



Folkhälsomyndigheten
PUBLIC HEALTH AGENCY OF SWEDEN

Influenza in Sweden

Season 2013-2014



Influenza in Sweden

Season 2013-2014

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Preface

This report describes the monitoring systems for influenza in use during the winter season of 2013-2014 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 Folkh alsomyndigheten. <http://www.folkhalsomyndigheten.se/publicerat-material/publikationer/>. Search for "Influenza in Sweden".

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Summary

The influenza season of 2013-2014 was relatively mild in Sweden, especially in comparison to the preceding season of 2012-2013, which was particularly severe. The number of laboratory-confirmed influenza cases in Sweden was the lowest reported since the pandemic of 2009, and the all-cause mortality among persons above 65 years old remained at the seasonal baseline. The low influenza activity this season could possibly be explained by the circulating viruses being similar to the vaccine strains and to the strains that circulated the previous season.

This season was dominated by influenza A(H1N1)pdm09 with co-circulation of influenza A(H3N2) and sporadic detections of influenza B. Due to the circulation of different influenza types, all age groups were affected, but the highest incidence was seen among children below five years old (those most likely to be influenza-naïve) and among adults 40–64 years old. In previous seasons, the incidence of laboratory-confirmed influenza A(H1N1)pdm09 among the elderly had been markedly lower than among other adults, but this season the incidence of this strain among the elderly was higher - demonstrating a change in the age distribution of cases.

Ninety-three patients with influenza A(H1N1)pdm09 were treated in intensive care units, or with a ventilator or extracorporeal membrane oxygenation (ECMO). This constitutes 5.4% of the laboratory-confirmed cases of influenza A(H1N1)pdm09, which is comparable to all three previous post-pandemic seasons dominated by this virus. The majority of the severe cases occurred among persons who belonged to a medical risk group. The age distribution of the more severe cases mirrors the overall age distribution, with most cases being 40-64 years old followed by the elderly. The youngest age groups, however, were less often reported to be in intensive care.

Forty-six patients with laboratory-confirmed influenza A(H1N1)pdm09 infections died within 30 days of symptom onset. The vast majority of these patients belonged to a medical risk group, but only a few had been vaccinated during the season.

The viral characterisation showed that the circulating viruses were antigenically similar to the corresponding vaccine strain and sensitive to the antiviral drugs in use (neuraminidase inhibitors).

The vaccination coverage among the elderly (above 65 years old) increased modestly compared to last season, but this signifies a welcome change following consecutive seasons with falling coverage rates since the post-pandemic season 2010-2011.

The 2013-2014 influenza season shows that influenza seasons that are relatively mild for most parts of the population can still cause severe illness and deaths among those most at risk. Regardless of the expected seasonal developments, influenza vaccinations should always be offered to those belonging to a risk group.

Sammanfattning

Influensasäsongen 2013-2014 var relativt mild och står i stark kontrast mot föregående säsong (2012-2013) som var ovanligt svår. Samtliga övervakningssystem har denna säsong visat på låga nivåer av influensaaktivitet jämfört med tidigare säsonger. Antalet laboratoriebekräftade fall av influensa under säsongen var det lägsta sedan pandemin 2009 och ingen överdödlighet noterades.

Influensa A(H1N1)pdm09 dominerade och influensa A(H3N2) utgjorde något mindre än en tredjedel av influensa A-fynden. Influensa B förekom inte i särskilt stor utsträckning denna säsong.

Flest fall sett till befolkningen har, liksom tidigare säsonger, diagnosticerats bland barn under fem år. Tidigare säsonger har inte så många äldre insjuknat med influensa A(H1N1)pdm09, men denna säsong var incidensen bland vuxna som högst i åldersgruppen 40-64 år, tätt följt av åldersgruppen 65+, vilket innebär att åldersspektrumet har ändrat sig något över åren sedan pandemin 2009.

Nittiofyra patienter med influensa A(H1N1)pdm09 fick intensivvård, behandling i respirator eller med ECMO, vilket motsvarar 5,4 procent av de anmälda fallen. Detta är lika stor andel som under tidigare säsonger. Åldersfördelningen bland de svårt sjuka speglar den bland samtliga laboratoriebekräftade fall. Majoriteten tillhörde en medicinsk riskgrupp. Även bland de dödsfall som inträffat inom en månad efter insjuknandet dominerar personer med underliggande sjukdomar. Bara ett fåtal var däremot vaccinerade.

De influensavirus som cirkulerat i Sverige under säsongen har varit lika de tre stammar som ingått i säsongsinfluensavaccinen. De cirkulerande stammarna av A(H3N2) liknade även de som cirkulerade förra säsongen (2012/2013), då många i Sverige insjuknade. Detta kan möjligtvis förklara säsongens låga influensaaktivitet.

Analys av svenska prover kunde inte påvisa någon resistens mot de antivirala substanserna som ingår i läkemedlen Tamiflu och Relenza, vilket innebär att dessa läkemedel har haft bibehållen effekt vid behandling av svårt sjuka patienter och patienter i riskgrupper.

Även om säsongen blev relativt mild på populationsnivå, drabbades många personer med underliggande sjukdomar svårt. Vaccination mot säsongsinfluensa bör därför alltid erbjudas de definierade riskgrupperna, oavsett hur säsongen förväntas utveckla sig.

Background

Each winter, influenza epidemics of different magnitudes 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. If the elderly are affected, many become severely ill and this leads to a great strain on hospitals and increased mortality. If small children are affected, they also might need hospital care but deaths are rare. Slightly older children handle influenza infections fairly well, but the need to care for an ill child might lead to substantial absenteeism from work among parents.

If a new strain of influenza were to emerge and cause a pandemic, this could lead to such an extensive absence of the working population that it would constitute a threat to important public functions and services. New influenza strains 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 consequences are detectable through a single reporting system. In order to get an overall picture of on-going influenza activity, the Swedish Institute for Communicable Disease Control (*Smittskyddsinstitutet*, SMI) established a number of different epidemiological reporting systems for influenza, from direct reporting by people who are ill to the collection of data from different healthcare providers and scanning of the Internet. 1 January 2014, SMI ceased to exist, and its tasks are now carried out by the Public Health Agency of Sweden.

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. 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 (WHOCC) in 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 seeks 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 in Sweden during the 2013-2014 season.

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

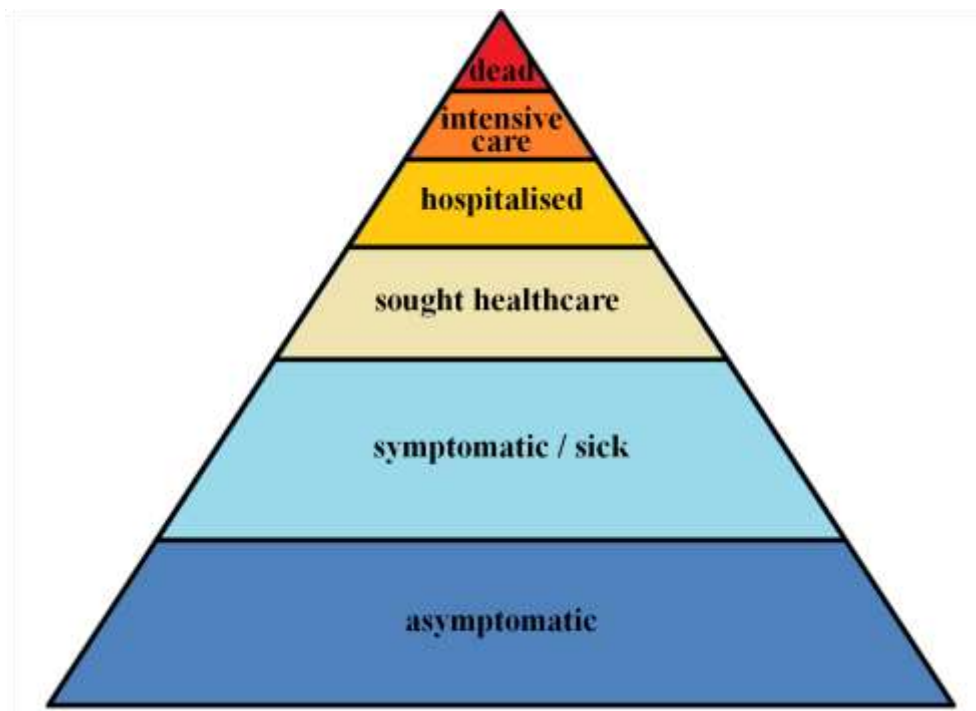


Table 1. Description of all systems used to monitor influenza activity during the 2013-2014 season. The data refer to the period between week 40, 2013, and week 20, 2014, if no other dates are given.

Reporting system/method	Implementation	What does the system/method show?	Number/percentage reported during the season
1a. 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.	1,737 laboratory-confirmed cases of influenza A(H1N1)pdm09.
1b. Statutory clinical reporting of hospitalised cases of influenza A(H1N1)pdm09	Hospitalised cases must 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, ECMO).	872 laboratory-confirmed cases of A(H1N1)pdm09 were reported to have been hospitalised. Of those, 93 were reported to be in either intensive care, on a ventilator, or receiving ECMO, of which 42 were also reported through the Swedish intensive care registry.
2. 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 B.	Number of laboratory-confirmed cases of influenza types other than A(H1N1)pdm09, together with the patients age and gender distribution. Proportion of samples tested that are positive for an influenza virus.	22,330 samples analysed of which 2,585 (11.6%) tested positive: 1,737 (67.2%) for A(H1N1)pdm09, 635 (24.4%) for non-A(H1N1)pdm09 influenza A, and 213 (8.2%) for influenza B.
3. Voluntary clinical reporting of laboratory-confirmed influenza cases (all types) in intensive care	Collaboration with the Swedish Intensive Care Registry (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.	55 laboratory-confirmed cases of influenza were reported from the SIR. Of those, 50 were reported as A(H1N1)pdm09, 1 was A(H3N2), 3 were influenza A of unknown subtype, and 1 was influenza B.
4a. Sentinel reporting	Participating general practitioners (GPs) report the number of patients experiencing influenza-like illness (ILI) each week and their approximate catchment population at the beginning of the season.	Proportion of the catchment population that visits their GP for ILI.	658 cases of ILI were reported from 72 GPs with a combined total of 611,000 listed persons (0.11%).

4b. Sentinel sampling	Samples from some of the ILI patients in the sentinel surveillance, 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.	1,302 samples were analysed of which 222 (17%) tested positive for influenza: 69.5% A(H1N1)pdm09, 10.5% B/Yamagata-like, 14.0% A(H3N2), and 1.5 % B/Victoria-like. 3.6% of the influenza A-positive samples and 0.9% of the influenza B-positive samples could not be typed for subtype or lineage. Between week 27, 2013, and week 26, 2014, about 64,000 queries related to influenza were entered.
5. "Webbsök" (Web Search)	An automated system that uses search data from the 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 ILI.	Complements the sentinel reporting in estimating the proportion of patients with ILI.	
6. Telephone Advice Line (1177)	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 380,000 calls regarding one of the following symptoms: breathing difficulties, fever, sore throat, or coughing.
7. 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 by statistical models.	All-cause mortality (i.e. not influenza-specific).	During the influenza season, 57,173 persons died in Sweden. No excess mortality was seen among persons above 65 years old.
8. 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.	88 strains were characterized for vaccine resemblance and antiviral resistance. The strains resembled different genetic groups. Most of them were not antigenically distinguishable from the vaccine strains and none of them were resistant.

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. An additional clinical report is mandatory for patients with laboratory-confirmed infections who have been admitted to 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. Unfortunately, this voluntary information is often left incomplete. It is furthermore possible to add the date of death (if applicable) to the case report in SmiNet.

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. As of the 2013-2014 season, reporting via fax was no longer possible. Denominator data (the total number of samples analysed) is also reported via SmiNet or e-mail.

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 the 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 of influenza patients under treatment.

Sentinel surveillance

Sentinel reporting

As in previous seasons, the Public Health Agency recruited a number of GPs willing to act as sentinels, or informants, within the influenza surveillance system covering Swedish outpatient care. Each week, they report the number of patients with influenza-like illness (ILI) that they examined during the past week through a web-based form connected to SmiNet. At the beginning of the season, they also report how many patients belong to their catchment area, also referred to as *listed persons*, which is used as a denominator to calculate incidence rates.

Sentinel surveillance in Sweden is generally done in accordance with the recommendations developed by the European Influenza Surveillance Network (EISN), which is the influenza-monitoring group of the European Centre of Disease Prevention and Control (ECDC). However, Sweden receives a relatively low number of reports compared with other countries. This might be because Swedish citizens can go on sick leave for up to seven days without requiring a doctor's certificate or because patients turn to emergency departments rather than their general practitioners when their influenza illness is severe enough to warrant medical attention. If patients are not severely ill, they tend to stay at home.

Furthermore, no financial incentive is given to the sentinel physicians, and this might explain why recruitment has been difficult over the years with poor coverage both nationally and regionally.

Sentinel sampling

ILI is caused by influenza in a minority of cases, and 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 majority of the sentinel physicians both report ILI and collect samples.

The Public Health Agency carries out the laboratory analyses for influenza free of charge. The positive samples are also used to characterize the circulating strains of influenza.

Webbsök

Webbsök ("Web search") is an automated system established in 2008 that uses completely anonymous data from a medical advice website to estimate the development of the sentinel reporting through a statistical model. 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 four days ahead of the publication of the weekly influenza bulletin that includes the results from the sentinel surveillance.

During the 2013-2014 season, the source website changed from Vårdguiden (www.vardguiden.se), mostly servicing Stockholm county, to 1177 Vårdguiden (www.1177.se), now covering all of Sweden.

Telephone advice line

In collaboration with the telephone advice service 1177, 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).

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 and regionally for the Northern, Eastern, and Southern parts of Sweden.

Virus characterisation

Subtyping and lineage typing

All regional laboratories perform subtyping by real time PCR for influenza A(H1N1)pdm09. Three 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. As 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 of three of the eight influenza gene segments, including hemagglutinin (HA), neuraminidase (NA), and matrix (M). The HA gene is 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, are analysed for sequence mismatches. The NA gene is analysed with respect to amino acid substitutions known to result in reduced or highly reduced inhibition to NA inhibitors according to guidelines from WHO. Two aspects of the M gene are

analysed by sequencing. The M2 gene of influenza A is 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 are analysed for sequence mismatches.

Some genetic characterisations are also performed by real-time PCR, including influenza B lineage typing, H275Y mutation analysis of influenza A(H1N1)pdm09 viruses, and discriminating A/H3N2 from A/H3N2v.

Phenotypic analysis of sensitivity to NA inhibitors is performed by NAI assay, which needs viruses isolated on cell culture. This analysis generates IC₅₀ (half maximal inhibitory concentration) values for oseltamivir (Tamiflu®) and zanamivir (Relenza®) from which sensitivity of the influenza virus to these inhibitors is calculated and interpreted according to the criteria given by the WHO.

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

Additional monitoring activities

Individual deaths

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 ten 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. Various methods for estimation have been used in different places, such as 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 three years.

The data from the 21 county councils has been collated yearly after the influenza season by one of the county medical officers or their staff 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.

The responsibility for the collation of vaccination coverage data was transferred to the Public Health Agency in 2014.

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 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.

On-going projects

Influenza-attributable mortality

An extended statistical model that incorporates the weekly number of deaths, influenza-positive samples, and temperature has previously been used annually, after the influenza season, to estimate the influenza-attributable mortality.

Following the change in the organisation responsible for the analysis, the model is currently being updated. When finished, data from seasons 2012-2013 and 2013-2014 will be analysed.

Hälsorapport

The system Hälsorapport (“Health report”) is a web-based reporting system that builds on the experience and knowledge gained from the Sjukrapport and Influenzakoll systems (see previous annual reports). Approximately 35,000 persons aged 0 to 85 years were randomly selected and invited to participate in Hälsorapport from November 2013 to November 2014. About 3,200 of the invited persons or parents of the invited children agreed to participate and have been reminded weekly through email to make their reports. Every week, the participants report their health status for the preceding week. If the participants report that they have been ill, they are asked to report their symptoms. Based on these reports, the Public Health Agency of Sweden can estimate the weekly cumulative incidence of acute respiratory illness, ILI, and acute gastrointestinal illness in Sweden. Other aims of Hälsorapport are to facilitate recruitment of controls for case-control studies of national outbreaks and to facilitate cross-sectional studies in the population.

Because Hälsorapport is a pilot study and its data collection was still on-going at the time of this report’s publication, its results will not be presented here.

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.² A preliminary summary of the season is included in the bulletin that is published in week 21.³

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 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 are isolated and sent to the WHOcc in London for further characterisation.

Characterisation data, including NAI results from the WHOcc, 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 is sent to the WHO and the ECDC and is published on the Public Health Agency's webpage.

² <http://www.folkhalsomyndigheten.se/amnesomraden/statistik-och-undersokningar/sjukdomsstatistik/influensa-veckorapporter/aktuell-influensarapport/>

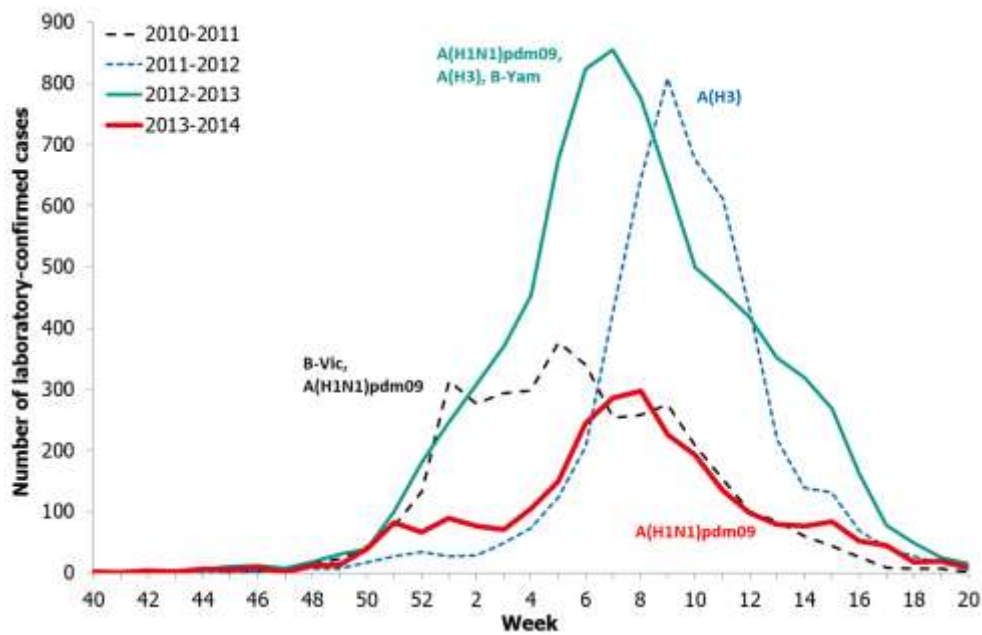
³ http://www.folkhalsomyndigheten.se/documents/statistik-uppfoljning/smittsamma-sjukdomar/Veckorapporter-influensa/2014/Influensarapport_v20-2014.pdf

Epidemiological data

Statutory and laboratory-based surveillance

A total of 2,585 laboratory-confirmed cases of influenza were reported during the 2013-2014 season (Figure 2). More than 100 confirmed cases were reported per week between weeks 4 and 11 with a peak of 297 cases during week 8. This is the lowest number of influenza cases recorded during a season since the pandemic of 2009 (Figure 2) and is an indication of a mild season.

Figure 2. Total number of laboratory-confirmed cases of influenza (all types) per week and the dominating influenza type(s) per season from 2010 to 2014.



Viral distribution

Influenza A(H1N1)pdm09 dominated the 2013-2014 season with co-circulation of seasonal influenza A (Figure 3). Only sporadic cases of influenza B were detected, with a slight increase toward the end of the season. Only 7% as many influenza B infections were detected this season compared to last season.

Swedish laboratories analysed 22,330 samples for influenza during the season, of which 2,585 (12%) tested positive for influenza A or B (Table 2). This is a decrease of more than 9,000 samples compared to the previous season when 26% of the samples were positive. This also indicates that the 2013-2014 season was mild.

Of the positive samples, 1,737 were influenza A(H1N1)pdm09, and 213 were influenza B (Table 2). The rest of the 635 samples were positive for influenza A but negative for influenza A(H1N1)pdm09. Of these, 169 were subtyped by the Public Health Agency or the regional laboratories in Gothenburg, Malmö and Umeå and all were A/H3. All influenza A positive samples negative for

A(H1N1)pdm09 were therefore classified as seasonal influenza A(H3N2). The Public Health Agency further determined the lineage of 26 influenza B-positive samples.

Figure 3. Number of laboratory-confirmed cases by influenza type and week, 2013-2014.

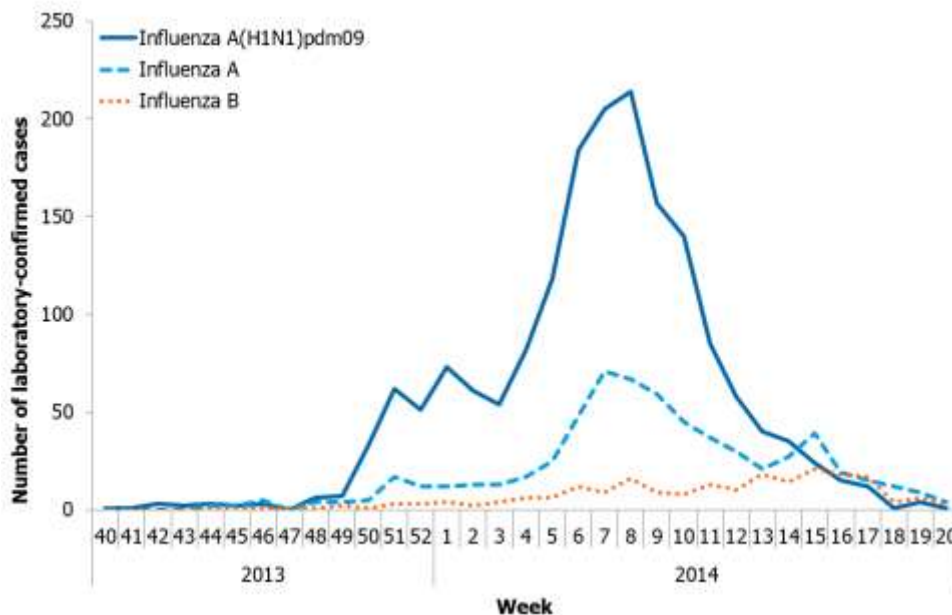


Table 2. Laboratory results of patients reported through the statutory and voluntary laboratory reporting systems combined during the last three seasons.

	2011-2012	2012-2013	2013-2014
Analysed samples	22,283	31,750	22,330
Proportion positive samples	21.7%	25.8%	11.6%
Total positive for influenza A	4,685	5,340	2,372
A(H1N1)pdm09 *	153	2,435	1,737
A(H3)	1,252	548	169
A, not subtyped but A(H1N1)pdm09 negative	3,280	2,357	466
Total positive for influenza B	160	2,857	213
B/Victoria lineage	21	8	2
B/Yamagata lineage	22	148	24
B, not typed to any lineage	117	2,701	187

* Not typed as N1, but classified as A(H1N1)pdm09 based on H1-typing.

Age and sex distribution

The three viruses differed concerning the age groups that were most affected (Table 3 and Figures 4A-C). The highest incidence of influenza A(H1N1)pdm09 was found in children 0–4 years old and in adults 15–64 years old. It is interesting to note that the 5–14 year olds, who were hardest hit during the pandemic of 2009 and who had the highest vaccine coverage at that time, continue to be the age group with the lowest incidence.⁴ Seasonal influenza A was most frequently diagnosed in persons

⁴ SMI. The Influenza A(H1N1)2009 Pandemic in Sweden, 2009-2010. Available from: <http://www.folkhalsomyndigheten.se/publicerat-material/publikationer/The-Influenza-AH1N12009-Pandemic-in-Sweden-2009-2010/>

above 65 years old, and influenza B was most frequent among adults of all ages. The median ages of the cases of the respective influenza types are presented in Table 4.

The sex distribution was equal for influenza A(H1N1)pdm09, seasonal influenza A, 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, seasonal influenza A, and seasonal influenza B, Sweden, 2013-2014.

Age group	Influenza A(H1N1)pdm09		Seasonal influenza A *		Seasonal influenza B		Total influenza	
	No.	Inc.	No.	Inc.	No.	Inc.	Total no.	Total inc.
0-4 years	174	30.1	35	6.0	11	1.9	220	38.0
5-14 years	42	3.9	25	2.3	9	0.8	76	7.1
15-39 years	487	15.9	153	5.0	48	1.6	688	22.5
40-64 years	682	22.2	160	5.2	83	2.7	925	30.1
>65 years	352	18.8	262	14.0	62	3.3	676	36.1
Total	1,737	18.0	635	6.6	213	2.2	2,585	26.8

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

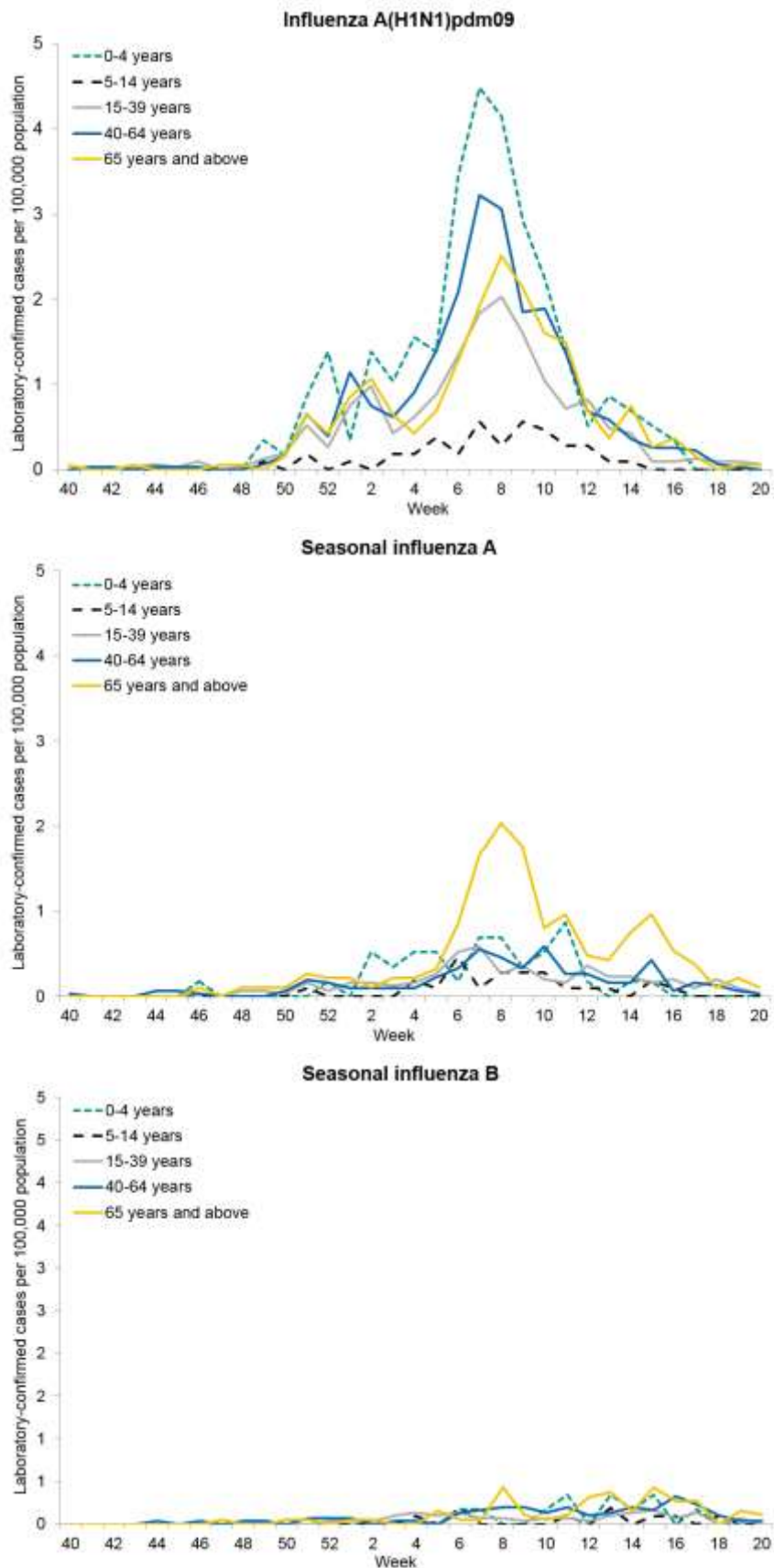
Table 4. Median age (years) of patients reported through the statutory and voluntary laboratory reporting systems combined during the last three seasons.

	2011-2012	2012-2013	2013-2014
Influenza A(H1N1)pdm09	41	39	45
Seasonal influenza A *	64	64	58
Seasonal influenza B **	48	46	49

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

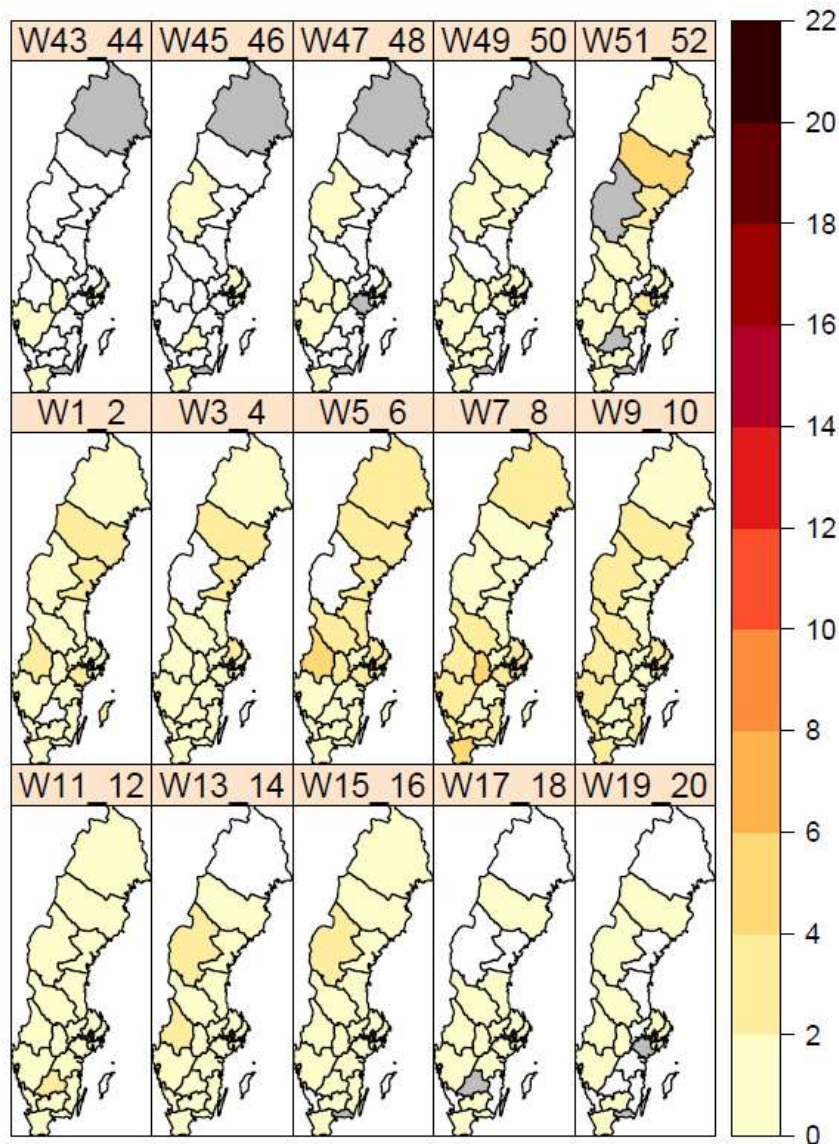
Figure 4. Weekly incidence of the respective influenza types per age group in Sweden for the 2013-2014 season.



Geographic distribution

The influenza epidemic peaked in the whole country between weeks 7 and 8 of 2014, as shown in figures 2, 3, and 5. The average incidence of reported laboratory-confirmed cases in Sweden was 27 per 100,000 population, but this varied from 10 per 100,000 population in the county of Blekinge in the southeast to 48 per 100,000 population in Västerbotten in the north. As in the last season, the incidence seems to have been the highest in the western part of Sweden. 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 because of the large variations in the sampling frequency. Unfortunately, we cannot judge whether the sampling differences are due to a higher incidence of disease or to more active sampling.

Figure 5. 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.)



Clinical features of influenza A(H1N1)pdm09 cases

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

During the 2013-2014 season, 872 patients with influenza A(H1N1)pdm09 were reported as hospitalized, of which 93 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.

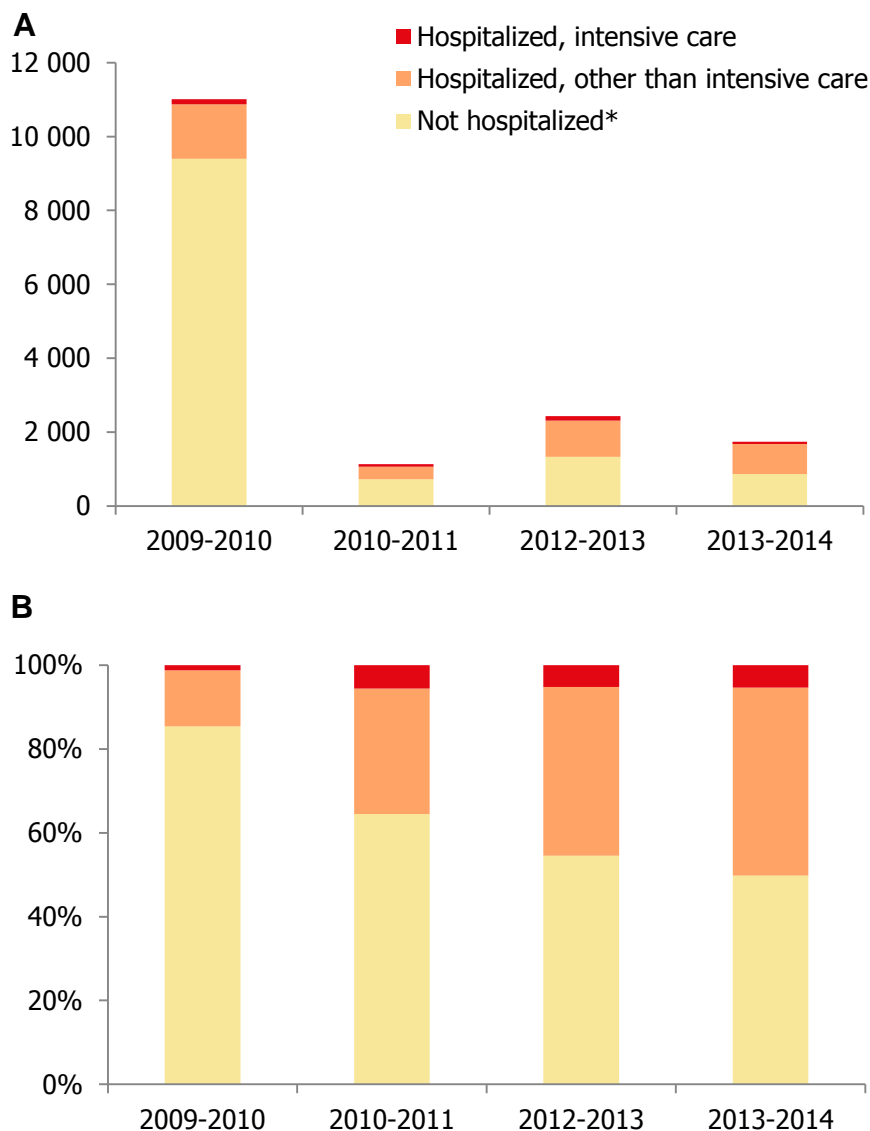
Level of care	Number	Proportion
Not hospitalised *	865	49.8 %
Hospitalised	872	50.2 %
- Hospitalisation, other than intensive care	779	44.8 %
- Intensive care	93	5.4 %
o Intensive care	59	3.4 %
o Ventilator treatment	25	1.4 %
o Extracorporeal membrane oxygenation (ECMO)	9	0.5 %
Total	1,737	100 %

* 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 are missing.

The proportion of laboratory-confirmed cases of A(H1N1)pdm09 that have been reported as hospitalised has increased with each season since the pandemic of 2009 (Figure 6). The proportion of patients in intensive care, however, has been the same (around 5.4%) through all three post-pandemic seasons dominated by influenza A(H1N1)pdm09. This might reflect a change in testing practices towards preferential testing of patients with more severe clinical presentations.

The median age of patients in intensive care was 58 years compared to 54 years for patients in other forms of hospitalization and 39 years for the cases not hospitalized. The gender distribution was equal.

Figure 6. 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 IRIS.
The 2011-2012 season was dominated by influenza A(H3N2) and is therefore excluded from the comparison.

Information about risk group status was available for 663 of the 779 hospitalized patients not in intensive care. Of these, 377 (57%) belonged to a medical risk group. The most common risk factors were chronic heart-lung disease and immunosuppression. Among the patients in intensive care, 63 (68%) were less than 65 years old. Risk group status was known for 49 of them, and 29 (59%) belonged to at least one risk group. This was a similar proportion to last season, and the most common risk factors were the same as for all hospitalized patients. The exact number of persons below 65 years belonging to a risk group in Sweden is not known, but it is estimated to be around 15%. The risk for persons below 65 years old to be treated in intensive care in association with influenza A(H1N1)pdm09 is thus four times higher if they belong to a risk group than if they do not.

Of the 779 hospitalized cases, 449 (58%) were targeted for seasonal vaccination (that is, they belonged to a medical risk group or were above 65 years of age). Vaccination status was known for 199 of them, and 67 (34%) of these were vaccinated. The corresponding proportion among cases in intensive care was 23%.

Of 364 female patients between 15 and 45 years of age diagnosed with influenza A(H1N1)pdm09, 24 were reported to be pregnant. Of these, one was treated in intensive care, 20 in other forms of hospitalisation, and for the remaining three women no information regarding hospitalisation was available. None of the hospitalised women had a second risk factor for severe influenza illness besides pregnancy. All three pregnant women with known vaccination status were unvaccinated in the 2013-2014 season, and for the remaining 21 pregnant women the vaccination status was unknown.

It is not mandatory to report the death of a patient after clinical notification. Nevertheless, 14 cases were reported as deceased within 30 days of being diagnosed with laboratory-confirmed influenza A(H1N1)pdm09. An additional 32 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. In total, 46 patients diagnosed with influenza A(H1N1)pdm09 were found to have died within 30 days of laboratory confirmation. Their median age was 69 years (min: 21 years, max: 90 years). Twenty-six (57%) were male. Of the 38 deceased with known risk group status, 36 (95%) belonged to a medical risk group. Twenty-three (50%) had been in intensive care, 22 (48%) had been hospitalised in other wards, and one (2%) was not reported as having been hospitalised. Although 41 of the 46 deceased belonged to a target group for vaccination, only three were reported as vaccinated with the 2013-2014 seasonal influenza vaccine (14 were unvaccinated and for 24 the vaccination status was unknown).

Influenza cases in intensive care

Through the continued collaboration with the Swedish Intensive Care Registry (SIR), we received reports of patients in intensive care with laboratory-confirmed influenza infections. Excluding cases treated in and reported from multiple intensive care units (duplicates) resulted in a total of 55 unique cases.

The median age of the patients were different for the three reported influenza types; it was lower for influenza A(H1N1)pdm09 and influenza B than for influenza A/H3N2 (Table 6). The age-distribution was similar to last season.

Forty-two patients (76%) belonged to a medical risk group. As in previous seasons, chronic heart-lung disease and immunosuppression were the most common risk factors. One patient with influenza A(H1N1)pdm09 was reported to be pregnant.

Antiviral treatment (oseltamivir or zanamivir) was given to 47 patients. The treatment start date was reported for 44 patients, of which 12 patients (27%) received treatment within three days of onset (median: 5 days, range: 0–13 days).

Forty-seven patients needed invasive or non-invasive ventilation, of which six received ECMO treatment. Fifteen were given an open or percutaneous tracheostomy.

Sixteen patients had a secondary bacterial infection. Sixteen patients (four of those with secondary bacterial infections) died within 30 days of hospitalization; fifteen of these patients had influenza A(H1N1)pdm09 and fourteen belonged to a medical risk group. They did not differ significantly in age compared to those who survived.

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	50	59.5 (7, 80)
A/H3N2	1	80 (-)
A, no subtype stated	3	63 (46, 71)
B	1	58 (-)
Total	55	60 (7, 80)

* The influenza type was only validated for A(H1N1)pdm09 cases, where cross-checking with SmiNet was possible through the personal identification number.

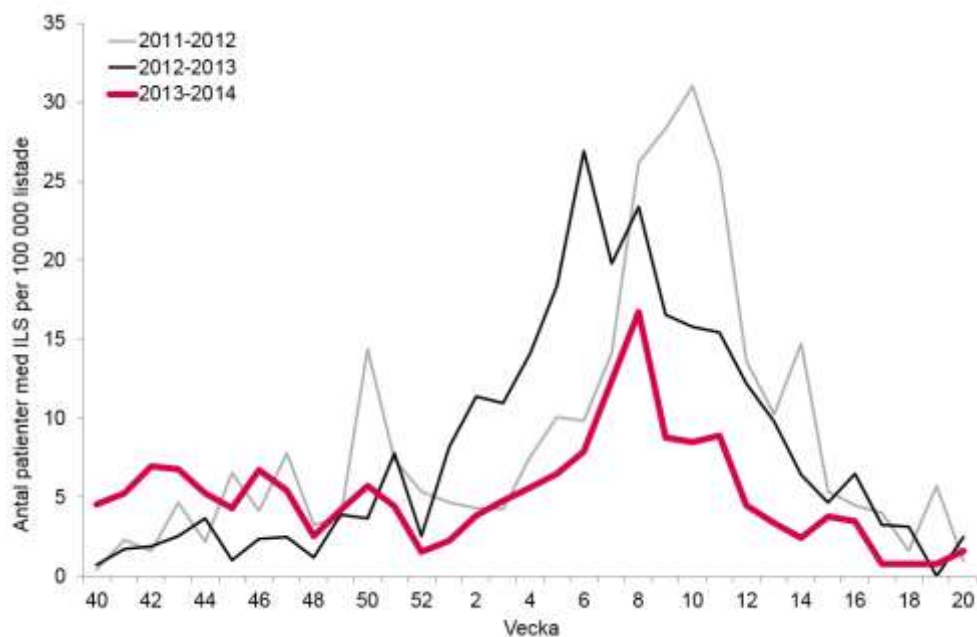
Sentinel surveillance

Sentinel reporting

In the 2013-2014 season, 81 GPs had agreed to participate in the sentinel surveillance, and this represented a combined catchment population of approximately 611,000 inhabitants. The sentinel physicians were distributed across Sweden, but five counties had no participating units. During the season, 72 GPs submitted reports. A median of 50 units reported each week. Week 49 of 2013 showed the highest participation in terms of catchment population with 58 units reporting. These represented 475,600 persons, or approximately 4.2% of the Swedish population. Week 52 of 2014 had the lowest participation rate, with only 26 units reporting. This represented a catchment population of 193,338 persons or slightly above 1.6% of the population.

In all, there were 658 reports of patients with ILI. Figure 7 shows the incidence of ILI each week. The incidence of ILI per 100,000 listed patients was about four times lower than the incidence of laboratory-confirmed cases. Despite the low number of reported cases, which is a poor indicator of the true level of influenza activity in the population, the shape of the sentinel graph corresponds well with the ones seen through other reporting systems (see also Webbsök, below).

Figure 7. Weekly number of patients with ILI per 100,000 listed patients of reporting sentinel units, 2010-2014.



Age distribution

The highest incidence of reported ILI from the sentinel surveillance system was seen in persons between the ages of 40 years and 64 years and the lowest was seen among persons above 65 years of age (Table 7). This was in contrast with the age distribution seen among laboratory-confirmed cases where the highest incidence was seen among persons between the ages of 0 years and 4 years closely followed by those above 65 years old.

This shows that those seeking health care through GPs are likely to be less vulnerable than those going directly to emergency departments. The sentinel reporting system, therefore, does not reflect the age-distribution of influenza cases well. Considering the health-seeking behaviour in Sweden, it is also likely that those who visit GPs are less ill than those who visit emergency departments.

Table 7. Number, distribution, and incidence per 100,000 population and age group of reported ILI cases and laboratory-confirmed influenza cases (all types) per age group, 2013-2014.

Age group (years)	ILI (Sentinel system)			Laboratory-confirmed influenza cases (all types)		
	Number	Proportion of total	Incidence	Number	Proportion of total	Incidence
0-4	34	5.2%	5.9	220	9.0%	38.0
5-14	43	6.5%	4.0	76	3.0%	7.1
15-39	218	33.1%	7.1	688	27.0%	22.5
40-64	294	44.7%	9.6	925	36.0%	30.1
65 and above	69	10.5%	3.7	676	26.0%	36.1
Total	658	100%	6.8	2,585	100.0%	26.8
number / Average incidence						

Sentinel sampling

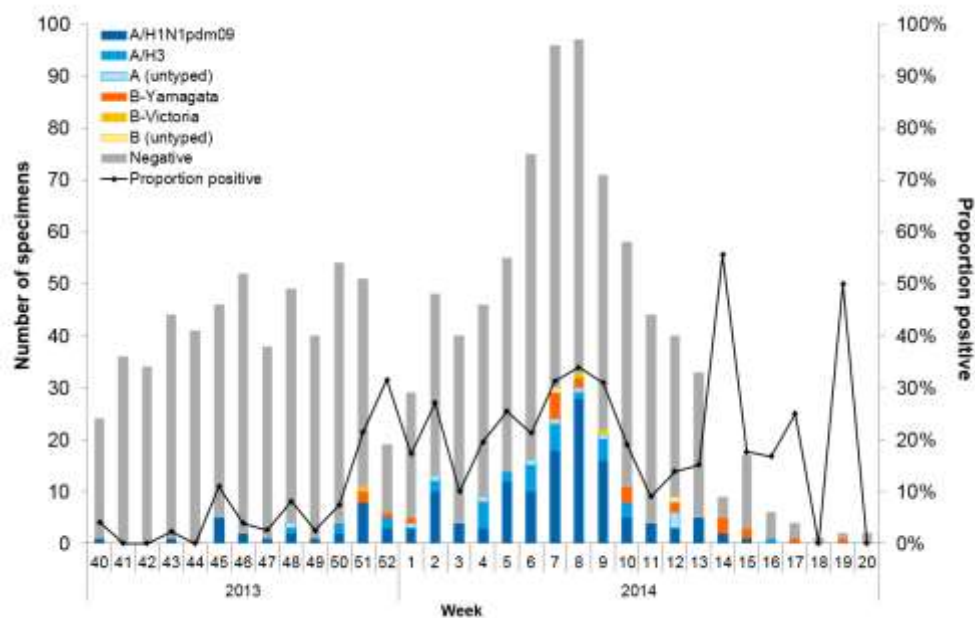
Virological findings

During the 2013-2014 season, which was mild, 1,302 sentinel samples were submitted from 83 GPs. The number of samples analysed was 41% lower compared to the previous season. In total, 220 samples (16.9%) tested positive for influenza, which was lower than the 29.3% seen during the preceding season.

Weeks 7–9 were the peak weeks and the number of positive samples peaked in week 8 at 34%. Influenza A(H1N1)pdm09 was the dominant subtype and co-circulated with A/H3 during the same period (weeks 4–10). The majority of the influenza B/Yamagata positive samples were diagnosed during weeks 7–15 (Figure 8).

Of the positive samples, 192 (87.3%) were positive for influenza A and 28 (12.7%) were positive for influenza B. Of the influenza A positives, 154 (80.2%) were influenza A(H1N1)pdm09 and 31 (16.1%) were influenza A/H3 (Figure 8). Eight influenza A samples could not be subtyped due to low virus concentration (all had Ct values in real-time PCR > 35). In total, 23 (82.1%) of the influenza B-positive samples belonged to the influenza B/Yamagata/16/88 lineage and 3 (10.7%) to the influenza B/Victoria/2/87 lineage. Two influenza B-positive samples could not be typed to any lineage due to low viral concentrations.

Figure 8. Number of sentinel samples submitted each week and the number and percentage of the positive samples by subtype/lineage, 2013-2014.



Age and gender distribution of sentinel samples

In total, 59.6% of the samples came from women, with a median age of 41 years, while the median age for males was 39.5 years.

The median age for the influenza A subtypes were similar to the last two seasons (Table 8). Like in previous seasons, the median age of influenza B/Yamagata-lineage cases was higher than that of the influenza B/Victoria-lineage cases, although the difference was not statistically significant in this season's data.

Clinical features

Of the patients sampled through the sentinel system, the vast majority had ILI (Table 8), and only a few had acute respiratory illness (ARI).

Table 8. Summary of laboratory results, median age and proportion of patients with ILI from the sentinel sampling system for the last three seasons.

	Season 2011-2012			Season 2012-2013			Season 2013-2014		
	Analyses	Median age (years)	ILI	Analyses	Median age (years)	ILI	Analyses	Median age (years)	ILI
Analysed	1,770			2,048			1,302		
Negative	1,424	40	83%	1,448	40	82%	1,082	41	84%
Proportion positive	19.5%			29.3%			16.9%		
Positive for influenza A	329			398			193		
A(H1N1)pdm09	12	34	83%	215	34	89%	154	37	94%
A/H3N2	316	35.5	92%	160	35	89%	31	35	100%
A, not subtyped	1	60	100%	23	38	86%	8	49.5	100%
Positive for influenza B	17			202			28		
B/Victoria lineage	9	5	100%	14	10.5	88%	3	15	100%
B/Yamagata lineage	7	44	86%	183	36	88%	23	51	100%
B, not typed to any lineage	1	31	100%	5	35.5	84%	2	65	86%

Vaccination status

Vaccination status was reported for 1,268 of the 1,302 patients sampled during the season. Of these, 71 were vaccinated (5.6%). A total of eight vaccine failures were detected: four in influenza A(H1N1)pdm09-positive patients (43-62 years old, median age 48.5 years), one in a patient with influenza A/H3N2 (76 years old), two among influenza B/Yamagata-positive patients (50 and 79 years old), and one in an influenza A-positive patient whose sample could not be subtyped (80 years old).

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/H3 within the sentinel system compared to the laboratory reporting system (Table 9).

Sentinel patients were also younger (Tables 4 and 8). 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 and instead visit primary care.

Table 9 Proportion of samples positive for different influenza types within the sentinel sampling system (*Sentinel*) and statutory and voluntary laboratory reporting systems (*Lab.*).

Influenza type	2011-2012		2012-2013		2013-2014	
	Sentinel	Lab.	Sentinel	Lab.	Sentinel	Lab.
A(H1N1)pdm09	3.5%	3.0%	37.6%	29.7%	73.1%	67.2%
A/H3N2	91.8%	93.9%	28.0%	35.4%	14.4%	24.6%
B/Victoria lineage	2.6%	1.5%	2.4%	1.9%	1.3%	0.6%
B/Yamagata lineage	2.1%	1.6%	32.0%	34.1%	11.2%	7.6%

Webbsök

From week 27, 2013, to week 26, 2014, about 64,000 queries related to *influenza* were submitted to the 1177 Vårdguiden search engine. This is 48,100 more than during the 2012-2013 season. The increase is an effect of the change of data sources from the regional www.vardguiden.se to the national www.1177.se.

As shown below, the Webbsök model gave similar results as the sentinel data, but gave a more accurate description of the epidemiological development in the beginning of the season (Figure 9). Furthermore, Webbsök also matched the development of the reported laboratory-confirmed cases with a one week lead both at the start of the season (week 47) and at the peak (Figure 10).

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

Figure 9. Webbsök's estimated proportion of the population with ILI per week compared to the incidence estimates from the sentinel reporting, 2013-2014.

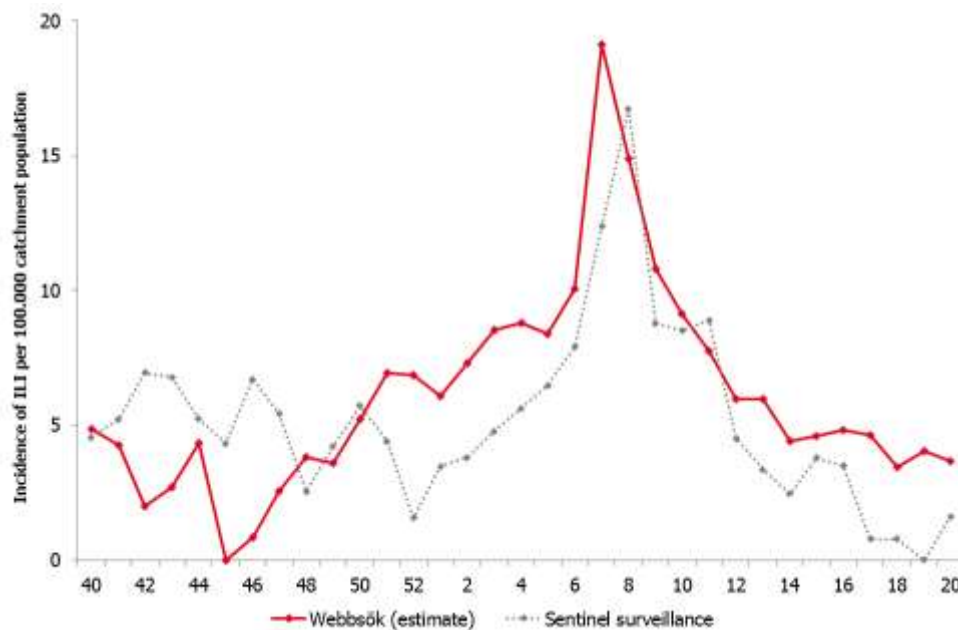
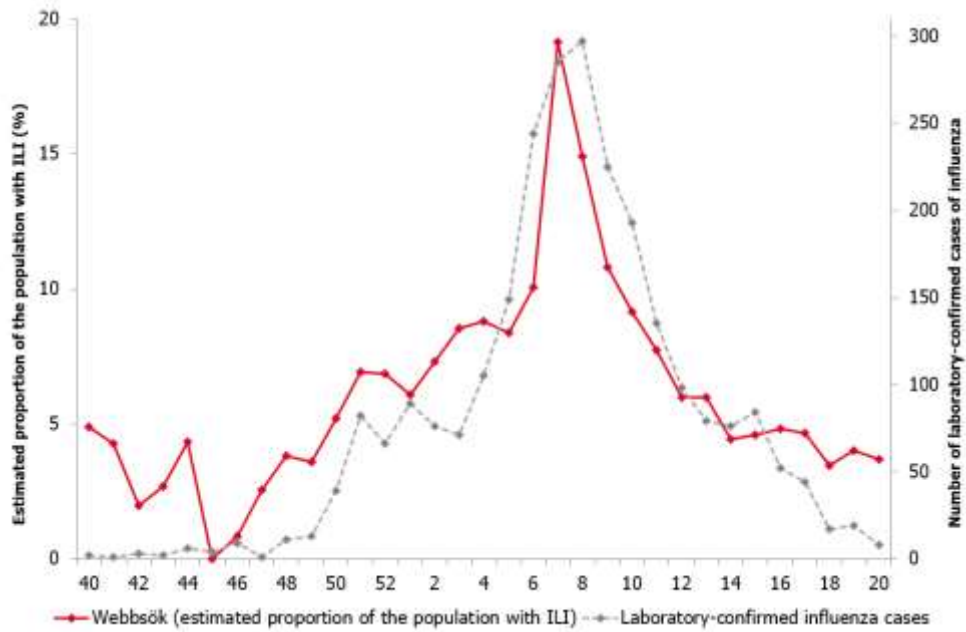


Figure 10. Webbsök's estimated proportion of persons with ILI and number of laboratory-confirmed cases, 2013-2014. The axes have been adjusted to highlight the matching development of the two systems.



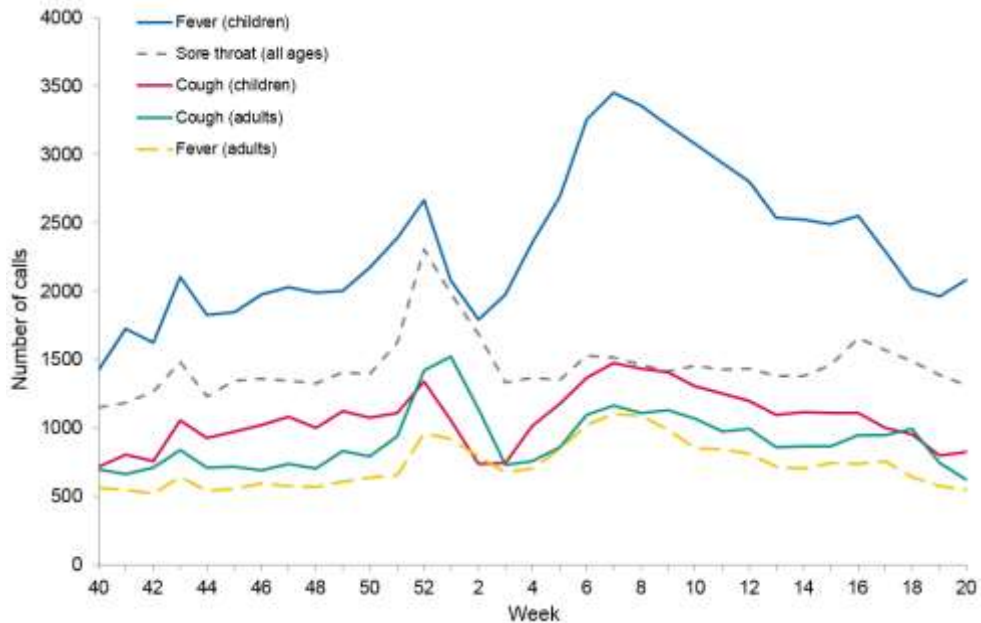
Telephone advice line

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.

Like in the three past seasons, fever in children was the most common cause for contact in connection with the influenza peak and was the symptom with the most noticeable peak at week seven (Figure 11). The number of calls regarding fever in children was lower by 23% compared to season 2012-2013. The symptom "sore throat" did not reflect influenza activity very well.

The peak in calls seen around Christmas, followed by a drop, occurs every year. The reason is possibly a decreased access to face-to-face health care services during the holidays leading to an increase in telephone consultations.

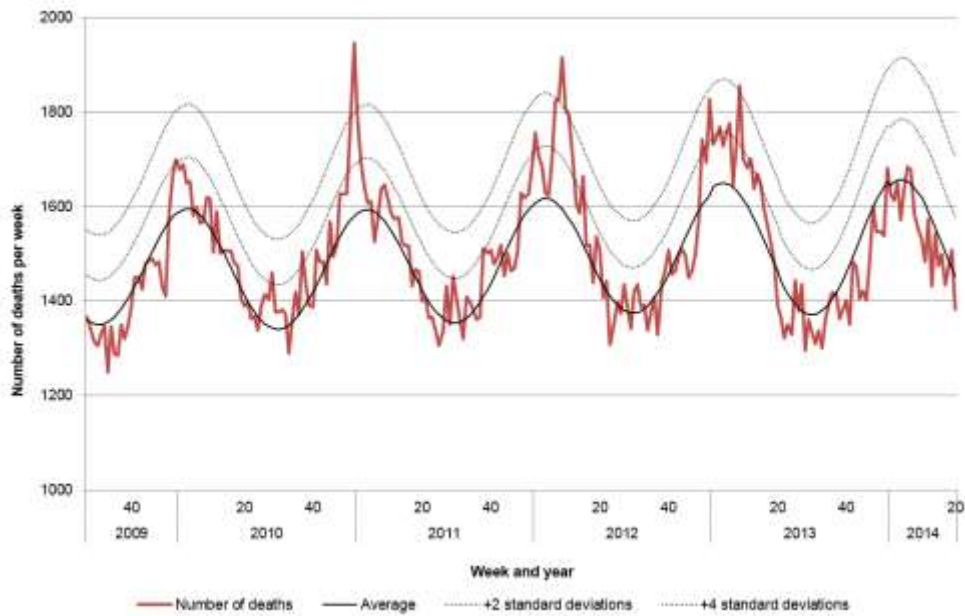
Figure 11. Number of telephone calls regarding influenza-related symptoms received by the medical advice line 1177, 2013-2014.



Crude excess mortality

During the 2013-2014 season, there was no excess mortality among persons 65 years and older (Figure 12). The slight excess mortality seen in the 15–64 year age group last year was not observed this season (results not shown).

Figure 12. Number of deaths per week among persons 65 years and older in Sweden from week 40, 2009, to week 20, 2014.



Virological data

Determination of subtype and lineage

In total, 169 of the influenza A positive A(H1N1)pdm09 negative samples were subtyped to influenza A(H3N2). Twenty-six influenza B-positive samples were typed according to lineage: 24 were influenza B/Yamagata, and 2 influenza B/Victoria. (Table 2).

Characterisation results

The number of sequenced gene segments for each subtype in the 2013-2014 season is shown in Table 10.

Table 10. Number of sequenced gene segments, 2013-2014

Subtype/Lineage	Gene Segment	Number of sequenced viruses
A(H1N1)pdm09	HA	45
	NA	48
	M	49
	NS1	3
	PB2	3
A(H3N2)	HA	26
	NA	23
	M	22
B/Yamagata	HA	17
	NA	13
	M ^a	18
B/Victoria	HA	0
	NA	4 ^b
	M ^a	2

HA - Hemagglutinin. NA - Neuraminidase. M - Matrix protein. NS1 - Non-structural protein 1. PB2 - Polymerase basic 2.

^a Matrix gene target sequence for real-time PCR.

^b Yamagata HA/Victoria NA reassortants

Characterisation of influenza A(H1N1)pdm09

All the A(H1N1)pdm09 viruses of which the HA gene have been sequenced belong to genetic subgroup 6B. One virus, which was sampled before the start of the season, clustered to subgroup 6C (Table 11 and phylogenetic tree in Appendix 1). Two viruses from vaccinated persons (aged 42 and 62 years) were sequenced, and both belong to subgroup 6B (marked as “Vacc” in the phylogenetic tree in Appendix 1). In Europe, viruses circulating during season 2013-2014 have belonged to subgroup 6B and 6C, with viruses in subgroup 6B predominating. Viruses in both of these subgroups have been shown to be antigenically similar to the vaccine virus A/California/07/2009⁵, including the six Swedish strains that were analysed with HAI by the WHO CC in London.

⁵ ECDC. [Surveillance Report, Influenza in Europe Season 2013-2014](#)

None of 48 viruses in which the NA gene was sequenced had any of the mutations known to result in reduced or highly reduced inhibition to NA inhibitors. An additional 82 viruses were analysed with real-time PCR with respect to the H275Y mutation associated with highly reduced inhibition to oseltamivir, but none of them carried this substitution. Twelve viruses were also analysed phenotypically by NAI assay, and all of them were sensitive to oseltamivir and zanamivir. Five of these viruses, and one additional, were also tested by the WHO CC in London with concordant results. In Europe, 1,216 influenza A(H1N1)pdm09 viruses have been analysed for susceptibility to NA inhibitors, of which 15 were carrying the H275Y mutation⁵. Like the previous season, all analysed influenza A(H1N1)pdm09 strains carried the S31N amantadine-resistance substitution in the M2 gene.

No amino acid substitutions associated with increased virulence were detected in the genes for NS1 and PB2 in three viruses from patients with severe disease (treated with ventilator or ECMO). Nor did these three viruses have any amino acid exchanges in position 222 of HA. All samples were however from the upper respiratory tract. In a virus from a patient who was not severely ill, mutation D222N associated with cases of severe disease possibly due to increased affinity for receptors in the lower respiratory tract, were found in virus from the upper respiratory tract.

Table 11. Distribution of Swedish influenza A(H1N1)pdm09-strains into genetic groups.

Genetic group	Number of viruses	Key substitutions (relative to A/California/7/2009)
Subgroup 6B (A/Norway/2417/2013)	44	K163Q, K283E, A256T
Subgroup 6C (A/Estonia/76677/2013)	1	V234I, K283E
Total	45	

Characterisation of influenza A/H3N2

All the A/H3N2 strains that have been sequenced for HA in Sweden belong to genetic subgroup 3C, with viruses in genetic subset 3C.3 predominating over those in subset 3C.2 (Table 12 and phylogenetic tree in appendix 2). The same pattern is seen among the characterized European viruses, and analyses indicate that the majority of circulating viruses are antigenically similar to those of season 2012-2013⁵.

Nine Swedish viruses have been antigenically characterized by the WHO CC in London. In seven of these there was no evidence for antigenic drift. One of the viruses, influenza A/Stockholm/18/2013 (in genetic subset 3C.2), reacted poorly against the panel of test viruses. The reason for this is suspected to be a P221L mutation that was seen in the virus grown on cell culture but not in the direct material, thus this could well be an artefact of cell culturing. The other virus showing signs of antigenic variation in comparison to recently circulating viruses was A/Stockholm/6/2014 in subset 3C.3. This virus belongs to an emerging group of viruses, 3C.3a, with the characteristic amino acid changes A138S, F159S, and N225D in HA1. Viruses in this new cluster have been reported at an increasing

frequency by WHO CCs in North America and Asia⁵. A/Stockholm/6/2014 was isolated from a person who had recently travelled to Hong Kong. One additional family member was infected with the same strain and was simultaneously infected with an A(H1N1)pdm09 strain. Three of the Swedish strains in subset 3C.3 (A/Stockholm/22/2013, A/Gavle/1/2014, and A/Stockholm/12/2014) that have been genetically characterised have the mutations S122D and L157S in HA. These mutations are both located in antigenic sites and have been speculated to account for suboptimal vaccine effectiveness in Spain according to a preliminary study.⁶ The vaccination status of the three Swedish patients is unknown.

All the A/H3N2 strains were NA subtype 2. None of the 23 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. Six of these viruses were also tested by the WHO CC in London with concordant results. In Europe, 419 A/H3N2 viruses were tested for susceptibility to neuraminidase inhibitors. One virus carrying the E119V mutation in NA showed reduced inhibition by Oseltamivir and normal inhibition by zanamivir in phenotypic testing. This virus carried the E119V amino acid substitution and showed reduced inhibition by oseltamivir and normal inhibition by zanamivir⁵. Like in the previous season, all analysed influenza A/H3N2 viruses carried the S31N amantadine-resistance substitution in the M2 gene.

Table 12. Distribution of Swedish influenza A(H3N2) strains into genetic groups.

Genetic subset	Number of viruses	Key substitutions (relative to A/Perth/16/2009)
Subset 3C.2 (A/Ireland/M28426/2013)	10	Q33R, N145S, N278K
Subset 3C.3 (A/Samara/73/2013)	16	Q33R, T128A, R142G, N145S, N278K
Total	26	

Screening for H3N2v

The A/H3N2v strain was first identified in pigs in the USA in 2010. Twelve further human cases of A/H3N2v infection were detected there in 2011, another 309 cases in 2012, and an additional 19 cases in 2013. These infections have mostly been associated with prolonged exposure to pigs at agricultural fairs. Limited human-to-human spread of this virus has been described. Most A/H3N2v infections in the USA have occurred in children.

A total of six A/H3N2-positive samples from Swedish children 10 years and younger were analysed by real-time PCR discriminating between A/H3 and A/H3v. All tested samples were negative for A/H3N2v.

⁶ [Eurosurveillance, Volume 19, Issue 9, 06 March 2014](#)

Characterisation of influenza B

A total of 54 influenza B-positive samples (including the 28 influenza B-positive samples collected through the sentinel system) were further analysed by lineage-specific real-time PCR. Of these, 5 were B/Victoria-like and 47 were B/Yamagata-like. Two of the influenza B positive samples could not be analysed due to low amount of virus in the clinical samples.

Further analysis of 17 B/Yamagata-like strains by sequencing of the HA gene showed that these belonged to two different clades, with viruses in clade 3 predominating over those in clade 2 (Table 13 and phylogenetic tree in appendix 3). In Europe, viruses in these two clades have been detected in similar numbers, but viruses in clade 3 have been predominating in samples collected in 2014⁵. Antiserum generated against the cell-generated variant of the vaccine strain B/Massachusetts/02/2012 in clade 2 has been shown to react well against the majority of the circulating B/Yamagata viruses, including two of the three Swedish B/Yamagata virus (clade 2) that was antigenically characterized by the WHO CC in London. Antiserum generated against the previous vaccine virus B/Wisconsin/01/2010 (in clade 3) have reacted well against the majority of the tested European viruses^{7, 8, 9, 10}. Four of the viruses with HA belonging to B/Yamagata lineage clade 3 were reassortants with NA genes belonging to the B/Victoria lineage. Several such viruses displaying such an HA/NA reassortment have been reported^{9, 10}.

Table 13. Distribution of Swedish B/Yamagata like-strains into genetic clades.

Genetic clade	Number of viruses	Key substitutions (relative to B/Florida/4/2006)
Clade 2 (B/Massachusetts/02/2012)	2	R48K, P108A, T181A
Clade 3 (B/Wisconsin/1/2010)	15	S150I, N165Y, G229G
Total	17	

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 17 analysed viruses. In Europe, all of the 78 viruses screened for susceptibility to NA inhibitors were sensitive to both oseltamivir and zanamivir⁵. Two viruses were also analysed phenotypically by NAI assay, and both were sensitive to oseltamivir and zanamivir. One additional virus tested by the WHO CC in London was sensitive to both antivirals.

The retrieved B/Victoria samples all contained viruses in low copy and could not be further characterised by HA or NA gene sequencing or phenotypic analysis of susceptibility to NA inhibitors.

⁷ ECDC. Influenza virus characterisation. Summary Europe, February 2014

⁸ ECDC. Influenza virus characterisation. Summary Europe, March 2014

⁹ ECDC. Influenza virus characterisation. Summary Europe, May 2014

¹⁰ ECDC. Influenza virus characterisation. Summary Europe, June 2014

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. 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 2013-2014 season, a new probe was validated and implemented in the H1pdm09 PCR system. 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. The Public Health Agency furthermore 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.

Avian influenza A/H7N9

In March 2013, the Chinese Centre for Disease Prevention Control and Prevention confirmed three human cases of an avian influenza A(H7N9) that had not previously been shown to cause disease in humans. As soon as it was available, the Public Health Agency received H7N9 virus and viral RNA from the WHOcc in London. An influenza A(H7N9) specific real-time PCR was set up, evaluated and implemented using the RNA as a positive control.

During the fall of 2013, the Public Health Agency contacted the Swedish laboratories and offered inactivated H7N9 control material to allow the labs to test their capacity to detect this avian flu strain with their regular influenza A PCR protocol. The laboratories that use the PCR system established by the Public Health Agency were informed that their influenza A system detected H7N9.

Ten regional laboratories asked for control material. Seven of these reported successful detection of H7N9, two detected virus in one of two different PCR sets, and one could not detect H7N9 at all. Two of the three failures were seen when a commercial “rapid PCR” kit was used.

External quality assurance programmes

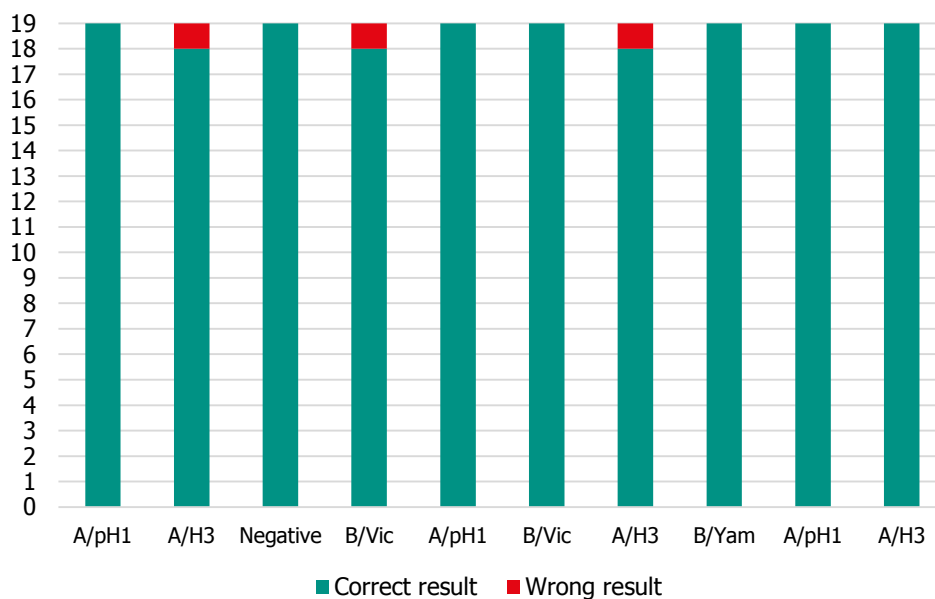
The Public Health Agency participates in the following external quality assurance (EQA) programmes:

1. The annual WHO EQA for influenza A. The result for 2013 was 8/10 correct results; one A/H9-positive sample gave a false negative result and one A/H5 sample was detected as influenza A positive, but its subtype could not be identified.
2. The INFRNA panel from Quality Control for Molecular Diagnostics (QCMD). The result for 2013 was 12/12 samples correctly typed. Three samples could not be subtyped due to low viral concentration in the samples.
3. The ERLINet influenza virus EQA program 2013. 10/10 correct results.

National quality assurance programme

All regional laboratories in Sweden perform influenza A and influenza B PCR and a subtype-specific A(H1N1)pdm09 PCR. Three regional laboratories also perform an A/H3 PCR. In September 2013, SMI (currently the Public Health Agency of Sweden) produced a PCR panel for the Swedish laboratories. This was made on behalf of the External Quality Assessment for Clinical Laboratory Investigations (EQUALIS). Nineteen laboratories participated in the EQA and eighteen of these reported 10/10 correct answers (Figure 13). This is an increase compared to 2012 when seventeen laboratories reported 10/10 correct answers. One laboratory reported three false negative results.

Figure 13. Results of the Swedish EQA panel 2013.



Vaccination coverage

The rough estimate of the national average vaccination coverage among persons 65 years and older for the past ten seasons is presented in Table 14. As shown, vaccination coverage experienced a drop during season 2010-2011, probably due to the reports of severe side effects (narcolepsy) among younger persons caused by the pandemic vaccine (Pandemrix). Vaccination coverage decreased further in the following seasons. However, in the 2013-2014 season there was a slight increase in vaccination coverage, from 44% to 46%, indicating that the downward trend might now be broken, although the 75% vaccination target is still far from being achieved.

Table 14. Mean yearly proportion of vaccinated persons older than 65 years in Sweden, as estimated by the 21 county medical officers.

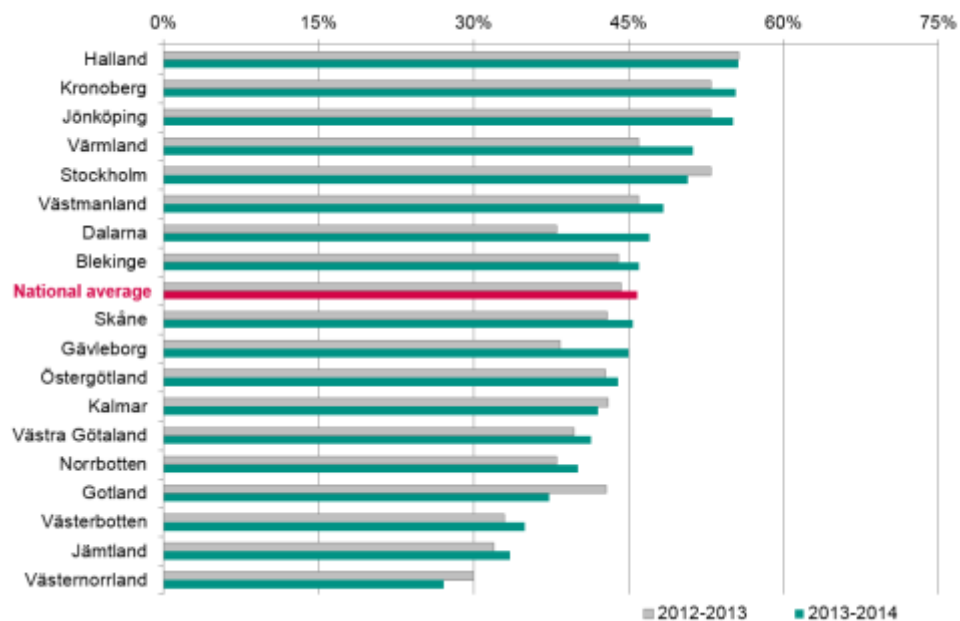
Season for vaccination	Estimated proportion of the population above 65 years old vaccinated with seasonal vaccine (%) *
2003-2004	51
2004-2005	55
2005-2006	61
2006-2007	56
2007-2008	60
2008-2009	65.8
2009-2010	44 **
2010-2011	55.2
2011-2012	46.1
2012-2013	44.2
2013-2014	45.8

* Please note that the figures have been adjusted for season 2010-2011 compared to previous annual reports in light of new information.

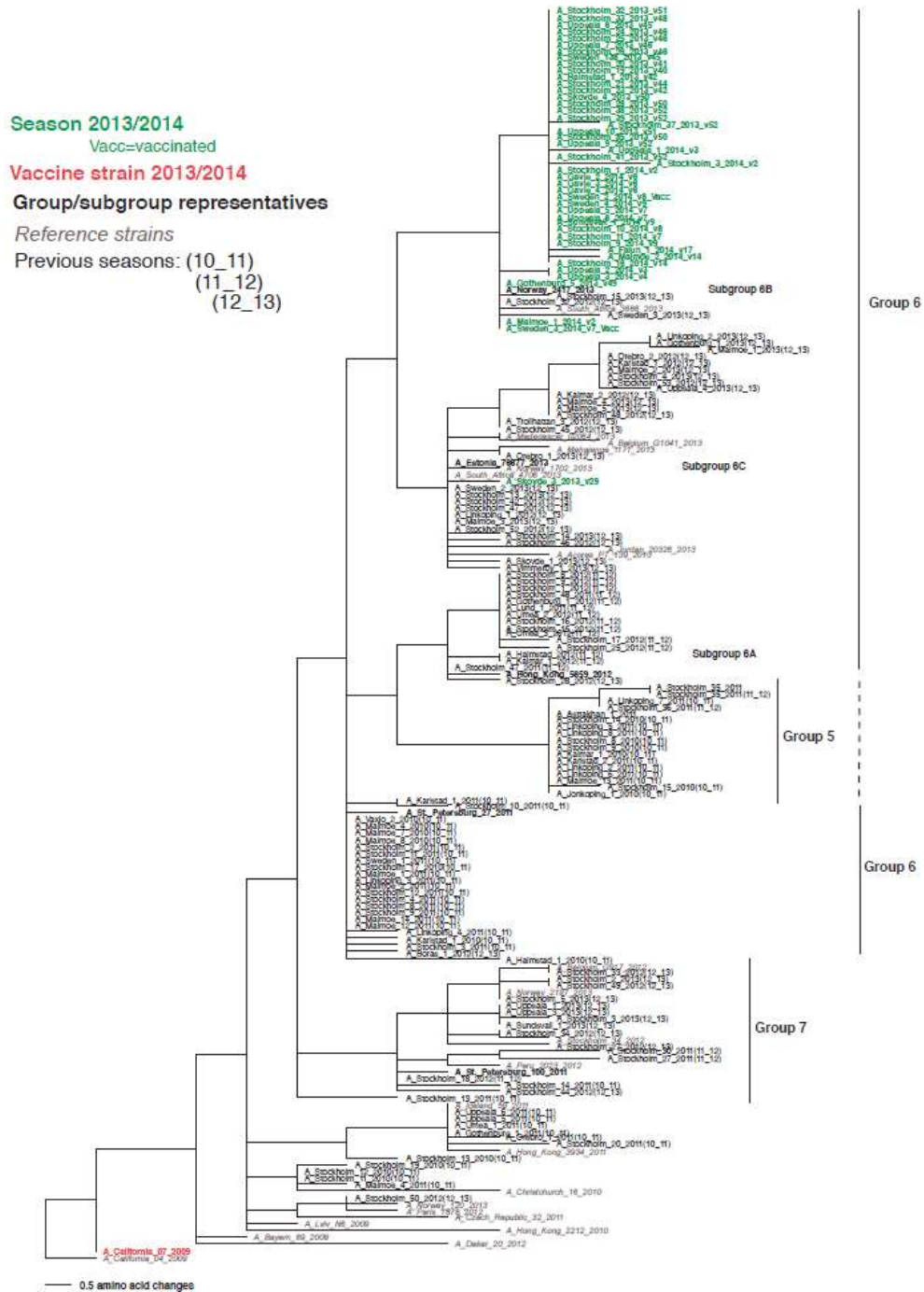
** Very few counties reported seasonal vaccination coverage in 2009 because the focus was on the pandemic vaccination. Sixty per cent of the Swedish population was vaccinated with an adjuvanted monovalent vaccine in 2009.

Vaccination coverage differed between county councils, with the highest estimated coverage being in Halland (56%) and the lowest in Västernorrland (27%), and this was the same as last season (Figure 14). Three county councils were not able to estimate the coverage, but their impression was that the trend in coverage was increasing in their counties as well.

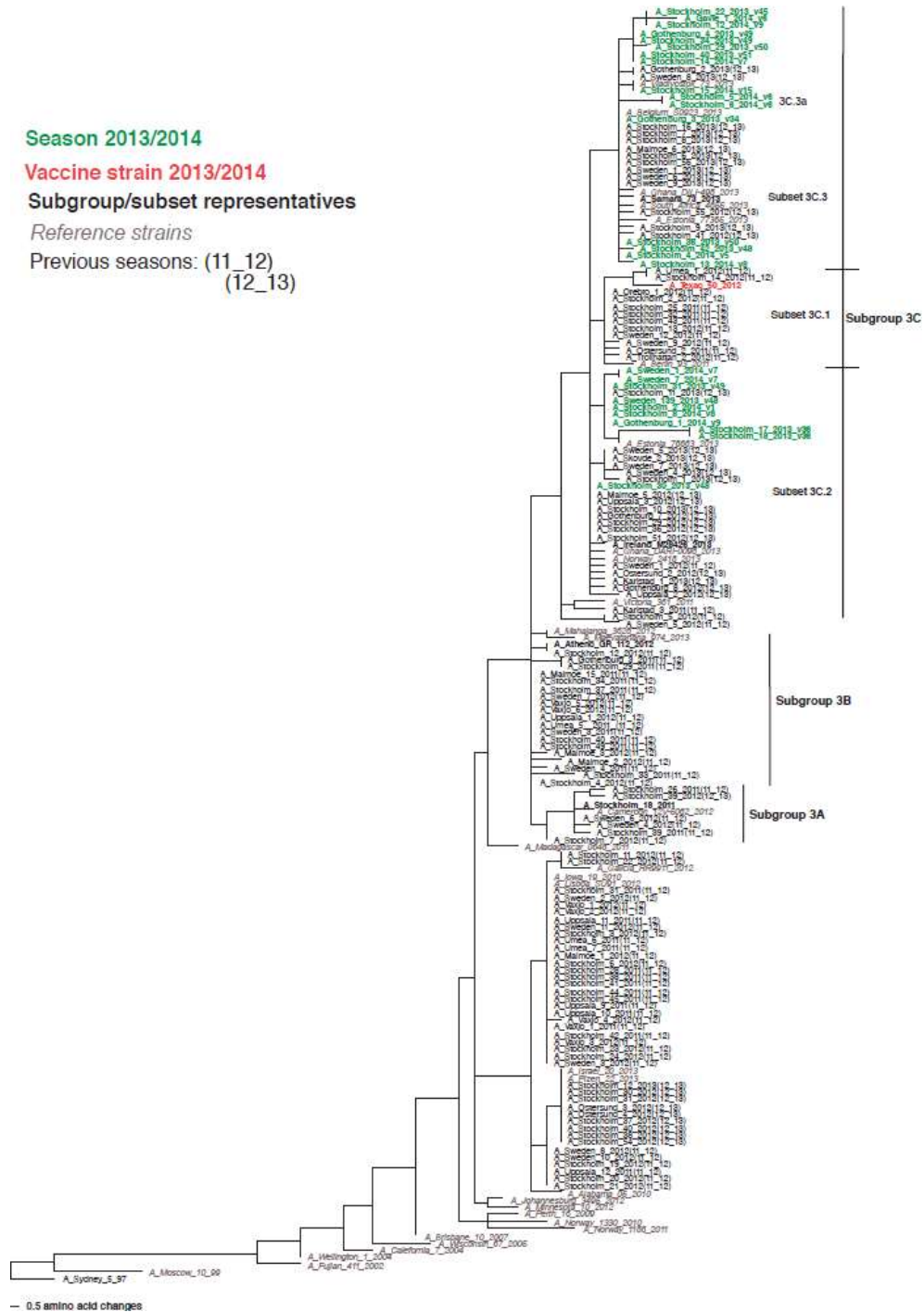
Figure 14. Estimated proportion of vaccinated persons above 65 years old per county council in Sweden, seasons 2012-2013 and 2013-2014. (Data is missing from the county councils of Sörmland, Uppsala, and Örebro.)



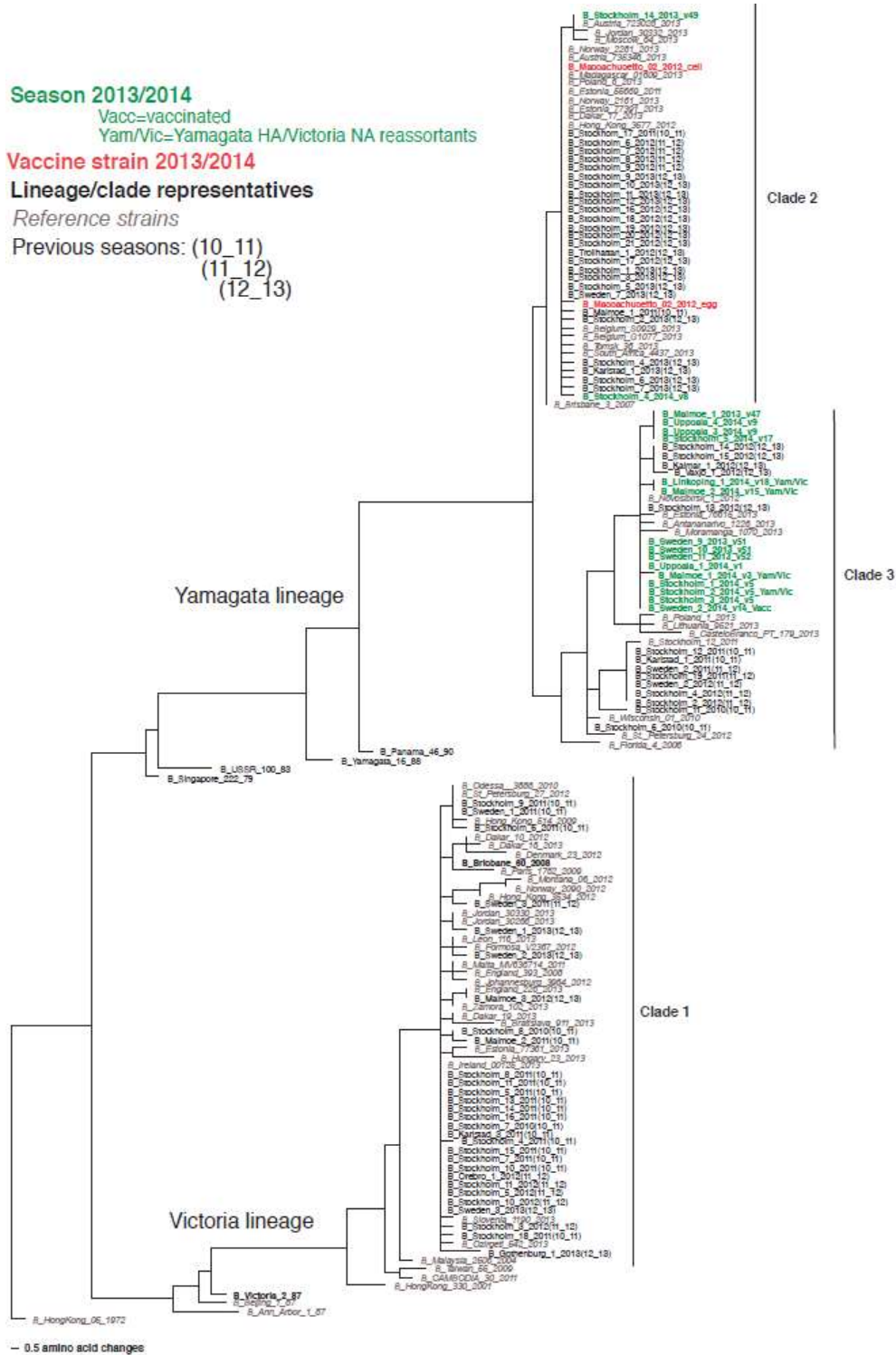
Appendix 1. Phylogenetic tree of the amino acid sequence for hemagglutinin (HA1), influenza A(H1N1)pdm09



Appendix 2. Phylogenetic tree of the amino acid sequence for hemagglutinin (HA1), influenza A(H3N2)



Appendix 3. Phylogenetic tree of the amino acid sequence for hemagglutinin (HA1), influenza B



The report describes the monitoring systems for influenza in use during the winter season of 2013-2014 and the results of both epidemiological and virological surveillance. Data are also compared to previous influenza seasons.

The influenza season of 2013-2014 was relatively mild in Sweden, but still affected a lot of people severely.

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).



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