Influenza in Sweden

Season 2011-2012
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Preface

Each winter, influenza epidemics of different magnitudes occur. Depending on the characteristics of the circulating viruses and the immunity towards them in different age groups, people and society are affected in different ways. If the elderly are affected, many get severely ill, leading to a great strain on hospitals and excess mortality. Small children may also need hospital care but deaths are rare. Slightly older children handle influenza infection fairly well but extensive care of a sick child may lead to substantial absence from the work place for the parents.

If a new strain of influenza was to emerge and create a pandemic it could lead to such an extensive absence of the working population that it would constitute a threat to important public functions. New influenza strains can be very aggressive and cause severe illness, leading to 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) has 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 web. In order to assess immunity to an expected virus in different age groups, SMI conducts yearly studies of influenza-specific antibodies in blood samples.

Virological surveillance is at least as important as epidemiological surveillance. When new strains of the influenza virus emerge, reference methods for diagnostics are established at SMI. Viruses from around the country are characterized with regard to vaccine resemblance, sensitivity to antivirals and other factors that may affect the severity of the infection they cause.

This report describes the monitoring systems in use during the winter season 2011-2012 and the results of both epidemiological and virological surveillance. Data are analyzed in relation to data from earlier influenza seasons and the measures taken to limit the consequences of the epidemic. Some international data are also included.

Annual influenza reports in English have been available since 2000, and may be found on SMI’s website.¹

¹ http://www.smittskyddsinstitutet.se/publikationer/arsrapporter-och-verksamhetsberättelser/smis-arsrapporter-om-influenzasasongen/
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Summary

The second post-pandemic season in Sweden (2011-2012) was dominated by a late and intense return of seasonal influenza A(H3N2), which hit the elderly very hard. A low rate of vaccine coverage of around 50 percent in the elderly and low effectiveness of the vaccine probably aggravated the outbreak. The outbreak also affected Norway, but the severity seen in Sweden was otherwise unique in Europe. Excess mortality was estimated at around 1000 persons, of which 75 percent were above 85 years of age.

A total of 4859 laboratory-confirmed diagnoses of influenza were reported during the season. Of these, 4546 (94 percent) were seasonal influenza A. Subtype H3N2 was identified in all strains of seasonal influenza A that were examined. In total, 160 (3 percent) were influenza A(H1N1)pdm09 and 153 (3 percent) were influenza B. More than half of the cases of diagnosed seasonal influenza A were in persons above 65 years of age, and many hospitals were under heavy pressure at the peak of the outbreak due to the high number of elderly with influenza.

All strains of influenza that were characterised at SMI fell into different genetic groups containing viruses antigenically indistinguishable from the vaccine strain, despite the low efficacy against influenza A(H3N2) noted in Sweden and elsewhere. No resistance to the type of antivirals recommended in Sweden was found.
Monitoring and reporting systems

The influenza pyramid (Figure 1) illustrates the different ways that influenza affects those who are infected. A portion of infected people do not get any symptoms, while others get sick but simply stay home or continue with their daily activities. Of those sick, a portion seek healthcare, and a portion of these are so ill that they are hospitalised. Finally, some of the ill require intensive care, and a small portion die as a result of influenza infection. Table 1 describes the data collection systems that we have used to monitor flu activity from the base of the pyramid to the top.

Figure 1. The “influenza pyramid” showing possible outcomes of an influenza infection.
Table 1. Description of all systems used for monitoring of influenza activity during the 2011-2012 season from week 40, 2011, to week 20, 2012.

<table>
<thead>
<tr>
<th>Reporting system/method</th>
<th>Implementation</th>
<th>What does the system/method show?</th>
<th>Number/percentage reported during the season</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Statutory Laboratory Reporting of Cases of Influenza A(H1N1)pdm09</td>
<td>Duty for all laboratories to report influenza diagnoses along with identity in the web-based reporting system, SmiNet, in accordance with the Communicable Diseases Act.</td>
<td>Number of laboratory-confirmed cases of influenza A(H1N1)pdm09</td>
<td>145 cases. (Another 10 cases without full identity have been reported in the voluntary systems, and 155 cases are included in the total in tables and figures in the report)</td>
</tr>
<tr>
<td>2. Statutory Clinical Reporting, all Hospitalised Cases of A(H1N1)pdm09</td>
<td>Hospitalised cases must be clinically reported. Risk group, vaccination status and level of care are requested but the information is voluntary.</td>
<td>Number of hospitalised cases (along with symptoms, risk group, vaccination status and level of care, though information is incomplete)</td>
<td>42 of 145 laboratory-confirmed cases were reported to have been hospitalised</td>
</tr>
<tr>
<td>3. Intensive Care Data for A(H1N1)pdm09</td>
<td>Voluntary supplement to the statutory reporting form.</td>
<td>Severity of the disease based on level of care (intensive care, respirator, extracorporeal membrane oxygenation, ECMO)</td>
<td>5 out of the 42 hospitalised patients (11%) were reported in intensive care</td>
</tr>
<tr>
<td>4. Aggregate laboratory reporting and denominator data</td>
<td>Weekly reports from laboratories to SMI on the number of samples that have been analyzed for influenza and the proportion of positive samples.</td>
<td>Number of positive samples and denominator data for calculating the proportion of influenza-like illness (ILI) caused by influenza virus.</td>
<td>22,283 analyzed samples of which 4,840 (22%) tested positive. 4532 for seasonal influenza A, 160 for A(H1N1)pdm09 and 148 for influenza B.</td>
</tr>
<tr>
<td>5. Deaths. Duty to Report /Record Search, A(H1N1)pdm09</td>
<td>Duty for pathologists to report deaths due to A(H1N1)pdm09, in accordance with the Communicable Diseases Act.</td>
<td>Number of deceased</td>
<td>No deceased patients identified</td>
</tr>
</tbody>
</table>
| Section | Description | Proportion of the catchment population that visits their general practitioner for ILI. | In total, 1,144 of 645,000 listed persons (0.18%) had visited a sentinel doctor due to ILI.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Sentinel Surveillance</td>
<td>Selected general practitioners report the number of patient experiencing ILI each week. Approximate catchment population (“listed persons”) is reported in the beginning of the season.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Sentinel Sampling</td>
<td>Samples from some of the ILS patients in the sentinel surveillance system are analyzed by SMI for influenza.</td>
<td>The proportion of sentinel patients with ILI who have influenza infection</td>
<td>1706 samples analyzed of which 334 (19.6%) tested positive for influenza</td>
</tr>
<tr>
<td>8. Virus Characterization</td>
<td>Continual characterization of laboratory samples positive for influenza. Characterization through genotypic assays.</td>
<td>Viruses’ vaccine resemblance and possible resistance to antivirals</td>
<td>108 strains were characterized for vaccine resemblance and 73 for antiviral resistance. All strains resembled into different genetic groups containing viruses antigenically not distinguishable from the vaccine strains and no strain was resistant to the approved antivirals</td>
</tr>
<tr>
<td>9. Population-based Surveillance: “Sjukrapport”</td>
<td>A population-based, cohort study in Stockholm where the participants report respiratory infections via telephone or web. Their symptoms determine if they have ILI or acute respiratory infection (ARI). Approximately 2,700 participated 2010-2011.</td>
<td>Provides an estimated number of people in Stockholm who fall ill with ARI and ILI each week</td>
<td>Number with ARI: 2,250. Number with ILI: 772 Average cumulative incidence per week: 2.67 % ARI, 0.92 % ILI</td>
</tr>
<tr>
<td>10. “Webbsök” (Web Search)</td>
<td>An automated system that uses search data from the medical advice site Vårdguiden.se. The number of searches on influenza and influenza symptoms are entered into a statistical model which estimates the proportion of patients with ILI.</td>
<td>Works as a complement to sentinel reporting</td>
<td>Between week 27/2011 and week 26/2012, more than 15,000 searches including the word influenza were conducted.</td>
</tr>
</tbody>
</table>
11. Sero-epidemiology

Serologic analysis for haemagglutination inhibiting (HI) antibodies to A(H1N1)pdm09 on representative serum samples from May 2011.

Proportion by age group with HI antibodies

52% of the population sampled in May 2011 had antibodies. The proportion was highest among children 3-14 years old and lowest among those aged 0-1 years.

12. Vaccination Coverage

Report from the County Medical Officers of Communicable Disease Control (Smittskyddsläkarna) – on the proportion of seasonally vaccinated persons over the age of 65. Different methods of calculation were in different counties.

A rough estimate of the proportion of those over 65 who were vaccinated against seasonal influenza

Average vaccine coverage in the age group 65+ was estimated to be 44% (Smittskyddsläkarna)

13. Telephone Advice Line (1177)

Weekly data on the primary reason for contacting the medical advice line (phone number 1177), as well as the age group, is manually transferred to SMI. 14 county councils are connected to the service.

Primary reason for calling by age group (adults and children)

~327,000 calls regarding one of the following: breathing difficulties, fever, sore throat or coughing, from week 40 2011 to week 20 2012.

Statutory reporting of influenza A(H1N1)pdm09

When A(H1N1)pdm09 was identified in 2009, statutory reporting in accordance with the Communicable Diseases Act was approved by the Swedish Parliament. During the 2010-2011 and 2011-2012 seasons, the mandate remained for microbiological laboratories to report all verified cases. A clinical report was mandatory for patients who had been admitted to hospital. The reporting was done through SmiNet. In addition to identity, age, date of disease onset, and diagnosis, the clinical report form requested information on risk groups, level of care and vaccination status. Unfortunately, these forms were often incompletely filled during the season.

Sentinel surveillance

A selection of Sweden’s general practitioners act as sentinels, or informants, within the influenza surveillance system covering Swedish outpatient care. Each week, they send information via SmiNet on the number of patients with influenza-like illness (ILI) they have examined during the past week. At the beginning of the season, they also report how many patients belong to their catchment area (also referred to as listed persons).
Sentinel surveillance in Sweden is generally done in accordance with the recommendations developed by the influenza monitoring group of the European Centre of Disease Prevention and Control (ECDC), the European Influenza Surveillance Network (EISN). However, we receive a relatively low number of reports compared with other countries. This may be because influenza patients can be on sick leave for a week without a doctor's certificate in Sweden, or because patients turn to emergency departments rather than their general practitioners when their influenza illness is severe enough to warrant medical care. Despite the low numbers of reported cases, the shape of the sentinel graphs corresponds well with the ones we see through other reporting systems.

**Sentinel sampling**

It is difficult to diagnose a case of influenza based solely on the patient's symptoms. An ILI is not always caused by influenza, and other epidemics that lead to ILI are sometimes misconstrued as influenza epidemics. In order to estimate how large a proportion of the patients seeking care for ILI actually have influenza, nasal samples are taken from some of the patients seen through the sentinel system. Influenza diagnostics are carried out free of charge at SMI and the material is also used to characterize the circulating strains of influenza.

**Sjukrapport**

In an attempt to map illness in the general population outside the health care system, SMI has been operating the population-based surveillance system, *Sjukrapport* (roughly, “illness report”), since the 2007-08 season. Each year, between 12,000 and 15,000 residents of Stockholm County are invited to report when they fall ill with acute respiratory infection (ARI) or fever, providing their full identity. The reporting is done via automated telephone service or the web. When reporting, the participant answers questions regarding symptoms, such as coughing, fever and muscular pain that could be signs of influenza. The system classifies the reported symptoms as ILI or ARI, according to adapted European Commission case definitions.

The results of the reports are presented weekly on the web as graphs showing the proportion of the participants reporting ILI or ARI. By comparing this data with the proportion of ILI patients with a positive result in the sentinel sampling (see below) for each week, we can also produce an estimate of the proportion of people that has fallen ill with influenza in the community. Age and gender distribution can be controlled since the participants provide their full identity upon registration.

**Webbsök (web search)**

Webbsök is an automated system using completely anonymous data from the medical advice website *Vårdguiden* (www.vardguiden.se) to estimate the development of the sentinel reporting in a statistical model. The system was established in 2008. Data is received daily and Webbsök provides an estimate of influenza activity as much as a week earlier than the sentinel surveillance system.
The results from Webbsök are published on the web every Monday in the form of a graph created to predict the sentinel surveillance data to be published on Thursday.

Data on death rates
In order to identify excess mortality, the aggregate number of deaths is transferred from Statistics Sweden each week and analysed by the National Board of Health and Welfare in a generalised linear model of the Poison family. Variables are influenza positive samples reported weekly from the laboratories and temperature. Analyses are made for the whole country and regionally for the Northern, Eastern and Southern parts of Sweden.

Seroepidemiological studies
Serum samples representative of the population geographically and by age were obtained from leftover diagnostic samples at chemical laboratories across the country in May 2011. The samples were analyzed for antibodies that prevent influenza A(H1N1)pdm09 from agglutinating red blood cells (haemagglutination inhibition, HI). The proportion of samples for different age groups with noticeable or protective level of antibodies were compared with data from 2007, 2009 and 2010. Unfortunately, it is not possible to distinguish antibodies that have been induced by vaccination from those resulting from illness.

Telephone advice line (1177)
Through a partnership with 1177, SMI analyses data from calls to the medical advice line 1177 each week. Data on 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 complaints that indicate upper respiratory infection or gastroenteritis in children and adults, respectively, is manually transferred to SMI each week. Seven reasons for contact that may be related to influenza are analysed by SMI each week.

Other information sources
The County Medical Officers of Communicable Disease Control (CMOs) report anything noteworthy that has come to their attention in their counties. Foreign epidemiology is monitored through the websites of WHO and ECDC, and often through other, national websites. Informal information regarding outbreaks from the health care sector and the public is followed up on, as is national and international reporting on influenza in the media.

Reports to Swedish collaborators/authorities
During the influenza season, SMI condenses national and international data into a detailed weekly report, which is published on SMI’s website. A preliminary summary of the season is included in the final weekly report (week 20). A detailed
annual report is sent to WHO and ECDC following the end of the season. All
reports are available at SMI’s webpage.

SMI arranges regular information days (“SMI days”) on influenza each fall in
preparation for the upcoming influenza season and the start of vaccination. Where
necessary, the CMOs, microbiological laboratories, the National Board of Health
and Welfare and other affected authorities are informed of exceptional events.
Different groups such as the National Pandemic Group and the strategic group for
influenza vaccination handle issues of common interest.

Reports to international collaborators/authorities
SMI is the WHO National Influenza Centre for Sweden and part of ECDC’s
network dedicated to the monitoring of influenza, EISN. As such, SMI has an
important commitment to report weekly influenza data to the ECDC database
TESSy, which then forwards the data to the WHO database, Flunet. A
representative selection of the samples positive for influenza collected by SMI are
sent to WHO Collaborating Centre (WHOcc) for further characterization.

Swedish media
The media has access to the influenza data on SMI's website. During seasonal
epidemics, SMI is normally contacted by the national media. Time permitting, we
try to answer the questions we receive, and in most cases the media reports have
been accurate.
Epidemiological data

Laboratory-confirmed cases

A total of 4859 laboratory-confirmed diagnoses of influenza were reported during the season (Figure 2). This constituted nearly half of the number of diagnoses during the 2009 pandemic. Of the diagnoses during 2011-2012, 4699 were seasonal influenza A or B, the highest number of seasonal influenza diagnoses since 1993-1994, when registration of laboratory-confirmed cases first began (Figure 3 and Appendix 1. More than 50 cases per week were reported from week 4 to week 16, with a peak of 808 verified cases during week 9.

Figure 2. Total number of laboratory-confirmed cases of seasonal influenza (all types) per week 2007-2012 (Note: the pandemic season 2009-2010 is not shown)

As shown in Figure 3, the season was dominated by influenza A(H3N2). Overall, 94 percent of the viruses were seasonal influenza A(H3N2), 3 percent were influenza A(H1N1)pdm09, and 3 percent were influenza B (Figure 3). An overview of cases and incidence per age-group and type of virus is presented in Table 2.
Figure 3. Number of laboratory-confirmed cases per week by influenza type, 2011-2012.

Table 2. Number of laboratory-confirmed cases of A(H1N1)pdm09, seasonal influenza A and B, and incidence per 100,000 population by age group, 2011-2012

<table>
<thead>
<tr>
<th>Age group</th>
<th>A(H1N1)pdm09</th>
<th>Seasonal influenza A and B</th>
<th>A(H1N1), A and B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Incidence</td>
<td>Number</td>
</tr>
<tr>
<td>0-4 years of age</td>
<td>19</td>
<td>3,4</td>
<td>299</td>
</tr>
<tr>
<td>5-14 years of age</td>
<td>3</td>
<td>0,3</td>
<td>182</td>
</tr>
<tr>
<td>15-44 years of age</td>
<td>47</td>
<td>1,5</td>
<td>778</td>
</tr>
<tr>
<td>40-64 years of age</td>
<td>46</td>
<td>1,5</td>
<td>1005</td>
</tr>
<tr>
<td>&gt;65 years of age</td>
<td>30</td>
<td>1,7</td>
<td>2255</td>
</tr>
<tr>
<td>Total</td>
<td>145</td>
<td>1,5</td>
<td>4519</td>
</tr>
</tbody>
</table>

*For 46 cases, no information on age was provided. These cases are not included in the table. The total number of influenza diagnoses was 4,859.
Influenza A(H1N1)pdm09
In total, 145 laboratory-confirmed cases of influenza A(H1N1)pdm09 were diagnosed in Sweden during the 2011-2012 season. Of these, 42 were reported as hospitalised, with 5 needing intensive care. No deaths were reported.

Seasonal influenza A
A total of 4546 cases of laboratory-confirmed, seasonal influenza A were reported during the 2011-2012 season (Figure 4). This is an all time high number and the incidence of laboratory-confirmed seasonal influenza A was higher in Sweden than in all other European countries. The strains characterised were of the subtype H3.

The number of samples sent for laboratory confirmation throughout the health care system seems to have increased since 2009. Introduction of PCR for influenza in most diagnostic laboratories since the pandemic most likely has resulted in increased likelihood of a positive diagnosis, making sampling more valuable for the clinicians. Increased sampling and test sensitivity may have contributed to the high number of verified cases seen in the 2011-2012 season compared to 2008-09, which was just as severe an A/H3N2 seasons as 2011-1012 (fig 4)

Figure 4. Laboratory-confirmed cases of seasonal influenza A reported by week between 2006 and 2012 (from voluntary laboratory reporting)

Age Distribution of Cases
As shown in Figure 5, the highest incidence of laboratory-confirmed cases of influenza A was found among the very old with 125 laboratory-confirmed diagnoses per 100,000 population (see also Table 2). The lowest incidence was among those 5-14 years of age.
Figure 5. Weekly incidence per age-group of seasonal influenza A during 2008-2009, 2010-2011, and 2011-2012 (2009-2010 not shown due to pandemic.)

Geographic Distribution of Cases
As shown in Figure 6, the incidence of seasonal influenza A seems to have been highest in the western part of Sweden with a belt of low incidence from the northern east coast through the central part of the country (Figures 6 and 7). In total, the highest incidences were seen in Örebro län (83 per 100,000) and in Dalarna län (74 per 100,000) but another five counties had incidences above 60/100 00. The influenza epidemic peaked in week 9, 2012, as seen in Figure 7, which shows the progression of the influenza season from week 1 to week 20, 2012, in two-week intervals.

Figure 6. Total incidence of laboratory-confirmed seasonal influenza A per 100,000 population by county during the 2011-2012 season
Influenza B
In contrast to the 2010-2011 season, the spread of influenza B was very limited with a total of 148 laboratory-confirmed cases. The virus was reported from most counties, but two neighboring counties in central Sweden (Värmland and Örebro) had the highest incidence (4.7 and 4.5 cases per 100,000 population).

Sentinel surveillance
Sentinel reporting
In total, 74 units participated in the sentinel surveillance system, having a combined catchment area of approximately 645,000 patients. An average of 39 units reported each week. During the week with highest participation in terms of catchment population, 57 units reported, representing 516,100 persons, or approximately 5 percent of the Swedish population. During the week with lowest participation, only 19 units reported, representing a catchment population of 105,177 persons. In all, there were 1096 reports of patients with ILI. Figure 8 shows the percentage of patients with ILI reported each week through the sentinel surveillance system.

Like the previous season, there was a great discrepancy between the number of laboratory-confirmed cases and the number of sentinel surveillance reports of ILI.
A total of 4859 laboratory-confirmed cases and only 1144 ILI patients were reported, an imbalance that reflects healthcare utilization patterns in Sweden. The reporting covered between 1 and 5 percent of the population, but due to rules for sick-leave and health policies, few people go to their general practitioner with influenza-symptoms. If not severely ill, people stay at home, and if they need care they go directly to hospital emergency departments. The age distribution, with most sentinel-cases among those below 65 years of age (10-13/100 000 population) and laboratory-confirmed cases among those above 65 years of age (130/100 000) illustrates the difference in need for care, and that elderly, hospitalised persons are those mainly sampled for laboratory verification of influenza.

Figure 8. Number of patients with ILI per 100,000 listed patients in the catchment areas of reporting sentinel units, 2009-2012, per week.

The highest incidence of reported ILI from the sentinel surveillance system was seen in persons between the ages of 15 to 64 years (Table 3). This can be attributed to health care utilization patterns, as discussed above. Those seeking care through general practitioners are less sick than those going directly to emergency departments, thus preferentially adults not belonging to risk-groups.
Table 3. Number, distribution, and incidence of reported ILI cases and laboratory-confirmed influenza cases (all types) per age group, 2011-2012

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number</th>
<th>Percentage of total</th>
<th>Incidence</th>
<th>Number</th>
<th>Percentage of total</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4 years of age</td>
<td>72</td>
<td>6%</td>
<td>13</td>
<td>326</td>
<td>7%</td>
<td>59</td>
</tr>
<tr>
<td>5-14 years of age</td>
<td>117</td>
<td>10%</td>
<td>10</td>
<td>194</td>
<td>4%</td>
<td>19</td>
</tr>
<tr>
<td>15-64 years of age</td>
<td>812</td>
<td>71%</td>
<td>13</td>
<td>1959</td>
<td>41%</td>
<td>32</td>
</tr>
<tr>
<td>&gt;65 years of age</td>
<td>144</td>
<td>13%</td>
<td>8</td>
<td>2334</td>
<td>48%</td>
<td>130</td>
</tr>
<tr>
<td>Total</td>
<td>1145</td>
<td>100%</td>
<td>12</td>
<td>4813</td>
<td>100%</td>
<td>51</td>
</tr>
</tbody>
</table>

**Sentinel sampling**

During the season, 1706 sentinel samples were submitted from 65 sampling units. The number of samples was 32 percent higher than in 2010-2011. The rate of positives peaked in week 8 with 56 percent positives. In total, 334 samples (19.6 percent) tested positive for influenza, slightly less than the 25 percent seen during the preceding season. Figure 9 shows the number of sentinel samples submitted each week and number and percentage of those positive.

Of these, 318 (95.5 percent) were positive for influenza A and 15 (4.5 percent) for influenza B. Of the influenza A positives, 307 (96 percent) were influenza A(H3) and 11 (3.4 percent) were influenza A(H1N1)pdm09 (Figure 10). One influenza A sample could not be subtyped due to low virus concentration. The B samples were equally distributed between B/Victoria/2/87 and B/Yamagata/16/88 lineages.
Figure 9. Number of sentinel samples submitted each week and number and percentage of those positive, 2011-2012

Figure 10. Number of sentinel samples positive for influenza B-Yamagata (B-Yam), B-Victoria (B-Yam), influenza A(H1N1)pdm09, and influenza A(H3), season 2011-2012
Population-based surveillance

Sjukrapport

There were a total of 2,250 reports of acute respiratory illness (ARI) among the estimated 2,500 Sjukrapport participants (Figure 11). This was an increase compared to the proportion among participants during 2010-2011, when approximately 2,700 participants reported 1,859 ARI episodes. As shown in the figure, the rate of ARI was consistently higher than the previous two seasons, likely reflecting the relatively severe influenza season and a severe mycoplasma epidemic seen in Sweden during the Fall of 2011.

The proportion of ILI (a total of 772 reports) in Sjukrapport was also somewhat higher than in the previous season, when 658 episodes of ILI were reported (Figure 12). ILI can have a variety of causes, as indicated by the considerable activity reported during the early and late periods of the season. Still, the influenza peak is clearly shown as a high peak of ILI reports.

According to the laboratory reports, influenza activity peaked in week 9. ILI peaked among the Sjukrapport participants that same week in the age groups 15-39 and 39-64.

Figure 11. ARI reported weekly to Sjukrapport, 2009-2010, 2010-2011, and 2011-2012
Estimate of the number of people ill with influenza

The data from Sjukrapport lacks laboratory confirmation of influenza cases. Therefore, we have used the proportion of positive sentinel samples in Stockholm for a rough estimate of how large a proportion of the people reporting ILI through Sjukrapport actually were infected by an influenza virus. In order to avoid misleading figures, we have chosen to report an estimate only for the weeks 42 to 12, when sentinel samples were continuously taken from 5 or more people in Stockholm.

Using the proportion of ILI reported to Sjukrapport each week and the proportion of sentinel samples in Stockholm testing positive for influenza during the same period, we have estimated the proportion of the Stockholm population that has been ill with influenza. For each week, this proportion has been multiplied by the total population of Stockholm County in 2011 (source: Statistics Sweden) to find the total number of people ill each week. The weekly numbers have been added to calculate the total number of people ill with influenza in Stockholm during the season. This calculation results in the lower limit of our estimate.

By instead using the proportion of ARI reported to Sjukrapport (a broader category of illness), we have produced the upper limit of our estimate. Furthermore, if we assume that the infection is spread throughout the country in the same way as in Stockholm, an estimate can be made for Sweden's entire population.

This process gives us an estimate of the number of people ill with influenza during the 2011-2012 season (weeks 48-12) of between 120,000 and 340,000 for Stockholm and between 550,000 and 1,530,000 for all of Sweden. Based on what are now relatively old studies, a normal estimate is that between 5 and 15 percent of the population will fall ill with seasonal influenza, which matches our estimate.
Symptoms in connection with the influenza peak

As described earlier, SMI receives information each week from the medical advice line 1177 concerning the main reasons for contact. Data on the seven contact reasons related to influenza are presented in the diagram for the past two extended seasons (Figure 13); from week 27, 2010 to week 26, 2011 as dotted lines and from week 27, 2011 until week 26, 2012 as solid lines.

Figure 13. Statistics for telephone calls regarding influenza-related symptoms received by the medical advice line 1177

Like the two past seasons, fever in children was the most common cause for contact in connection with the influenza peak. The calls for fever in children and in adults were more frequent in 2011-2012 than in 2010-2011, but the difference between the years is less prominent than that for laboratory-confirmed influenza in the 0-4 years old (Figure 5).

For both seasons shown, a clear “Christmas vacation effect” can be seen, with an increase in calls during weeks 51 and 52, followed by a drop off in weeks 1 and 2. The reason for this small peak seen these two seasons may be a combination of a decreased holiday access to face-to-face health care services, leading to an increase in telephone advice.

Webbsök (“Web search”)

Through Webbsök, SMI models ILI reported through the sentinel surveillance system (see Figure 8 above) based on anonymous searches at Vårdguiden.se. As shown below, Webbsök estimates the proportion of persons with ILI per week (Figure 14).

From week 27, 2011, to week 26, 2012, slightly more than 15,000 queries on influenza were submitted to the Vårdguiden search engine. This is 2,000 less than
the 2010-2011 season, although the numbers of queries per week around the peak weeks were higher during 2011-2012. The peak deduced from Webbsök, modelling the sentinel graph, exceeded the peak obtained during the pandemic of 2009. As shown below, Webbsök’s model peaked one week before the laboratory surveillance graph (Figure 15), verifying that Webbsök is an early reliable indicator of epidemic development.

Figure 14. Webbsök’s model of the estimated proportion of persons with ILI per week for the last three seasons (2009-2010, 2010-2011, and 2011-2012)

Figure 15. Webbsök’s model of the estimated proportion of persons with ILI and the number of laboratory-verified cases, 2011-2012
Excess mortality
The excess mortality during the season was calculated to be 982 persons (95% CI: 624-1340). Excess mortality could be verified only in persons above 65 years of age. Of these, 10 percent were 65-74 years old, 17 percent were 75-84 years old and 73 percent were over 85 years of age. The evaluated excess during the seasons 2001-2012 is shown in Figure 16. Taking into account the all time high number of influenza A(H3N2) laboratory-verified diagnoses, the pressure reported from hospitals, low vaccination coverage among those over 65 years of age, and low vaccine efficacy, approximately 1000 persons is surprisingly low in comparison with previous seasons.

Figure 16. Estimated influenza-related excess mortality, 2001-2012.
Vaccine coverage

Vaccination coverage among persons above 65 years of age has been estimated by Sweden’s 21 CMOs for the past nine seasons (Table 4). As shown, vaccination coverage has declined since 2008. The severe side-effect (narcolepsy) caused by the pandemic vaccine i probably a major reason.

Table 4. Mean yearly proportion of vaccinated persons above 65 years of age in Sweden, as estimated by the 21 CMOs

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<tbody>
<tr>
<td>Estimated %</td>
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<td>55</td>
<td>61</td>
<td>57</td>
<td>58</td>
<td>64</td>
<td>44*</td>
<td>56</td>
<td>44</td>
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</table>

Note: Various methods for estimation were used in various counties such as vaccine registers, doses of vaccine used, sentinel-reports on vaccine coverage, quests to general practitioners or patient-record data, but methods were roughly the same over the years.

*Very few reported seasonal vaccination in 2009 since all focus was on the pandemic vaccination, covering 60% of the population.
Seroepidemiological data

The proportion of individuals with protective levels of antibodies (HI titer $\geq 40$) to influenza A(H1N1)pdm09 had increased from 48.6 percent to 52.2 percent between May 2010 and May 2011. Increased or unchanged seroprevalence was seen in almost all age-groups (Figure 17A). This could be explained by circulation of the virus during the 2010-2011 season to higher levels than previously appreciated, perhaps because acquired immunity in the population resulted in milder infections than during the first pandemic wave. An exception was the 0-1 year-olds, in which a decrease in seroprevalence was observed. This age-group consisted in May 2011 largely of infants that were neither vaccinated nor exposed to the virus during the pandemic 2009-2010. The proportion of individuals with noticeable levels of antibodies (HI titer $\geq 10$) in May 2011 was 83.8 percent, compared with 64.0 percent in May 2010, with increases in all age-groups except 0-1 years (Figure 17B).
Figure 17 (A and B). Seroprevalence of influenza A(H1N1)pdm09 antibodies at HI titer ≥40 (A) and HI titer ≥10 (B) by age group, 2007, 2009, 2010, and 2011
Virological data

Voluntary laboratory reporting

Swedish laboratories conducted 22,283 influenza analyses during the season, of which 4,840 (22 percent) tested positive for influenza A or B. Of the positive samples, 4,532 were positive for influenza A but negative for A(H1N1)pdm09. Of these, 1,253 were subtyped as A/H3, analysed in Gothenburg, in Umeå or at SMI.

A total of 43 influenza B positive samples were typed by lineage, 21 samples were of the B/Victoria/2/87 lineage and 22 of the B/Yamagata/16/88 lineage.

Characterization methods and selection of samples

Genetic characterization of influenza strains at SMI is mainly performed by sequencing analysis of three of the eight influenza gene segments: hemagglutinin (HA), neuraminidase (NA) and matrix (MA). The number of sequenced gene segments for each subtype for the 2011-2012 season is shown in Table 5. Some genetic characterization is also performed by real-time PCR. Phenotypic analysis of sensitivity to NA-inhibitors is performed at SMI by neuraminidase inhibition (NAI) assay. A representative selection of samples are also sent to the WHOcc for antigenic characterization of the HA gene by hemagglutination inhibition (HAI) assay and phenotypic analysis by NAI.

Hemagglutinin is characterized with respect to vaccine similarity and changes in receptor affinity (lung receptors versus respiratory tract receptors) by HAI and sequencing. In addition, the HA target sequences for the subtype/lineage-specific real time PCR systems are analyzed for sequence mismatches. The NA gene is analyzed with respect to amino acid substitutions resulting in resistance to NA inhibitors. The IC50 (half maximal inhibitory concentration) values for the NA inhibitors oseltamivir (Tamiflu®) and zanamivir (Relenza®) obtained with the phenotypic NAI assay are compared to the baseline and median value for the current season and subtype to reveal outliers and fold change. The MA gene is analyzed from two aspects. The M2 gene of influenza A is analyzed for amino acid substitutions resulting in resistance to amantadine. In addition, the MA target sequences of both influenza A and B of the real-time PCR systems (used for detection of influenza in clinical samples) are analyzed for sequence mismatches.

As isolation of influenza virus on cell culture is only performed at SMI and at Umea University Hospital and phenotypic analysis such as NAI and HI need grown virus, SMI continuously ask Swedish laboratories to provide a representative selection of specimens that can be isolated on cell culture. 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.
Table 5. Number of sequenced gene segments at SMI, 2011-2012

<table>
<thead>
<tr>
<th>Subtype/Lineage</th>
<th>Gene Segment</th>
<th>Number of sequences</th>
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<tbody>
<tr>
<td>H1N1pdm09</td>
<td>HA</td>
<td>20</td>
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<tr>
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<td>NA</td>
<td>20</td>
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<td></td>
<td>M2</td>
<td>6</td>
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<tr>
<td></td>
<td>Mpp*</td>
<td>20</td>
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<tr>
<td>H3N2</td>
<td>HA</td>
<td>72</td>
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<tr>
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<td>NA</td>
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<td>M2</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Mpp*</td>
<td>61</td>
</tr>
<tr>
<td>B/Victoria</td>
<td>HA</td>
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<tr>
<td></td>
<td>NA</td>
<td>8</td>
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<tr>
<td></td>
<td>Mpp*</td>
<td>8</td>
</tr>
<tr>
<td>B/Yamagata</td>
<td>HA</td>
<td>10</td>
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<tr>
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<td>NA</td>
<td>10</td>
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<td>Mpp*</td>
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</table>

*Target sequence for real-time PCR.

Characterization of influenza A(H1N1)pdm09

The HA-sequencing of A(H1N1)pdm09 revealed that these strains belong to three genetic groups. See Table 6 and the phylogenetic tree in Appendix 2. Nine of the 11 strains sent to WHOcc for HAI analysis could be analyzed and six of these reacted well to serum raised against the vaccine strain. The remaining three showed reduced titers by HAI with serum raised against the vaccine virus, but had all acquired amino acid substitution(s) during culture on MDCK cells. No substitutions resulting in resistance to NA-inhibitors were identified in any of the strains that were analyzed. In one strain, the substitution S247N known to result in reduced inhibition to oseltamivir and to act synergistically with the H275Y substitution with respect to oseltamivir and peramivir resistance, were identified.

In addition, 15 strains were analyzed with real-time PCR with respect to the H275Y substitution, and none of them were carrying the substitution. The nine strains analyzed phenotypically by NAI were all in the range of normal inhibition for oseltamivir and zanamivir, except the strain with the S247N substitution, which was a major outlier with a six-fold change in IC\(_{50}\) value for oseltamivir compared to the median. Like the previous season, all analyzed strains were carrying the S31N amantadine resistance substitution in the M2 gene.

Table 6. Distribution of A(H1N1)pdm09-strains into genetic groups

<table>
<thead>
<tr>
<th>Genetic group</th>
<th>Number</th>
<th>Key substitutions (relative to A/California/7/2009)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/St Petersburg/27/2011</td>
<td>15</td>
<td>D97N, S185T, A197T</td>
</tr>
<tr>
<td>A/St Petersburg/100/2011</td>
<td>3</td>
<td>G143G, S185T, A197T</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>20</strong></td>
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</table>
Characterization of influenza A/H3N2

The HA-sequences fell into five genetic groups under the clade representative of A/Victoria/208/2010 (Table 7 and the phylogenetic tree in Appendix 3). A total of 32 strains were sent to WHOcc of which 30 were analyzed by HAI. During this season, there have been some difficulties in performing HAI, due to the lost ability of some of the H3N2 strains to agglutinate red blood cells. In addition, the interpretation of results has been difficult due to the differences in results obtained with antigens from different origins (eggs or cell culture). However, all characterized strains were genetically closer to A/Victoria/361/2010 (the strain used in the vaccine for season 2012-2013) than A/Perth/10/2010 (the vaccine strain used 2011-2012).

Thirteen strains representing vaccine failures were analyzed by sequencing of the HA gene and fell into four of the genetic groups: A/England/259/2011 (four strains), A/Victoria/361/2011 (four strains), A/Iowa/19/2010 (three strains) and A/Perth/10/2010 (two strains).

None of the strains for which the NA gene was sequenced contained any substitutions known to result in resistance to NA inhibitors. Phenotypic analysis of ten strains showed that all of them were in the range for normal inhibition. Like the previous season, sequencing analysis of the M2 gene revealed that all H3N2 strains carry the S31N amantadine resistance mutation.

As a result of the finding of a mismatch to a probe (in 17/61 strains) for the MA real-time PCR assay, an additional probe was added to the assay in February 2012. In the end of the season, a mismatch was also identified in primer region, and SMI therefore recommended the introduction of an additional primer to this system.

### Table 7. Distribution of H3N2-strains into genetic groups

<table>
<thead>
<tr>
<th>Genetic group</th>
<th>Number</th>
<th>Key substitutions (relative to A/Perth/16/2009)</th>
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<tbody>
<tr>
<td>A/Iowa/19/2010</td>
<td>27</td>
<td>D53N, Y94H, S199A, I230V, E280A</td>
</tr>
<tr>
<td>A/Victoria/361/2011</td>
<td>15</td>
<td>S45N, T48I, A198S, N312S</td>
</tr>
<tr>
<td>A/Perth/10/2010</td>
<td>6</td>
<td>D53N, Y94H, I230V, E280A</td>
</tr>
<tr>
<td>A/Stockholm/18/2011</td>
<td>4</td>
<td>V223I, N144D, N145S</td>
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<td><strong>TOTAL</strong></td>
<td><strong>72</strong></td>
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</table>

Characterization of influenza B season 2011-2012

A total of 43 influenza B-positive samples (including 14 from the sentinel system) were further analyzed by lineage-specific real-time PCR. Of these, 21 were B/Victoria-like and 22 were B/Yamagata-like. Sequencing of the HA gene showed that all B/Victoria-like strains fell into the B/Brisbane/60/2008-clade, which is characterized by the amino acid substitutions N75K, K109N, N165K and S172P relative to B/Malaysia/2506/2004. The B/Yamagata-like strains fell into the two clades shown in Table 8. For the phylogenetic tree, see Appendix 4.

In total, nine influenza B isolates were sent to WHOcc for HAI analysis. The three B/Victoria-like strains reacted well to serum raised against the vaccine strain for
the 2011-2012 season. Three of the six B/Yamagata-like strains reacted reasonably well with the 2012-2013 vaccine strain (B/Wisconsin/1/2010), while the results obtained with the remaining three strains were difficult to interpret. No substitutions resulting in resistance to NA-inhibitors were identified in any of the strains that were analyzed. The five Victoria-like and the eight Yamagata-like viruses analyzed phenotypically with NAI all fell in the range for normal inhibition.

Table 8. Distribution of B-strains into genetic clades

<table>
<thead>
<tr>
<th>Genetic clade</th>
<th>Number</th>
<th>Key substitutions (relative to B/Florida/4/2006)</th>
</tr>
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<tbody>
<tr>
<td>B/Bangladesh/3333/2007</td>
<td>6</td>
<td>S150N, N165Y, G229D</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td><strong>10</strong></td>
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**H3N2v**

Reports about a new “swine flu” A/H3N2v in the USA were published in late summer 2011. Ninety-three percent of the laboratory-verified cases were in children under 18 years of age. A PCR system discriminating between A/H3N2 and A/H3N2v was established at SMI in the beginning of 2012. Based on the information reported from the USA, 164 A/H3 positive samples (from the 2011-2012 season) from children born after 1994 were analyzed using the discriminating PCR. All were found to be negative for A/H3N2v.

**Quality assurance**

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 diagnostics of avian flu. They are sensitive, rapid and could easily be scaled up, if necessary. SMI 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 2011-2012 season, a new probe and a new primer have been validated and implemented in the matrix A PCR. After validation, this information was shared with the Swedish laboratories. The laboratories that use the PCR systems established by SMI are encouraged to send all samples with deviating results to SMI for sequence analysis (see section on characterisation of A(H1N1)pdm09). SMI assists Swedish laboratories who have developed their own PCR systems by validating their methods by sequencing representative samples. SMI also provides positive control material to Swedish laboratories upon request.

SMI participates in several external quality assurance (EQA) programs. Once a year, WHO sends out an influenza PCR panel. In addition, SMI takes part in one of the panels sent out by Quality Control for Molecular Diagnostics (QCMD) and takes part in the EISN influenza virus EQA programme.
All laboratories in Sweden perform an A and B PCR and a subtype-specific A(H1N1)pdm09 PCR. In addition, three laboratories perform an A/H3 PCR. In September 2011, SMI produced a PCR panel for the Swedish laboratories. This was made on behalf of the External Quality Assessment for Clinical Laboratory Investigations (EQUALIS). Twenty laboratories participated in the EQA and fourteen of these reported 10/10 correct answers (Figure 18). Three laboratories reported one false negative result for one of the two samples with the lowest concentration of A(H3N2) or A(H1N1)pdm09 and three laboratories reported false positive results. One laboratory reported three incorrect results.

Figure 18. Result of the Swedish EQA panel 2011.
Appendix 1. Number of laboratory-confirmed cases of influenza (all types) each season (week 40 to week 20), 1993-1994 to 2011-2012 (Note: Peak week bold and underlined).

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Appendix 2. Phylogenetic tree of the amino acid sequence for haemagglutinin, influenza A(H1N1)pdm09

Summer 2009
Season 2009-2010
Season 2010-2011
Season 2011-2012
Vaccine strain (season)
Appendix 3. Phylogenetic tree of the amino acid sequence for haemagglutinin, influenza A(H3N2)
Appendix 4. Phylogenetic tree of the amino acid sequence for haemagglutinin, influenza B