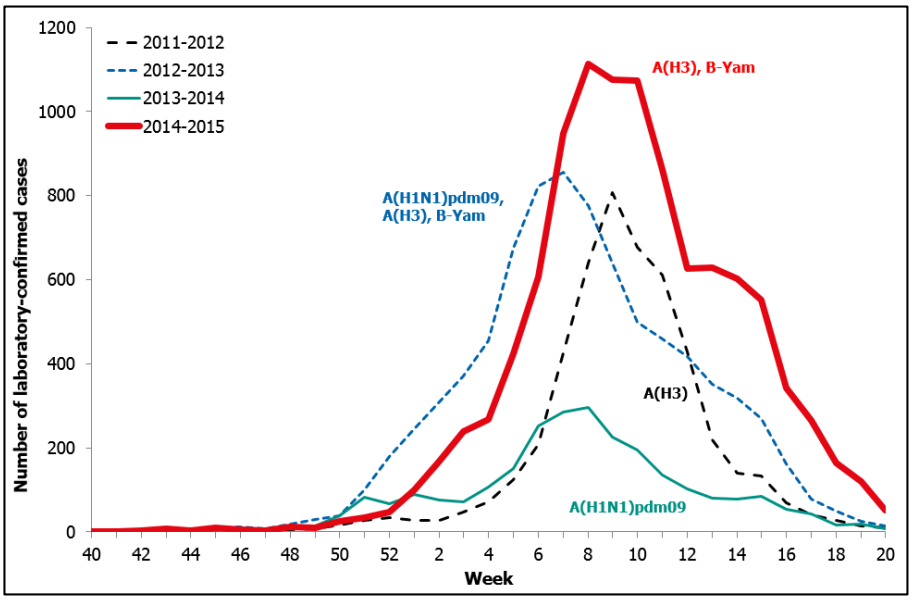
Figure 4. Number of telephone calls regarding fever in children received by the medical advice line 1177 Vårdguiden, 2014–2015.



Laboratory-based surveillance

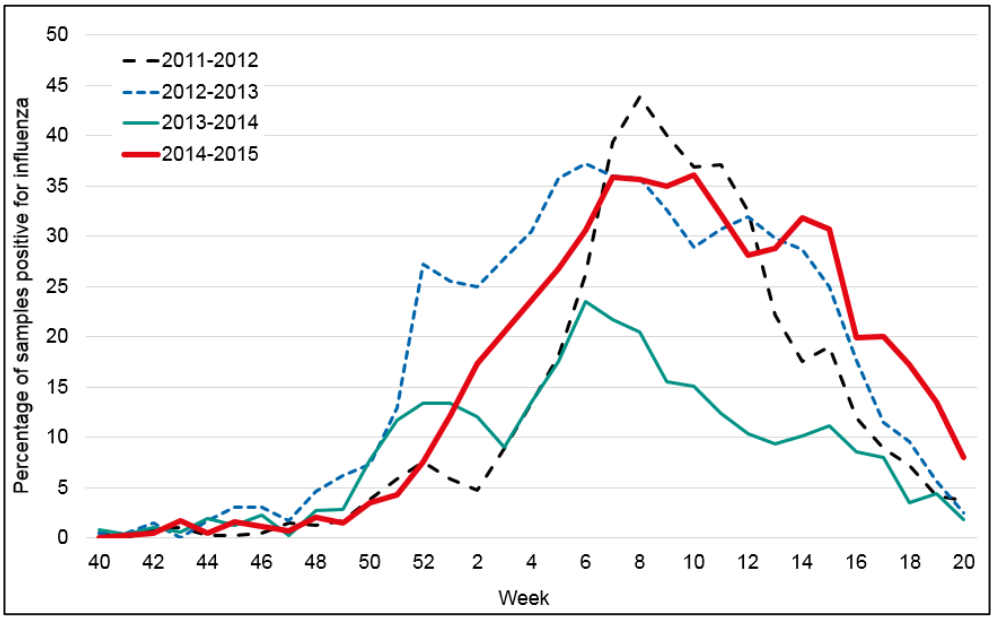
A total of 10,389 laboratory-confirmed cases of influenza were reported during the 2014–2015 season (Figure 5). The total number of laboratory-confirmed cases was higher compared to previous seasons (excluding the pandemic 2009), including the intense season of 2012–2013. The 2014–2015 season peaked during week 8 with 1,114 cases reported and continued through week 10 with nearly the same number of cases.

Figure 5. Total number of laboratory-confirmed cases of influenza (all types) per week and the dominating influenza type(s) per season from 2011 to 2015.



Swedish laboratories analysed 42,668 samples for influenza during the season, of which 10,389 (24%) tested positive for influenza A or B (Table 2). The total number of samples was higher than all previous post-pandemic seasons, including the intense season of 2012–2013. The peak percentage positive among analysed samples has been similar among recent intense seasons, indicating that the case definition for laboratory verification remains unchanged (Figure 6). The increased number of samples analysed indicates that more people, likely the elderly, sought care for influenza this season, probably due to the dominance of influenza A(H3N2). Overall, the data reveal that the influenza season was intense and prolonged.

Figure 6. Percentage of samples testing positive for influenza, per week, in the past four seasons.



Viral distribution

Because all influenza A-positive samples are analysed for influenza A(H1N1)pdm09, we have classified all those negative for A(H1N1)pdm09 as influenza A(H3N2) throughout this report (see Table 2). No other influenza A-subtypes were detected in Sweden during the season.

The 2014–2015 season was initially dominated by influenza A(H3N2) (69% of the season's positive samples), followed by influenza B (23%) towards the latter part of the season (Figure 7). A wave of influenza B reached a high level around week 7 and continued for seven additional weeks, with weekly case counts higher than previous high-activity influenza B-dominant seasons (Figure 8). As influenza A(H3N2) receded, influenza B continued at an elevated level nationwide for several weeks.

Figure 7. Number of laboratory-confirmed cases by influenza type and week, 2014–2015.

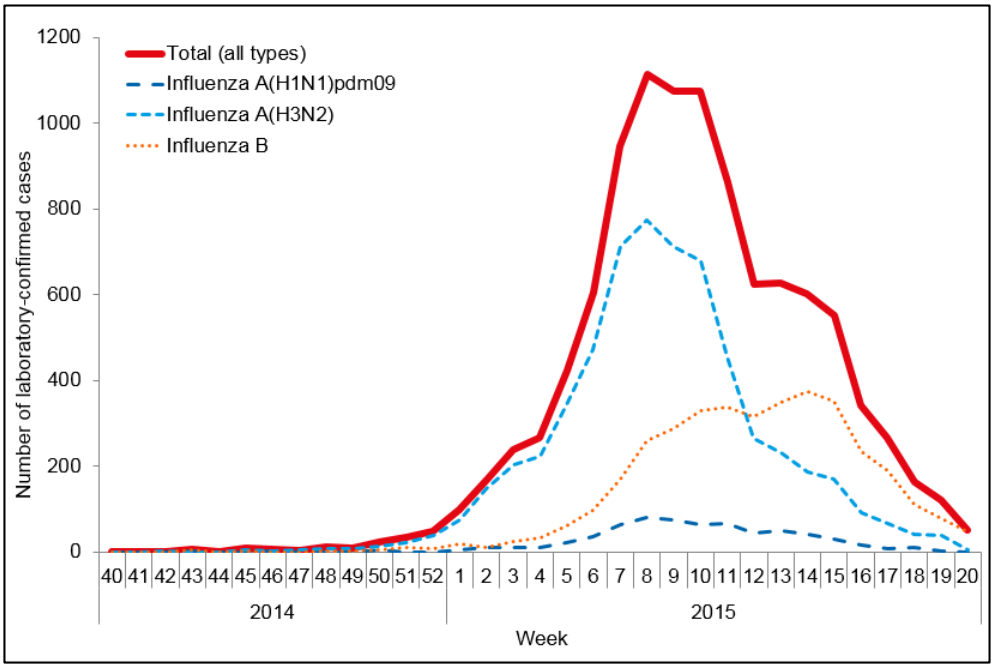
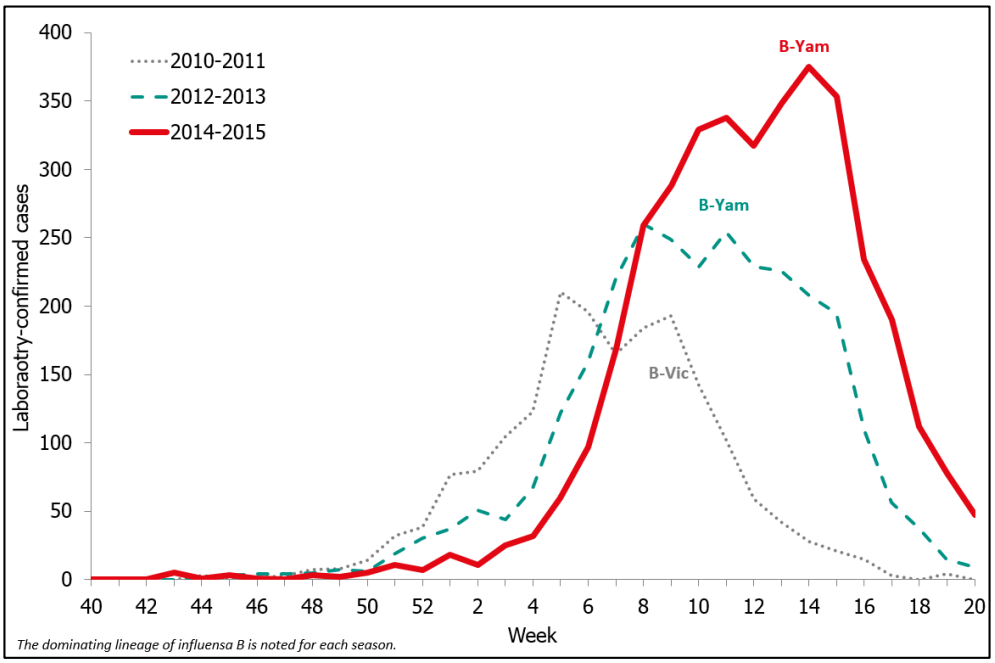


Figure 8. Number of laboratory-confirmed cases of influenza B per week during recent B-dominant seasons.



Note: During the 2010–2011 season, influenza B/Victoria and A(H1N1)pdm09 co-dominated with 50% and 31% of the positive cases, respectively. In the 2012–2013 season, dominance was split three ways by influenza B/Yamagata, A(H1N1)pdm09, and A(H3N2), with approximately one third of the positive cases each. In the 2014–2015 season, influenza A(H3N2) accounted for 69% of cases and B/Yamagata accounted for 23%.

Of the positive samples during this season, 6,671 were influenza A and 3,718 were influenza B (Table 2). Of those positive for influenza A, nearly half (3,100) were subtyped at laboratories in Gothenburg, Malmö, Stockholm, or Umeå. A majority (2,052) of these were found to be influenza A(H3N2), and just a fifth (663) were influenza A(H1N1)pdm09. The remaining 3,956 samples were positive for

influenza A but negative for influenza A(H1N1)pdm09. Because of the regional subtyping mentioned above and subtyping of sentinel samples at the Public Health Agency, all influenza A-positive samples that were negative for A(H1N1)pdm09 were classified as influenza A(H3N2), although they are separated in Table 2.

The Public Health Agency further determined the lineage of 65 influenza B-positive samples.

Table 2. Laboratory results of patients reported through the statutory and voluntary laboratory reporting systems combined during the last three seasons.

	2012–2013	2013–2014	2014–2015
Analysed samples	**31,750**	**22,330**	**42,668**
Proportion positive samples	25.8%	11.6%	24.30%
Total positive for influenza A	**5,340**	**2,372**	**6,671**
A(H1N1)pdm09 *	2,435	1,737	663
A(H3N2)	548	169	2,052
A, not subtyped but A(H1N1)pdm09 negative **	2,357	466	3,956
Total positive for influenza B	**2,857**	**213**	**3,718**
B/Victoria lineage	8	2	2
B/Yamagata lineage	148	24	63
B, not typed to any lineage	2,701	187	3,653

* Not typed as N1, but classified as A(H1N1)pdm09 based on H1 typing.
** Referred to in this report as influenza A(H3N2).

Age and sex distribution

The season was dominated by influenza A(H3N2), and this is reflected in the age distribution among the laboratory-confirmed cases (Table 3 and Figures 9A-C). The highest incidence of influenza A(H3N2) was seen among adults 65 years or older, which accounted for 62% of the cases. A large proportion influenza B (77%) was seen among individuals 40 years and older (34% 40–64 years, 43% 65 years or older). This is comparable to the previous intense season of 2012–2013.

Influenza A(H1N1)pdm09 was mostly seen in the youngest and oldest age group. The median age of the cases of the respective influenza types is presented in Table 4. The sex distribution was equal for influenza A(H1N1)pdm09, influenza A(H3N2), and influenza B cases.

Table 3. Number (No.) and incidence (Inc.) per 100,000 population and age group of laboratory-confirmed cases of influenza A(H1N1)pdm09, influenza A(H3N2)*, and seasonal influenza B in Sweden, 2014–2015.

	Influenza A(H1N1)pdm09		Influenza A(H3N2)*		Seasonal influenza B		Total influenza	
Age group	**No.**	**Inc.**	**No.**	**Inc.**	**No.**	**Inc.**	**Total no.**	**Total inc.**
0–4 years	54	9.2	192	32.9	96	16.4	342	58.5
5–14 years	14	1.3	172	15.7	160	14.6	346	31.5
15–39 years	158	5.1	770	25.1	594	19.4	1,522	49.6
40–64 years	242	7.8	1,128	36.6	1,244	40.3	2,614	84.8
>65 years	195	10.2	3,667	191.7	1,594	83.3	5,456	285.2
Total	**663**	**6.8**	**5,929**	**60.8**	**3,688**	**37.8**	**10,280**	**105.5**

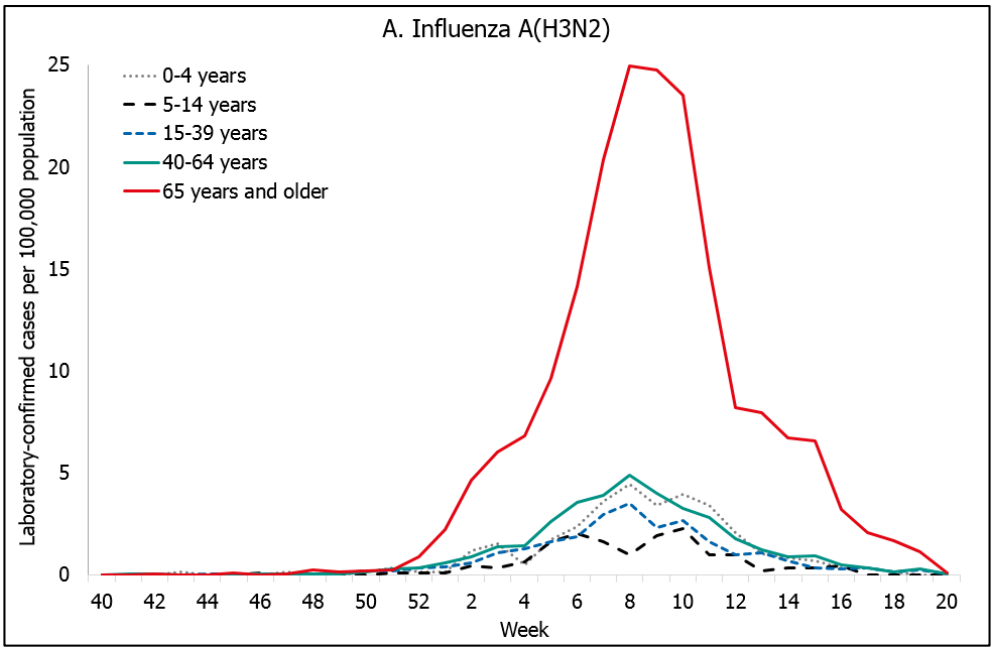
* All influenza A-positive samples negative for A(H1N1)pdm09 were classified as influenza A(H3N2).

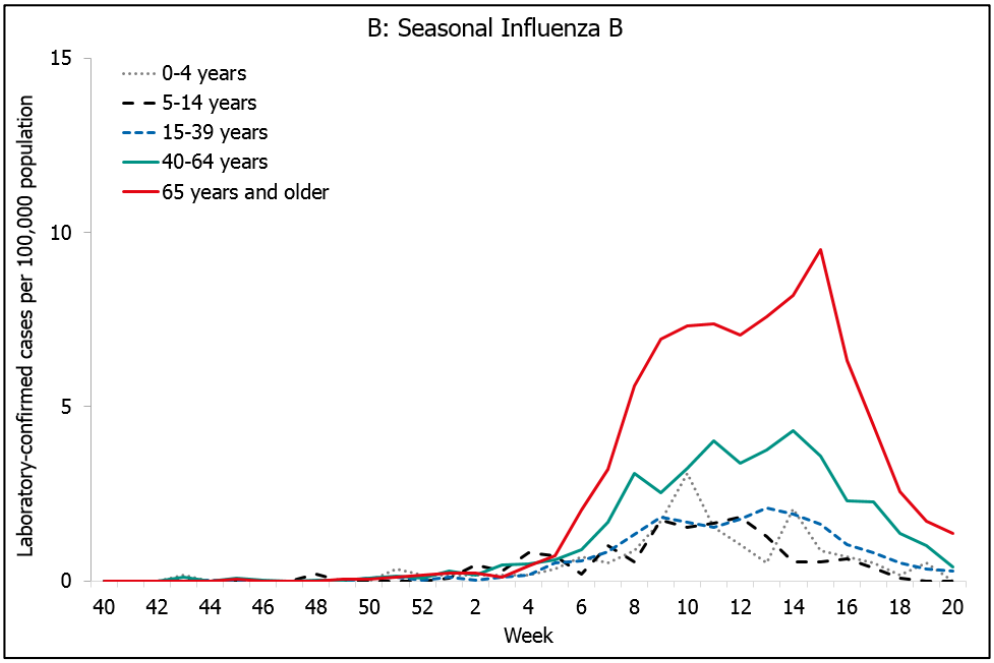
Table 4. Median age (years) of patients reported through the statutory and voluntary laboratory reporting systems combined during the last three seasons.

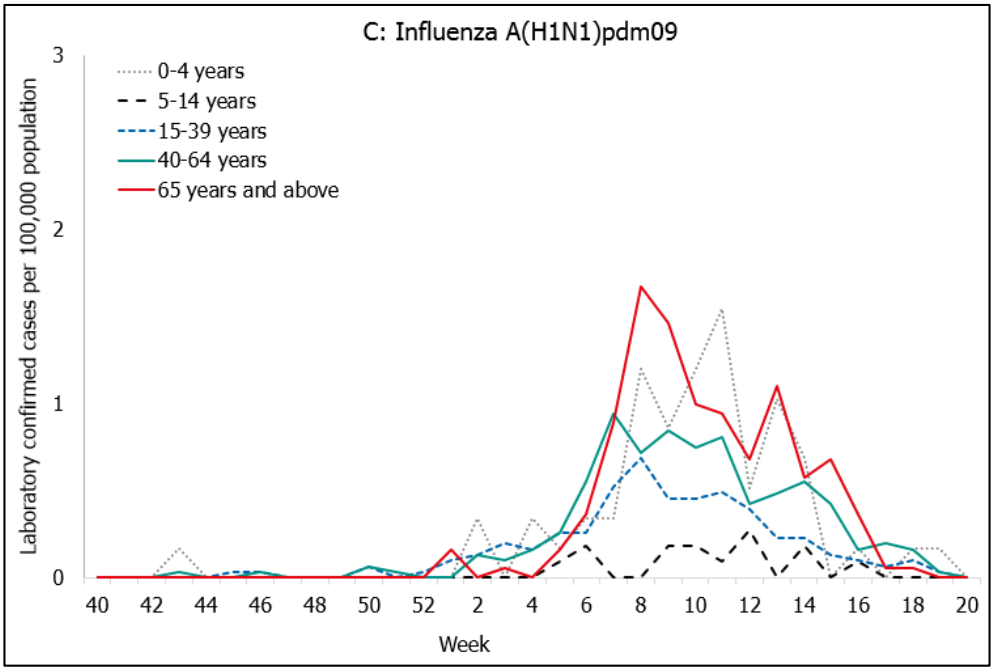
	2012–2013	2013–2014	2014–2015
Influenza A(H1N1)pdm09	39	45	50
Influenza A(H3N2)*	64	58	72
Seasonal influenza B**	46	49	60

* All influenza A-positive samples negative for A(H1N1)pdm09 were classified as influenza A(H3N2).
** The median age for influenza B-positive samples was calculated for all types combined because only a small portion of the samples were analysed for lineage.

Figure 9. Weekly incidence of the respective influenza types per age group in Sweden for the 2014–2015 season. *Note: the scale in the figures varies.*





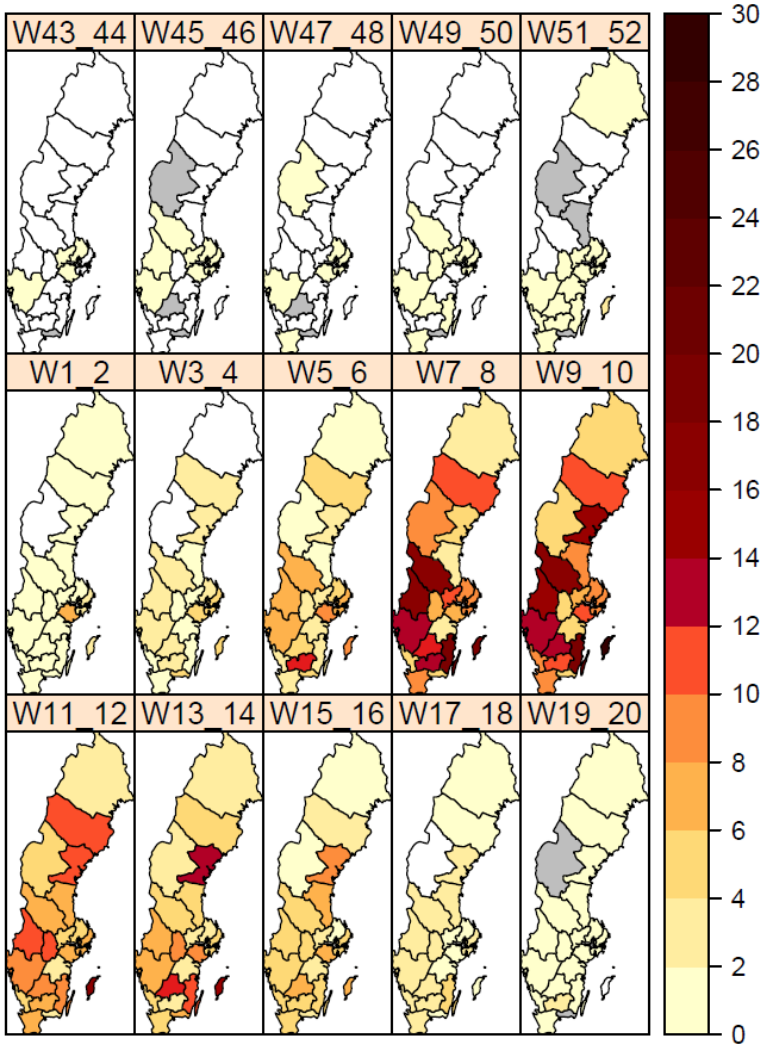


Geographic distribution

The influenza epidemic peaked in the whole country during weeks 8–10 of 2015, as shown in Figures 5 and 7. The cumulative incidence of the season was the highest in the regions of Gotland, Kalmar, Dalarna, and Värmland, where the incidence was 140 cases or higher per 100,000 population.

Overall, the southern and middle parts of Sweden had a higher incidence compared to the northern part of the country (Figure 10). However, it is not possible to draw any conclusions regarding differences in intensity of the epidemic based on differences in incidence of laboratory-confirmed cases due to the large variations in sampling frequency.

Figure 10. Bi-weekly incidence of laboratory-confirmed influenza per 100,000 population and county from week 43, 2013, to week 20, 2014. *(The colour scale indicates the incidence; white indicates an incidence of 0 and grey indicates that no report was received from the county laboratory.)*



Influenza cases in intensive care

We received reports of patients in intensive care with laboratory-confirmed influenza infections through continued collaboration with the Swedish Intensive Care Registry (SIR). During the season, 176 cases were reported, once cases treated in and reported from multiple intensive care units (duplicates) were combined.

The majority of the cases, 121 cases (69%), were infected with influenza A, and 55 cases (31%) were infected with influenza B (Table 6). The median age of patients for all influenza types was 65 years. The majority of the cases, 89 cases (51%), were 65 years or older, and 64 cases (36%) were between 40 and 60 years old. The gender distribution was equal.

Of the patients in intensive care, 115 cases (65%) belonged to a medical risk group. Chronic heart-lung disease (n = 70) and immunosuppression (n = 35) were the most common risk factors, just as in previous seasons. None of the cases reported through the SIR were pregnant.

A further 20 cases did not belong to a medical risk group but were 65 years or older. As such, 135 patients were recommended for seasonal influenza vaccination. Of these, vaccination status was known for 56 patients (42%), of whom approximately one third were vaccinated.

Antiviral treatment (oseltamivir or zanamivir) was given to 122 patients. One patient received ECMO treatment. Thirty-nine patients died within 30 days of hospitalization. Thirty-six of those belonged to a medical risk group or were 65 years or older and at greater risk for severe influenza.

Table 6. Age distribution of laboratory-confirmed influenza patients in intensive care by influenza type.

Reported influenza type *	Number of patients	Median age in years (min, max)
A(H1N1)pdm09	18	62.5 (41, 83)
A(H3N2)	33	70 (3, 88)
A, no subtype stated	70	70 (4, 89)
B	55	54 (0, 84)
Total	**176**	**65 (0, 89)**

* The influenza type was only validated for A(H1N1)pdm09 cases, where crosschecking with SmiNet was possible through the patient's personal identification number.

Clinical features of influenza A(H1N1)pdm09 cases

The following section is based on information collected through the statutory notification of hospitalised influenza A(H1N1)pdm09 cases.

During the 2014–2015 season, there were only 663 reported cases of influenza A(H1N1)pdm09. Other strains dominated the season. Hospitalization was reported for 250 (42.4%) of the cases, of which 31 individuals were placed in intensive care (including those reported as treated with a ventilator or ECMO) (Table 5).

Table 5. Number of notified cases of influenza A(H1N1)pdm09 by level of care.

Level of care	Number	Proportion in percent
Not hospitalised *	382	57.6
Hospitalised	281	42.4
- Hospitalisation, other than intensive care	250	37.7
- Intensive care	31	4.6
o Intensive care	17	2.4
o Ventilator treatment	11	1.1
o Extracorporeal membrane oxygenation (ECMO)	3	0.5
Total	**663**	**100**

* This includes all patients where the level of care has not been stated. That is, where a clinical notification has not been sent. Even though clinical notifications are mandatory for all hospitalized patients with influenza A(H1N1)pdm09, it is possible that some notifications are missing.

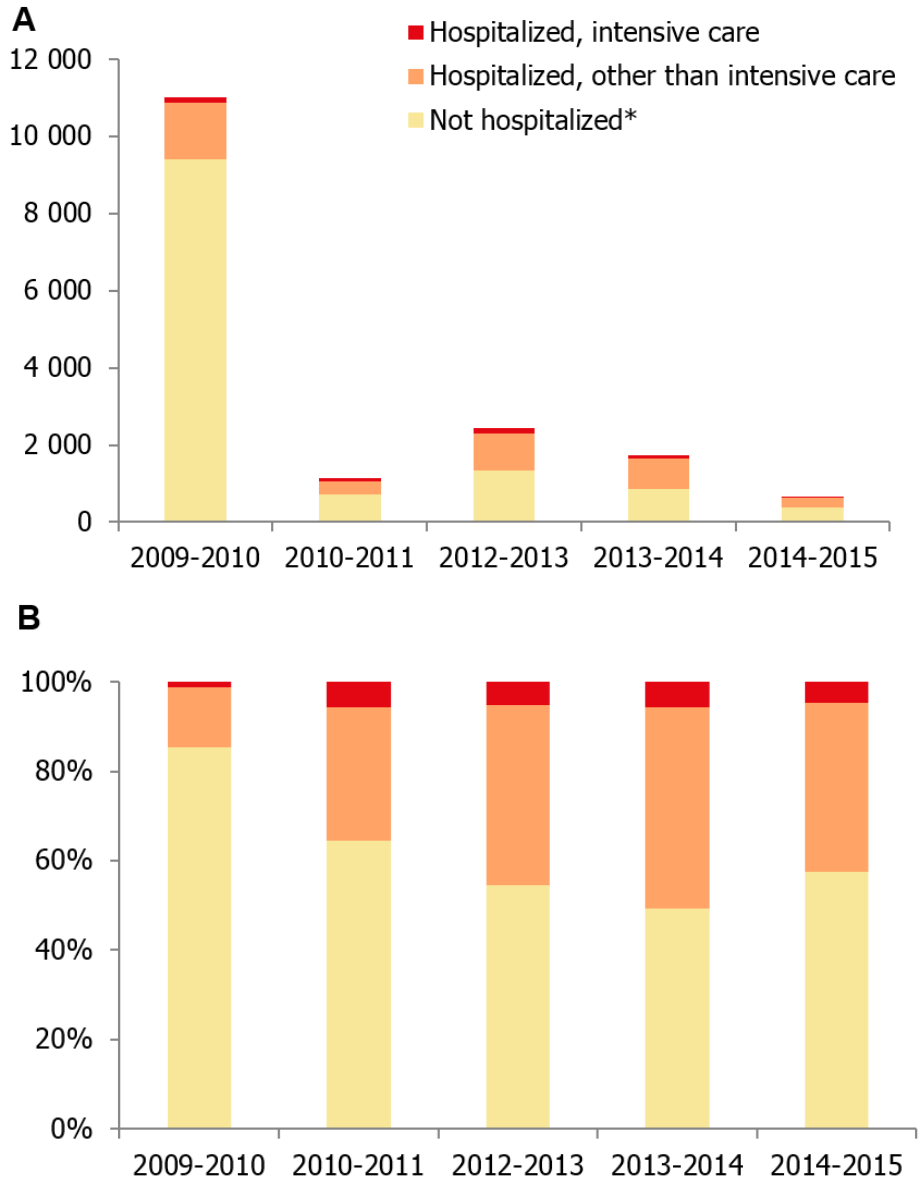
The proportion of the patients requiring hospitalization was in the range of previous post-pandemic seasons, which has ranged from 29% to 51% (Figure 11).

Medical risk group status was reported for 27 (7%) of the cases that were not hospitalised and 133 (47%) of the cases that were hospitalized, but the majority of cases were missing data on risk group status. Of the 31 cases who were placed in intensive care (4.7% of all cases), 23 (74%) were reported to belong to a medical risk group. The most common risk factors were chronic heart-lung disease and immunosuppression, which has been seen in previous seasons. Two of the hospitalized cases were pregnant women who did not have any other underlying risk factors for severe influenza.

The median age (42 years) of the patients who did not need hospitalization was lower compared to those who needed hospitalization (60 years). The patients placed in intensive care had a median age of 66 years. The median age for all categories of care was higher this season compared to the previous season. The gender distribution of cases was equal.

Vaccination status was missing for the majority of the influenza A(H1N1)pdm09 cases. Of the 250 hospitalized cases, 164 (66%) were recommended seasonal vaccination either due to belonging to a medical risk group or due to age (65 years or older). Vaccination status was known for 89 of them, and 31 (35%) of these were vaccinated. Only one of the patients in intensive care had been vaccinated, while six had not been vaccinated. For the remaining 24 patients in intensive care, vaccination status was unknown.

Figure 11. Notified number (Panel A) and proportion (Panel B) of cases of influenza A(H1N1)pdm09 by level of care and season.

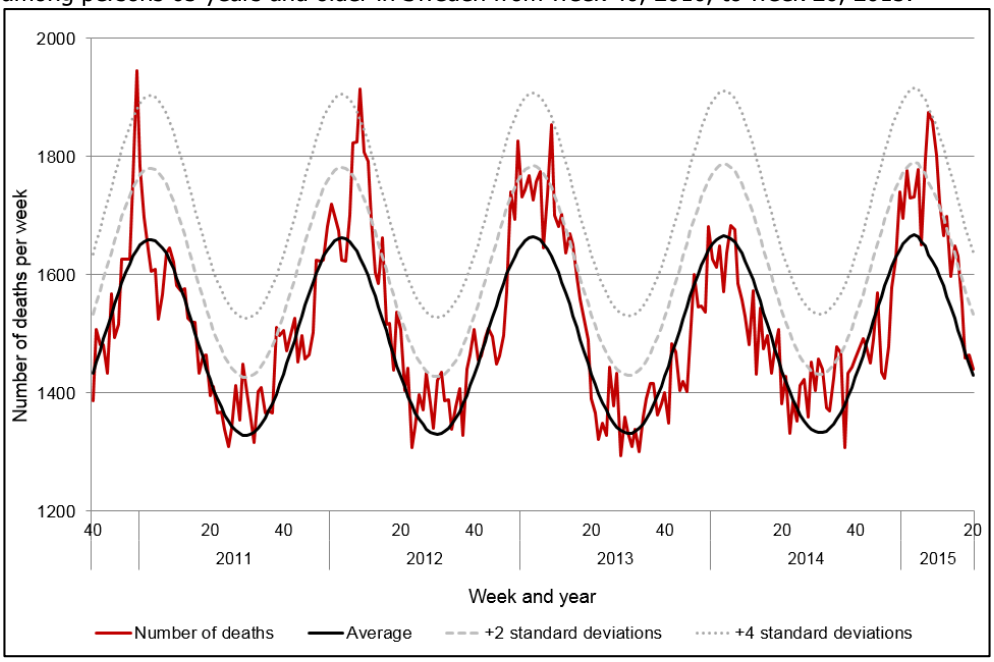


The number of cases in intensive care in 2009–2010 is based on data from both SmiNet and SIR.
The 2011–2012 season was dominated by influenza A(H3N2) and is therefore excluded from the comparison.

Crude excess mortality

During the 2014–2015 season, there was significant excess mortality seen among persons 65 years and older (Figure 12), with the number of deaths per week reaching nearly 4 standard deviations above the mean expected number. This excess mortality peaked during weeks 8 and 9, which coincides with the peak of influenza A(H3N2) activity in the country. However, this model cannot attribute the excess mortality seen specifically to influenza.

Figure 12. Number of deaths per week and average expected number of deaths per week among persons 65 years and older in Sweden from week 40, 2010, to week 20, 2015.



Deaths 30 days after A(H1N1)pdm09 diagnosis

It is not mandatory to report the death of a patient after clinical notification. This season, no cases were reported as deceased within 30 days of being diagnosed with laboratory-confirmed influenza A(H1N1)pdm09 through SmiNet. However, 25 patients were identified as deceased within 30 days of laboratory-confirmation through crosschecking with data from the Swedish Tax Agency's database of deceased persons. It is important to note that we cannot tell whether the cause of death in these cases was the previous influenza infection or something else entirely.

The median age of these 25 patients was 77 years (min: 46 years, max: 90 years). Fifteen (60%) were male. Of the 18 deceased with known risk group status, 15 (83%) belonged to a medical risk group. Four (16%) had been in intensive care and 13 (52%) had been hospitalised in other wards, but 8 (32%) were not reported as having been hospitalised. Although 21 of the 25 deceased belonged to a target group for vaccination, only two were reported as having been vaccinated with the 2014–2015 seasonal influenza vaccine. (One was known to be unvaccinated, and vaccination status was unknown for the remaining patients).

Virological data

Sentinel sampling

The following sections are based on the epidemiological and virological analysis of sentinel samples.

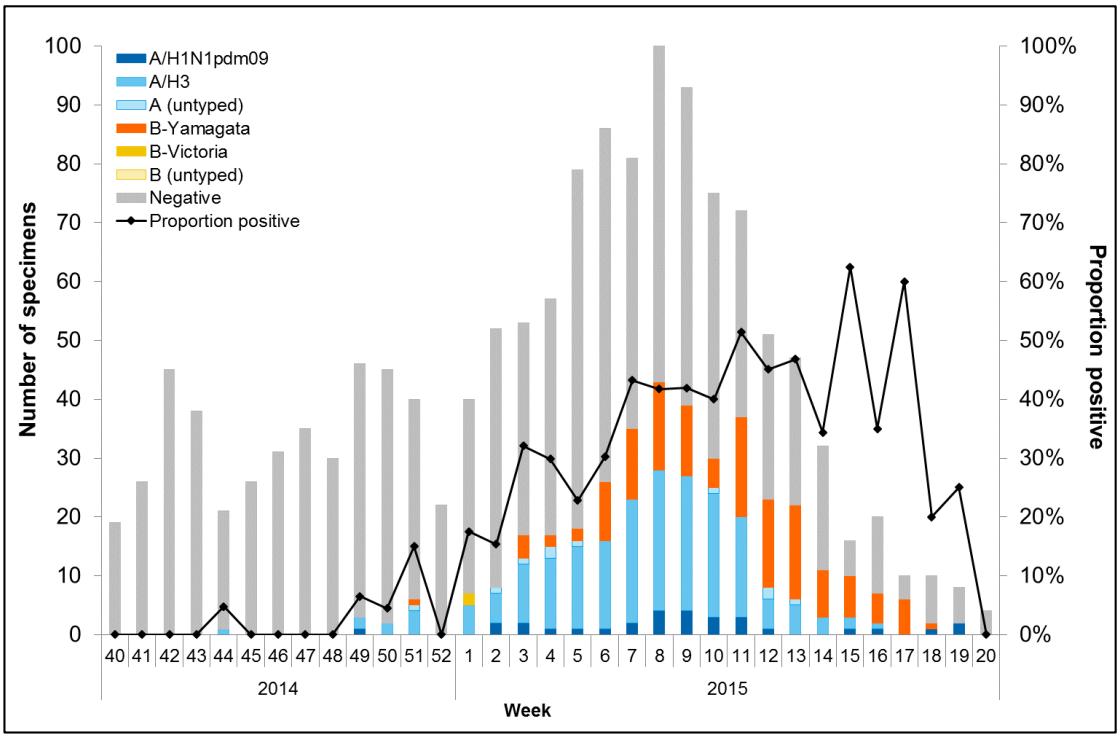
During the 2014–2015 season, 1,399 sentinel samples were submitted from 84 GPs. In total, 373 samples (26.7%) tested positive for influenza, which was higher than the 16.9% determined during the preceding season.

In the first part of the season, influenza A(H3N2) dominated with high intensity during weeks 3–11. Influenza B started later and had its peak during weeks 6–13 (Figure 13).

Of the positive samples, 232 (62.2%) were positive for influenza A and 141 (37.8%) were positive for influenza B. Of the influenza A positives, 187 (80.1%) were influenza A(H3) and 32 (13.8%) were influenza A(H1N1)pdm09. Thirteen influenza A samples could not be subtyped due to low virus concentration.

In total, 139 (98.6%) of the influenza B-positive samples belonged to the influenza B/Yamagata/16/88 lineage and 2 (1.4%) belonged to the influenza B/Victoria/2/87 lineage.

Figure 13. Number of sentinel samples submitted each week and the number and percentage of the positive samples by subtype/lineage, 2014–2015.



Clinical features

Of the patients sampled through the sentinel system, the vast majority had ILI (Table 7), and only a few had ARI. In total, 58.3% of the samples came from women. The median age for influenza A cases was similar to the previous two seasons.

Table 7. Summary of laboratory results, median age, and proportion of patients with ILI from the sentinel sampling system for the last three seasons.

	Season 2012–2013			Season 2013–2014			Season 2014–2015		
	Analyses	**Median age (years)**	**ILI**	**Analyses**	**Median age (years)**	**ILI**	**Analyses**	**Median age (years)**	**ILI**
Analysed	**2,048**			**1,302**			**1,399**		
Negative	1,448	40	82%	1,082	41	84%	1,026	42	75%
Proportion positive	29.3%			16.9%			26,.7%		
Positive for influenza A	**398**			**193**			**232**		
A(H1N1)pdm09	215	34	89%	154	37	94%	32	37.5	84%
A(H3N2)	160	35	89%	31	35	100%	187	40	88%
A, not subtyped	23	38	86%	8	49.5	100%	13	40	100%
Positive for influenza B	**202**			**28**			**141**		
B/Victoria	14	10.5	88%	3	15	100%	2	31	50%
B/Yamagata	183	36	88%	23	51	100%	139	45	89.9%
B, not typed to any lineage	5	35.5	84%	2	65	86%	0	0	0%

Influenza infection among vaccinated patients

Vaccination status was reported for 1,385 of the 1,399 patients sampled during the season. Of these, 136 were vaccinated (9.8%). A total of 32 influenza infections among vaccinated patients were detected: 25 in patients with influenza A(H3N2) (median age 74 years) and 7 among influenza B/Yamagata-positive patients (median age 45 years). Thirteen of the infections occurred in immunocompromised patients.

Comparison of laboratory and sentinel surveillance data

A comparison of the proportion of positive samples detected through sentinel sampling and those reported through the statutory and voluntary laboratory reporting systems combined showed that a lower proportion of samples were positive for A(H3N2) within the sentinel system compared to the laboratory reporting system (Table 8).

Sentinel patients were also younger (Tables 4 and 7). This probably indicates that elderly patients infected with A(H3N2) develop more severe symptoms and seek hospital care, while younger patients with A(H3N2) do not become severely ill to the same extent and instead visit primary care.

Table 8. Proportion of samples positive for different influenza types within the sentinel sampling system (*Sentinel*) and statutory and voluntary laboratory reporting systems (*Lab.*).

	2012–2013		2013–2014		2014–2015	
Influenza type	**Sentinel**	**Lab.**	**Sentinel**	**Lab.**	**Sentinel**	**Lab.**
A(H1N1)pdm09	37.6%	29.7%	73.1%	67.2%	9.4%	6.4%
A(H3N2)	28.0%	35.4%	14.4%	24.6%	52.3%	57.8%
B/Victoria lineage	2.4%	1.9%	1.3%	0.6%	0.5%	1.1%
B/Yamagata lineage	32.0%	34.1%	11.2%	7.6%	37.8%	34.7%

Characterisation of viruses

In total, 2,052 of the influenza A-positive, A(H1N1)pdm09-negative samples were subtyped to influenza A(H3N2). Lineage was determined for influenza B-positive samples: 63 were influenza B/Yamagata, and 2 were influenza B/Victoria (Table 2). The number of sequenced gene segments for each subtype or lineage is shown in Table 9.

Table 9. Number of sequenced gene segments for each subtype/lineage for the 2014–2015 season.

Subtype/Lineage	**Gene Segment**	**Number of sequenced viruses**
A(H1N1pdm09)	H	36
	N	39
	M	43
	NS	40
	PB2	33
	PB1	29
	NP	37
	PA	31
A(H3N2)	H	64
	N	66
	M	70
	NS	66
	PB2	60
	PB1	48
	NP	68
	PA	64
B/Yamagata	H	34
	N	28
	M	34
	Mpp	30
	NS	31
	PB2	30
	PB1	29
	NP	30
	PA	
B/Victoria	H	2
	N	8*
	M	2
	Mpp	1
	NS	1
	PB2	1
	PB1	1
	NP	1
	PA	

HA - Hemagglutinin. NA - Neuraminidase. M - Matrix protein. NS - Non-structural protein. PB2 - Polymerase basic protein 2 protein. PB1-polymerase basic protein 1. NP - Nucleoprotein. PA - Polymerase acidic protein. Mpp - Matrix gene target sequence for real-time PCR

* Including six Yamagata HA/Victoria NA reassortants

Characterisation of influenza A(H1N1)pdm09

All of the 36 A(H1N1)pdm09 viruses for which the HA gene was sequenced belonged to genetic subgroup 6B, which is characterised by K163Q, K283E, and A256T substitutions relative to A/California/07/2009 (see phylogenetic tree in Appendix 1). A clear dominance of group 6B viruses was also seen among the viruses circulating in the rest of Europe during season 2014-2015 season.[6] Viruses in this genetic subgroup have been shown to be antigenically similar to the vaccine virus A/California/07/2009.[7] Thirteen of the Swedish strains sent to the WHO CC in London for antigenic analyses have been included in the WHO's overall evaluation of antigenicity of the circulating A(H1N1)pdm09 viruses.

Of the 39 viruses for which the NA gene was sequenced, one carried the H275Y substitution, which confers resistance to oseltamivir (Tamiflu®) but not to zanamivir (Relenza®). The sample (tracheal fluid) contained a mixture of resistant (28%) and sensitive viruses and originated from an immunocompromised patient. In the same sample, a minor proportion (10%) of viruses having the D199G substitution was also detected. This substitution causes reduced inhibition to oseltamivir in vitro as measured by phenotypic assays, but its clinical relevance is unknown. The H275Y substitution was not detected in viruses from a nasopharyngeal sample from the same patient, but in this sample the proportion of viruses having the D199G substitution was higher (60%) compared to the tracheal sample. None of the other samples analysed, including one from an oseltamivir-treated patient, contained any of the mutations known to cause reduced or highly reduced inhibition in phenotypic assays. In addition, 17 samples were analysed exclusively for the H275Y substitution and none of them were 275H. The twelve viruses analysed phenotypically with NAI assays for sensitivity to oseltamivir and zanamivir were all sensitive to both inhibitors. The two samples described above containing H275Y+D199G and D199G could not be analysed phenotypically because no virus isolates could be obtained. In Europe, only 2 of the 556 analysed samples from season 2014–2015 were resistant to oseltamivir, and all were sensitive to zanamivir.[8] Like the previous season, all analysed influenza A(H1N1)pdm09 viruses carried the S31N amantadine-resistance substitution in M2.

No amino acid substitutions associated with increased virulence were detected in the NS1 or PB2 genes that were analysed, which included the NS1 gene of one ECMO-treated patient. It was not possible to sequence the PB2 gene in this latter case due to low viral load in the sample. In addition, none of the HA genes analysed (including the virus from the ECMO-treated patient described above)

[6] EDCD-WHO, Flu News Europe week 20/2015

[7] ECDC Influenza virus characterisation reports November-July 2015

[8] ECDC-WHO, Flu News Europe week 20/2015

contained any mutations at position 222, which can harbour mutations associated with an increased affinity for receptors in the lower respiratory tract.

Characterisation of influenza A(H3N2)

The distribution of the A(H3N2) viruses into genetic groups based on HA is shown in Table 10 and the phylogenetic tree in Appendix 2. A similar distribution was seen among the European viruses that have been genetically characterised this season.[9] Viruses in subset 3C.3a, which is the same subset as the recommended vaccine strain for season 2015–2016, and subset 3C.2a have been shown to be antigenically distinct and distinguishable. Cross-reactivity of antisera raised against these two groups has been seen. The 3C.3 viruses, including 3C.3b, on the other hand, have been shown to be antigenically similar to A/Texas/50/2012, the vaccine strain for the 2014–2015 season.[10] Twenty-four of the Swedish strains, representing subsets 3C.3, 3C.3b, 3C.2a, and 3C.3a sent to the WHO CC in London, have been included in the WHO's overall evaluation of antigenicity of the circulating H3N2 strains.

Of the 64 viruses for which the HA gene was sequenced, 18 originated from vaccinated individuals. Of these, 14 belonged to genetic subset 3C.2a, a subset that is antigenically different from the vaccine strain for the 2014–2015 season, while three belonged to subset 3C.b and one to 3C.3, both of which are antigenically similar to the vaccine strain. In addition to the similarity between the virus and the vaccine strain, other factors such as age and immune status also influence the ability of the vaccine to prevent disease. In this case, the majority (13 of the 18 cases) of the vaccine failures were among elderly patients (> 65 years) or patients with known immune deficiency.

None of the A(H3N2) viruses for which the NA gene was sequenced contained any of the substitutions known to result in reduced or highly reduced inhibition by oseltamivir and/or zanamivir. Twelve viruses were also analysed phenotypically by NAI assay, and all were sensitive to oseltamivir and zanamivir. Three of these and seven additional viruses (including five from the interseason, weeks 21–39 of 2014) were tested by the WHO CC in London and all were sensitive to both inhibitors.
In Europe, 1,535 A(H3N2) viruses were tested for susceptibility to NA inhibitors. Four showed reduced susceptibility to oseltamivir due to the E119V substitution in NA, and one showed reduced susceptibility to both oseltamivir and zanamivir due to the R292K substitution in NA.[11] Like the previous season, all analysed influenza A(H3N2) viruses carried the S31N amantadine-resistance substitution in M2.

No mutations associated with increased virulence were found in the 59 viruses for which both the NS and PB2 genes were analysed (including two cases of severe

[9] ECDC Influenza virus characterisation reports November-July 2015

[10] ECDC Influenza virus characterisation reports November-July 2015

[11] ECDC-WHO, Flu News Europe week 20/2015

disease), in the viruses for which only NS and not the PB2 gene was analysed (sevens cases including one ECMO-treated case), or in the single case were only PB2 and not NS was analysed.

Table 10. Distribution of characterised Swedish influenza A(H3N2) viruses among genetic groups.

Genetic subset	Number of viruses	Key substitutions (relative to A/Perth/16/2009)
3C.2a (Hong Kong/5738/2014)	41	L3I, N144S, F159Y, K160T, N225D, Q311H
3C.3b (A/Newcastle/22/2014)	14	E62K, K83R, N122D, L157S, R261Q
3C.3a (A/Switzerland/9715293/2013)	5	A138S, F159S, N225D, K326R
3C.3 (A/Samara/73/2013)	4	Q33R, T128A, R142G, N145S, N278K
Total	**64**	

Characterisation of influenza B

B/Yamagata

Further analysis of 34 B/Yamagata-like viruses by sequencing of the HA gene showed that these belonged to clade 3 (see phylogenetic tree in Appendix 3), which is characterised by amino acid substitutions S150I, N165Y, and G229D relative to B/Florida/02/2012, with a great majority of viruses also carrying N116K, N202S, K298E and E312K. Antisera raised against the vaccine strain for the 2014–2015 season (B/Massachusetts/02/2012, a clade 2 virus) do not recognise viruses in clade 3 as well as antisera generated against the vaccine strain for the 2015–2016 season (B/Phuket/3073/2013, a clade 3 virus).[12]

Five of the viruses originated from vaccinated patients. Two of these were younger than 65 years (37 and 63 years) and had no known immune deficiency. In Europe, 99% of the characterised viruses belong to genetic clade 3.[13] Five Swedish strains sent to the WHO CC in London have been included in the WHO's overall evaluation of antigenicity of the circulating B/Yamagata strains. Six of the Swedish B/Yamagata strains with HA belonging to B clade 3 (B/Yamagata) were reassortants with NA genes belonging to the B/Victoria lineage. A few such reassortant viruses were also seen in Sweden during season 2013-2014, and have also been detected during season 2014-2015 season in many parts of the world.[14]

None of the NA substitutions known to result in reduced or highly reduced inhibition to oseltamivir and/or zanamivir were identified in any of the 34 analysed viruses, including the six Yamagata HA/Victoria NA reassortants. In Europe, all of the 515 viruses screened for resistance to NA inhibitors were sensitive to both

[12] ECDC Influenza virus characterisation reports February-July 2015

[13] ECDC-WHO, Flu News Europe week 20/2015

[14] ECDC Influenza virus characterisation reports February-July 2015

oseltamivir and zanamivir.[15] Four viruses (including two of the Yamagata HA/Victoria NA reassortants) were also analysed phenotypically by NAI assay, and all were sensitive to oseltamivir and zanamivir.

B/Victoria

Two B/Victoria viruses were analysed by sequencing of the HA gene and found to belong to genetic clade 1A, which is characterised by amino acid substitutions N75K, N165K, and S172P relative to B/Malaysia/2506/2004 (see phylogenetic tree in Appendix 3). The two B/Victoria viruses did not contain any of the mutations known to result in reduced or highly reduced inhibition by oseltamivir and/or zanamivir.

Influenza in humans working on farms with swine

During the last three seasons, the Public Health Agency of Sweden has collaborated with the National Veterinary Institute to study swine influenza in humans and pigs.[16] Samples from farmers and veterinarians at a number of representative farms were collected according to a determined schedule along with samples from pigs. Samples from humans were analysed at the Public Health Agency, while samples collected from pigs were analysed at the National Veterinary Institute. During the 2013–2014 season, two cases of influenza A(H1N2) were detected in farmers (week 14 and 16 respectively). The same strain was detected in pigs at the same farm during weeks 8-16 (2014). The farmers did not had any clinical sign of illness. During the 2014–2015 season, there were no positive samples detected among the participants.

Virus isolation on cell culture

Isolation of influenza viruses on cell culture in Sweden is only performed at the Public Health Agency of Sweden. We continuously ask Swedish laboratories to provide a representative selection of specimens that can be isolated on cell culture. One problem with only using samples collected from other laboratories is that the quality differs depending on, for example, the kind of specimen, the time since sampling, and the storage and shipping temperatures. Seventy-eight of the collected samples with Ct $\leq$ 30 were cultured on MDCK cells. Eight samples were excluded due to contamination with bacteria or fungi. Sixty-four per cent of the remaining samples tested positive for influenza.

The cultures are used for phenotypic analyses at the Public Health Agency of Sweden and for further characterization at the WHO CC in London. During the 2014–2015 season, 45 virus isolates and 19 clinical samples were shipped to the WHO CC (one shipment in December and one in June).

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[15] ECDC-WHO, Flu News Europe week 20/2015

[16] WHO, 2015, Antigenic and genetic characteristics of zoonotic influenza viruses and development of candidate vaccine viruses for pandemic preparedness

Quality assurance

Seasonal influenza

One-step PCR assays are used to identify circulating influenza viruses. These assays are used to detect influenza A and B, to subtype the influenza A-positive samples, and to discriminate between the two influenza B lineages. These assays have also been evaluated and implemented for avian influenza diagnostics. They are sensitive, rapid, and can easily be scaled up if necessary. Several of these PCR assays have been developed to be performed as duplex PCR assays. This is true for the detection of influenza A and B, subtyping of influenza A(H1N1)pdm09 and A(H3), and for typing of B/Yamagata and B/Victoria lineages. The Public Health Agency continuously sequences the regions to which the PCR-systems are directed in order to detect mutations that could affect the sensitivity of the PCR assays used.

During the 2014–2015 season, two new probes were validated and implemented in the influenza A(H1N1)pdm09 PCR assay. After validation, this information was shared with the Swedish laboratories. The laboratories that use the PCR systems established by the Public Health Agency are encouraged to send all samples with deviating results to the agency for sequence analysis. Furthermore, the Public Health Agency assists Swedish laboratories that have developed their own PCR systems by validating their methods through sequencing of representative samples. The Public Health Agency also provides positive control material to Swedish laboratories upon request.

Control of sensitivity in commercial rapid PCR-kits

During the 2014–2015 season, an increasing number of laboratories included a commercial "rapid PCR" assay among their diagnostic tools. In order to ensure that circulating influenza strains were detected with these assays, the Public Health Agency of Sweden agreed to send supernatants from cell cultures to three laboratories using three different kits. The kits tested were Diagenode (Becton Dickinson), GeneXpert (Chepheid), and Simplexa (Focus Diagnostics). The three laboratories received a number of samples on three occasions – in the beginning, in the middle, and at the end of the season. A total of 34 positive samples were tested with the three different kits, and all gave 100% correct results. The results were shown on our homepage so that other laboratories using the same kits had knowledge about the results.

External quality assurance programmes

The Public Health Agency participates in the following external quality assurance (EQA) programmes:

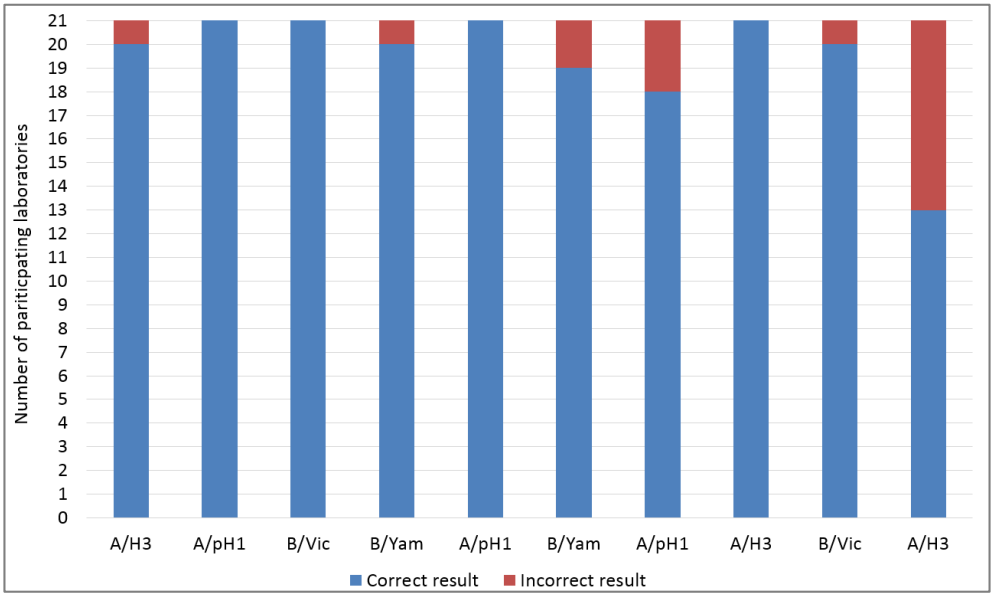
1. The annual WHO EQA for influenza A. The result for 2014 was 10/10 correct results.
2. The INFRNA panel from Quality Control for Molecular Diagnostics (QCMD). The result for 2014 was 12/12 samples correctly typed and subtyped.

3. The ERLI Net influenza virus EQA program, arranged every second year. The panel for 2015 was sent to the participating laboratories in June, and the results are expected later this fall.

National quality assurance programme

All regional laboratories in Sweden perform influenza A and influenza B PCR and a subtype-specific A(H1N1)pdm09 PCR. Four regional laboratories also perform an A/H3 PCR. In September 2014, The Public Health Agency of Sweden produced a PCR panel for the Swedish laboratories as an EQA on behalf of the External Quality Assessment for Clinical Laboratory Investigations (EQUALIS). Twenty-one laboratories participated in the EQA, and 11 of these reported 10/10 correct answers (Figure 14). This is a deterioration in quality compared to 2013 when 19 laboratories reported 10/10 correct answers. The 2014 panel consisted of samples with lower concentrations of virus compared with 2013, which could be a reason for the lower success rate.

Figure 14. Results of the Swedish EQA panel 2014



Vaccination coverage

Coverage among those 65 years of age and older

Vaccination coverage in those 65 years of age and older was estimated to be 49.7% in the 2014–2015 season. This corresponds to about 950,000 vaccinated persons and is an increase compared with the previous season. For a rough estimate of the national average vaccination coverage in this age group over the past twelve seasons, see Table 11. As shown, a drop in vaccination coverage was seen starting in 2011, probably due to the reports of severe side effects (narcolepsy) caused by the influenza vaccine used during the 2009 pandemic (Pandemrix®). Starting with the 2013–2014 season, however, we have seen a reversal of this trend. Still, the WHO and ECDC target of 75% vaccination coverage is far from being achieved.

Table 11. Mean yearly proportion of vaccinated persons older than 65 years in Sweden, as estimated by the 21 county medical officers.

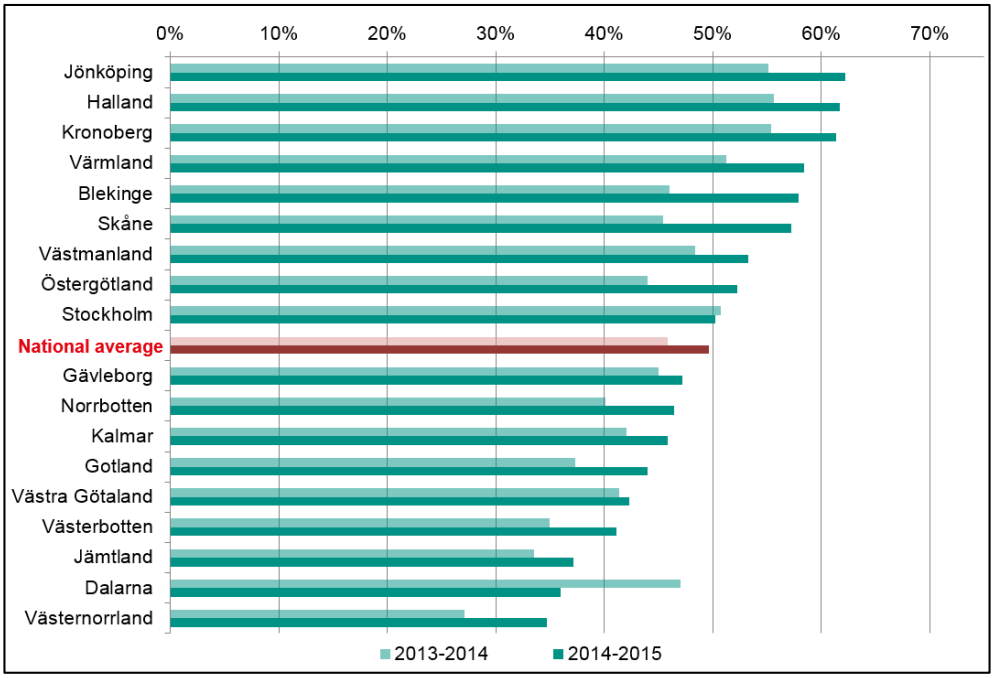
Season for vaccination	Estimated proportion of the population above 65 years old vaccinated with seasonal vaccine (%) *
2014–2015	49.7
2013–2014	45.8
2012–2013	44.2
2011–2012	46.1
2010–2011*	55.2
2009–2010**	44
2008–2009	65.8
2007–2008	60
2006–2007	56
2005–2006	61
2004–2005	55
2003–2004	51

* Please note that the number has been adjusted for the 2010–2011 season compared to previous annual reports in light of new information.

** Very few counties reported seasonal vaccination coverage in 2009 because the focus was on the pandemic vaccination. Sixty per cent of the Swedish population was vaccinated with an adjuvanted monovalent vaccine in 2009.

Vaccination coverage differed among county councils, with the highest estimated coverage being in Jönköping (62%), Halland (60%), and Kronoberg (60%) (Figure 15). Most county councils increased vaccination coverage, and the average increase was five percentage points. However, coverage decreased in Stockholm and Dalarna. In Stockholm, this was likely due to simply having many more elderly people to vaccinate due to the aging of the population. Reasons for the decrease in Dalarna are unclear, but a survey showed that anxiety about side effects (46%), perceived low severity of the disease (18%), and perceived ineffectiveness of the vaccine (16%) were the main reasons for not getting vaccinated.

Figure 15. Estimated proportion of vaccinated persons above 65 years old per county council in Sweden, seasons 2013–2014 and 2014–2015.



Note: Data from Jämtland and Västernorrland do not include doses given in long-term care facilities, etc., which will underestimate the coverage rate. In Uppsala and Sörmland, coverage is measured using the number of delivered doses, which cannot reliably be used to estimate doses given to elderly persons. Data from Örebro are not available until the fall.

Vaccination coverage in medical risk groups

It is difficult to estimate vaccination coverage among the medical risk groups because these groups are hard to define and because data are often missing. The Swedish Board of Health and Social Welfare (*Socialstyrelsen*) has estimated that 5–10% of the population under 65 years of age belongs to a medical risk group. Twelve county councils[17] have data on the number of persons vaccinated under 65 years of age, although risk group status is often unknown. An analysis of these data show that only about 2% of this age group were vaccinated during the 2014–2015 season – a rate similar to that seen the previous season. In other words, we fail to reach all who could benefit the most from vaccination.

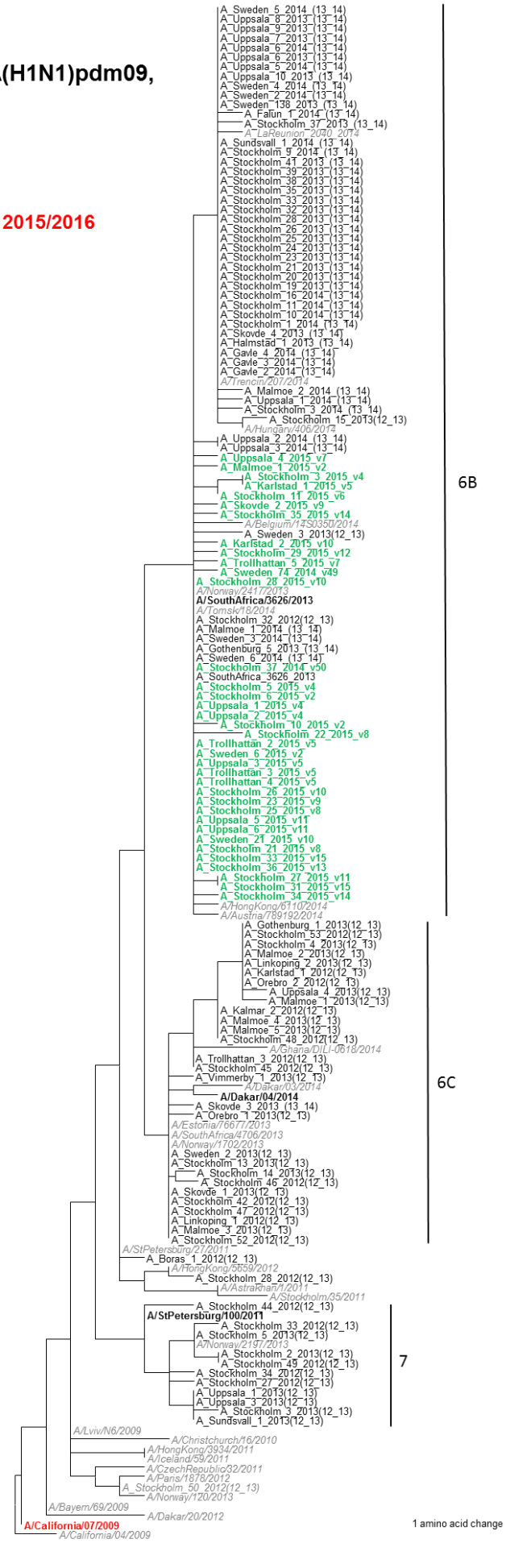
[17] Gävleborg, Halland, Jämtland, Jönköping, Kalmar, Kronoberg, Norrbotten, Stockholm, Värmland, Västernorrland, Västra Götaland, and Östergötland.

Appendix 1.

Phylogenetic tree influenza A(H1N1)pdm09, hemagglutinin (HA1)

Season 2014/2015
Vaccine strain 2014/2015 och 2015/2016

Subgroup-representatives
Reference strains
Previous seasons: (12_13)
(13_14)



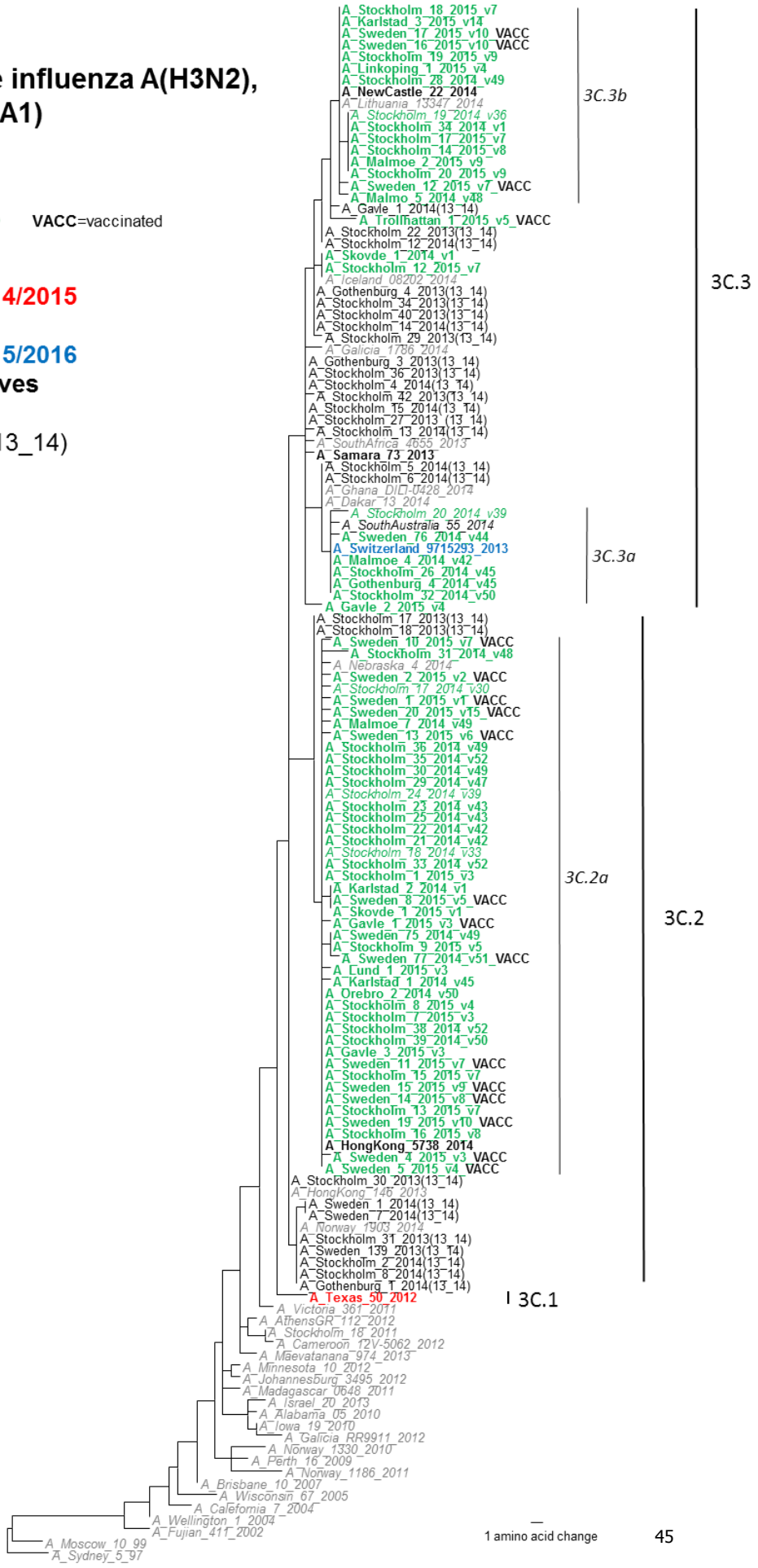
Appendix 2.

Phylogenetic tree influenza A(H3N2), hemagglutinin (HA1)

Season 2014/2015 **VACC**=vaccinated
Week 21-39, 2014

Vaccine strain 2014/2015

Vaccine strain 2015/2016
Subset-representives
Reference strains
Previous season: (13_14)



Appendix 3.

Phylogenetic tree influenza B, hemagglutinin (HA1)

Season 2014/2015 **Yam/Vic**=Yamagata HA/Victoria NA reassortant
VACC=vaccinated

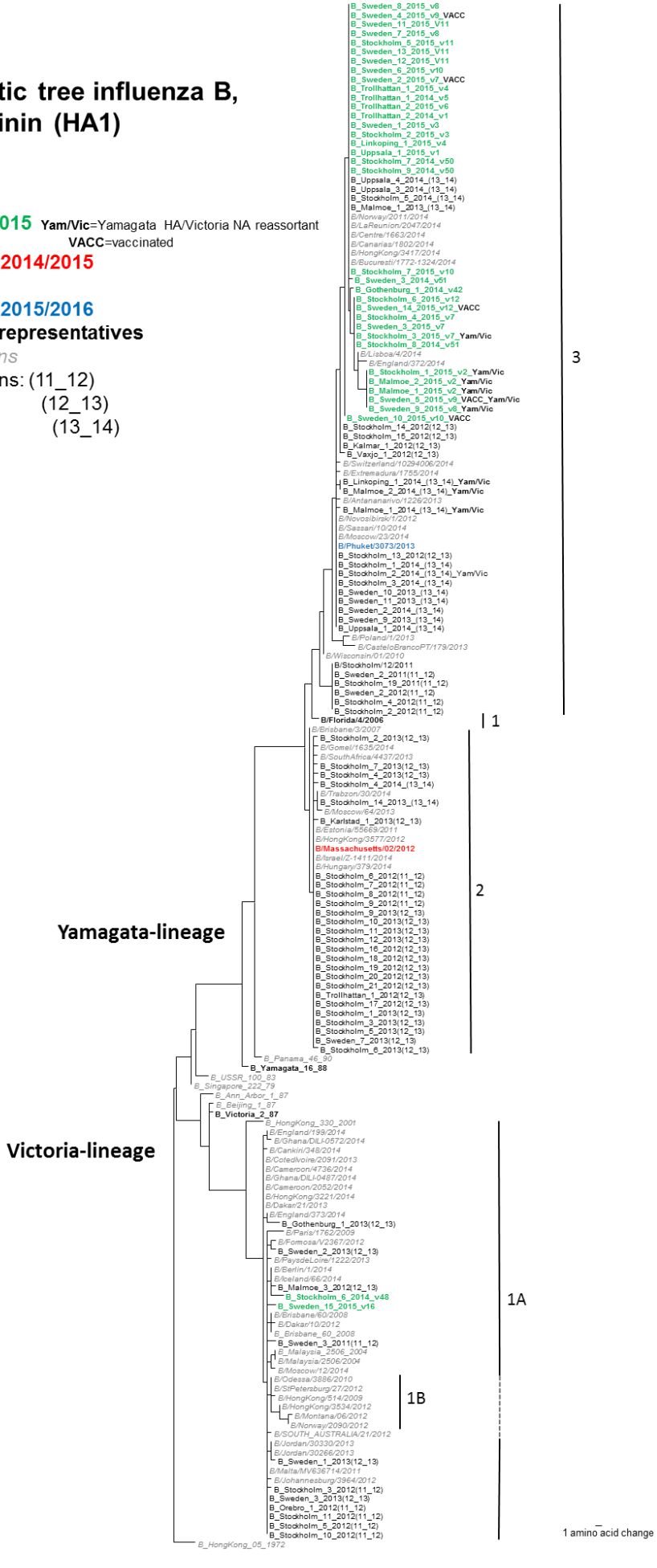
Vaccine strain 2014/2015

Vaccine strain 2015/2016

Lineage/clade representatives

Reference strains

Previous seasons: (11_12)
(12_13)
(13_14)



The influenza season of 2014–2015 was long and intense. However, despite genetic drift among the circulating influenza A(H3N2) strains, the season was no more severe than previous intense seasons.

This report describes the monitoring systems for influenza in use during the winter season of 2014–2015 and the results of both epidemiological and virological surveillance. Data are also compared to previous influenza seasons.

The Public Health Agency of Sweden has prepared this report for the World Health Organization (WHO) as part of the agency's function as a National Influenza Centre (NIC).

Rapporten innehåller en svensk sammanfattning.

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