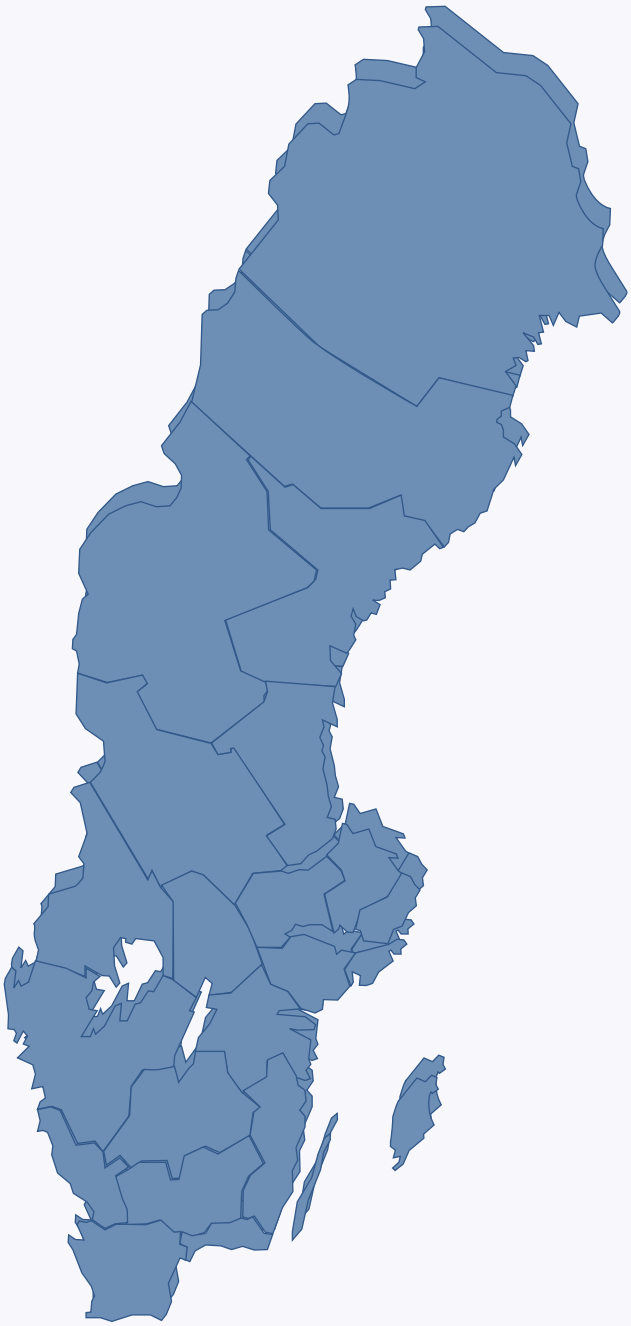
# INFLUENZA

## Annual Report 2005-2006



*The National Influenza Reference Centre*
*Swedish Institute for Infectious Disease Control (SMI)*

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Swedish Institute for Infectious Disease Control
(SMI)

# ANNUAL REPORT

SEPTEMBER 2005-AUGUST 2006

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**Activities.**

1. Monitoring of influenza activity in Sweden
2. Reports from SMI on influenza activity in Sweden
3. Characterisation of influenza strains
4. Data from the 2005–2006 season
5. Quality control of laboratory diagnosis of influenza
6. Method Development and Research

## 1) MONITORING OF INFLUENZA ACTIVITY IN SWEDEN

### 1:1) The Sentinel System.

The Swedish influenza sentinel reporting system 2005–2006 consisted of 96 sentinel units recruited by the County Medical Officers. It included both individual GPs and larger health care centres of 2-5 GPs. Twenty out of twenty-one counties participated in the system (Gotland, the smallest county was not included). Date of visit, age and sex of the patients were reported, and the reports were sent to the county medical officers and to the National Influenza Centre at the Swedish Institute for Infectious Disease Control (SMI) either by fax or the web-based reporting system, SentiNet. Each week reports were received from between 39 –95 of the sentinel units. The total weekly number of out-patient visits at the reporting units ranged between 170918–518576.

### 1:2) Reports of laboratory verified influenza diagnoses.

Influenza isolation was performed at five virus laboratories, placed at University Hospitals and at SMI. The laboratories are relatively evenly distributed with regard to the population in different areas. The laboratories also performed antigen detection with immunoflourescense (IF) and genome detection by polymerase chain reaction (PCR) and influenza serology. Another 19 microbiology laboratories diagnosed influenza by IF assays, commercial ELISA KITs or nucleic acid amplification (NAA). During the influenza season, the 25 laboratories sent weekly reports on the number of influenza cases, diagnosed by antigen detection, NAA and/or virus isolation. Serology results were not included in these reports.

## 1:3) Death rates.

Information on the weekly death rate in Sweden was purchased from Statistics Sweden. Mean weakly death rate for each influenza-free set of weeks with the same number between week 40 year 1993 and week 20 year 2006 has been calculated, and was used as reference for the evaluation of weekly excess mortality.

## 2) REPORTS FROM SMI ON THE INFLUENZA ACTIVITY IN SWEDEN

### 2:1) Weekly reports to the Swedish Collaborators.

Each Wednesday, national and international influenza information collected during the week, including the WHO country reports, were summarised and made available at the SMI home-page (www.smittskyddsinstitutet.se). An electronic Newsletter was also sent to all interested parties, including the County Medical Officers of Communicable Disease Control, Departments of Infectious Diseases in Sweden, Microbiological Laboratories and to the National Board of Health and Welfare. A summary of the activity during the entire season was distributed towards the end of the summer, when all definitive data are available.

## 2:2) Other spread of information in Sweden.

The media are constantly interested in influenza, and usually contact SMI to get information. In most instances those contacts resulted in correct and informative articles. The institute has a journal ”Smittskydd” and an electronic newspaper “EpiAktuellt”, and during the influenza season reports on the situation were printed there, when appropriate. An information day attended by 200 persons, including media representatives was arranged in Stockholm at SMI in September 2005.

## 2:3) Reports to WHO and other National Influenza centres.

Sweden reports to WHO via Flunet, and starts reporting when the first laboratory verified case occurs. Since 2000 we have also joined the European Influenza Surveillance Scheme (EISS), and provide weekly information to the EISS home-page.

# 3) CHARACTERISATION OF INFLUENZA STRAINS

## 3:1) Genotypic and fenotypic characterisation.

Influenza strains were sent to SMI from the laboratories performing virus isolation. Isolated virus strains were examined for the type and subtype of virus by hemagglutination inhibition (HAI; reagents have been kindly donated from WHO and the Influenza Reference Centre in Rotterdam) and IF with monoclonal antibodies (from Laboratories de Virologie, Lyon). HA and NA-sequencing was also performed. For further characterisation with ferret sera, the strains were also sent to Mill Hill in London.

# 4) DATA FROM THE 2005-2006 SEASON

## 4:1) Summary of the influenza activity in Sweden.

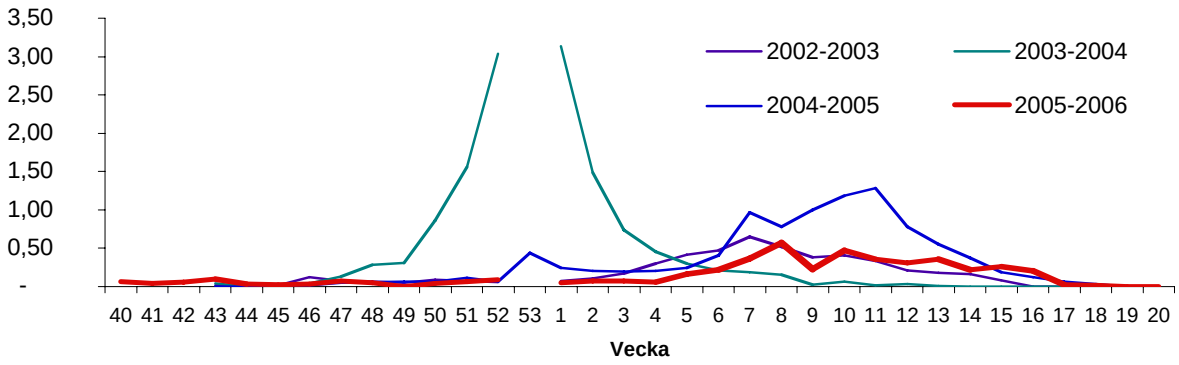
This season, the influenza activity started during the first two weeks in 2006 and peaked around week 12 (Fig 4:1:1 and Fig 4:1:2). It continued until the middle of May. Overall, the activity was widespread and of low intensity. The total number of laboratory diagnoses was 908 (446 A and 462 B) compared to 2016 (1802 A and 214 B) the previous season. The majority of the reported cases were youngsters and adults, with cases aged 15-64 dominating both in the laboratory and in the sentinel system (Fig 4:2:1). The yearly age distribution is much more varied in the laboratory than in the sentinel system, most likely reflecting that GPs practices mostly cover otherwise healthy adults. The young children and elderly often get more severely ill and seek hospital care directly if they need medical attention. It is from theses more seriously ill patients that specimens are drawn. The weekly incidence in the two systems has also been analysed in relation to the expected, with regard to the size of the respective populations (Fig 4:3:1). It can be seen that the youngest, and above all those 5-14, were overrepresented in the sentinel system and even more in the laboratory reports. Age 65+ was overrepresented in the laboratory reports, but less than expected in the sentinel reports. The change over the season in the age distribution followed a pattern of typical for influenza. Early in the season the number of sick children increased, while in the end of the season, the elderly patients constituted the majority of cases (fig 4:3:1). The gender distribution in each age group for both laboratory verified cases and sentinel cases is presented in Table 1 and 2.

Excess mortality related to a peak of influenza activity is not easily identified. (Fig 4:5). Demographic studies in Sweden indicate that mortality among elderly has dropped with about 2000 persons in relation to the prognosis made by Statistics, Sweden, the last two years (2004 and 2005). A correction of the line for expected mortality has not been made in the graph, since this sudden drop in mortality makes the adjustment quite complicated. Most likely, however, there was a slight excess mortality during the unusually late influenza season. An increase in vaccination of the +65 to a county mean of 60% may have contributed to the low mortality, but there is no clear proof of that.

Of strains sent to SMI for further subtyping 51% were influenza A H3, 31% were H1N1 and 18% were B (Table 4:6). Influenza H1N1, H3N2 and Influenza B of both Yamagata and the Victoria lineage were co-circulating during the whole season.

All the influenza strains further characterised were similar to the strains prevalent in Europe (Fig 4:7-4:10). No mutation known to induce resistance against neuraminidase inhibitors in the genes encoding neuraminidase for influenza A (N1 and N2) and B was identified. However, 45% of the H3N2 isolates had mutations in M2-gene, inducing amantadine resistance (Table 4:6 and Figure 4:8).

***4:1:1)*** Proportion (%) cases with influenza-like illness (ILI) out of total number of patient visits in the sentinel system



***4:1:2)*** Number of laboratory verified influenza cases

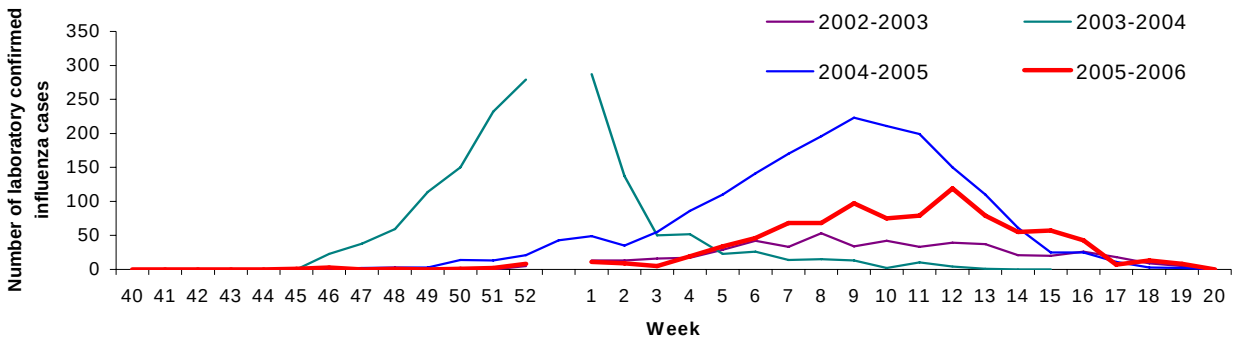


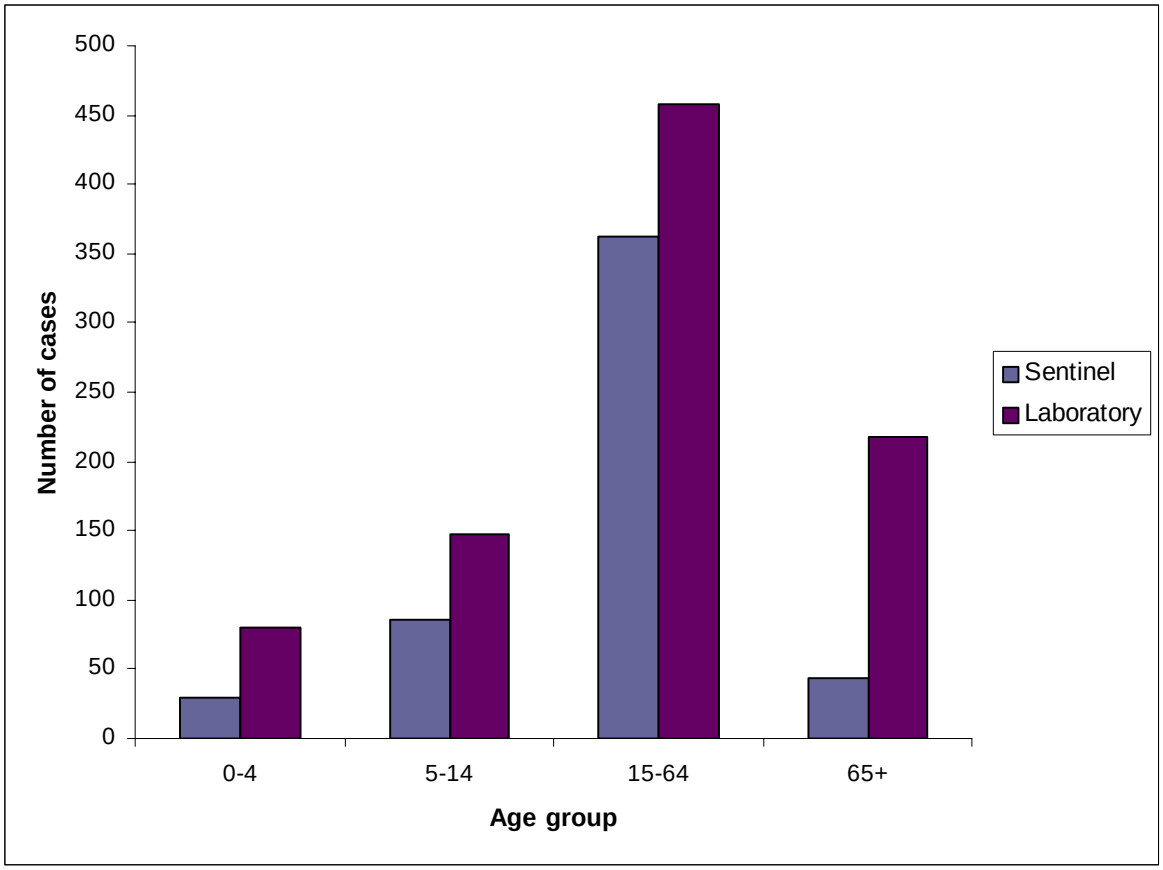

***Table. 1*** Laboratory verified cases by gender and age group

| Age group | Female | % Female | Male | % Male | Unknown | % Unknown | Total | % All groups |
|---|---|---|---|---|---|---|---|---|
| 0-4 | 31 | 38 | 43 | 53 | 7 | 9 | 81 | 9 |
| 5-14 | 59 | 41 | 83 | 58 | 2 | 1 | 144 | 16 |
| 15-64 | 234 | 51 | 210 | 46 | 13 | 3 | 457 | 50 |
| 65+ | 98 | 21 | 105 | 49 | 11 | 5 | 214 | 24 |
| Age unknown | 3 | 25 | 2 | 17 | 7 | 58 | 12 | 1 |
| **Total** | **425** | | **443** | | **40** | | **908** | **100** |

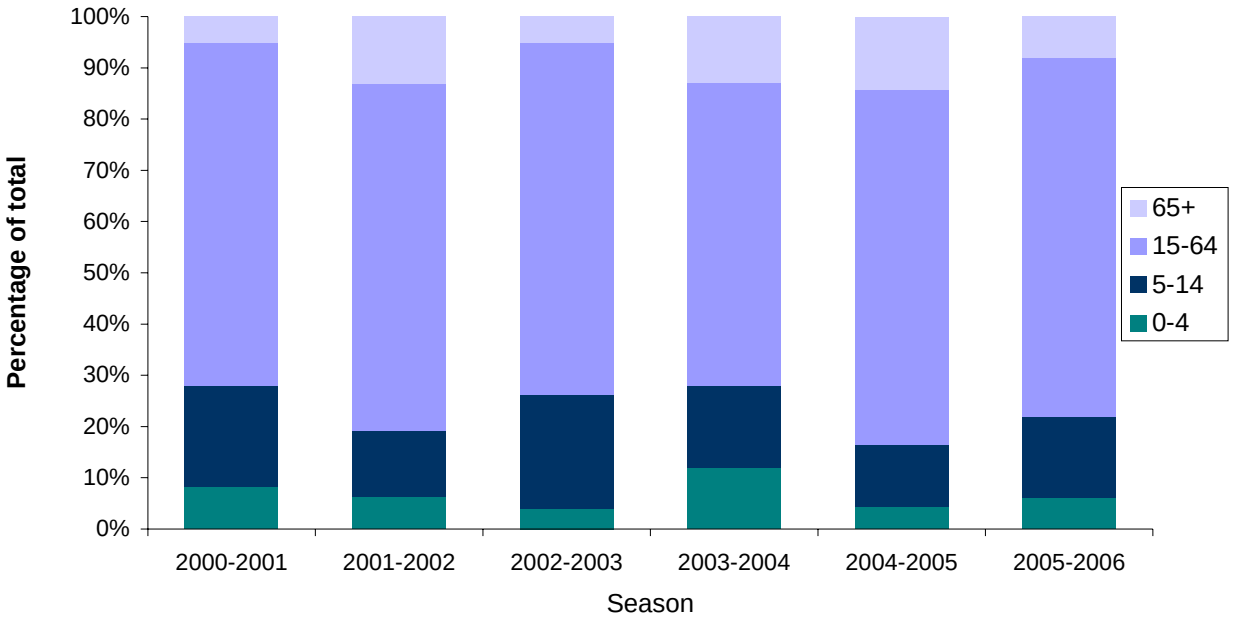
***Table. 2*** ILI cases by gender and age group

| Age group | Female | % Female | Male | % Male | Unknown | Total | % All groups |
|---|---|---|---|---|---|---|---|
| 0-4 | 14 | 48 % | 15 | 52 % | 0 | 29 | 6 % |
| 5-14 | 39 | 45 % | 47 | 55 % | 0 | 86 | 16 % |
| 15-64 | 219 | 60 % | 143 | 40 % | 0 | 362 | 70 % |
| 65+ | 29 | 67 % | 14 | 33 % | 0 | 43 | 8 % |
| **Total** | **301** | | **219** | | **0** | **520** | **100 %** |

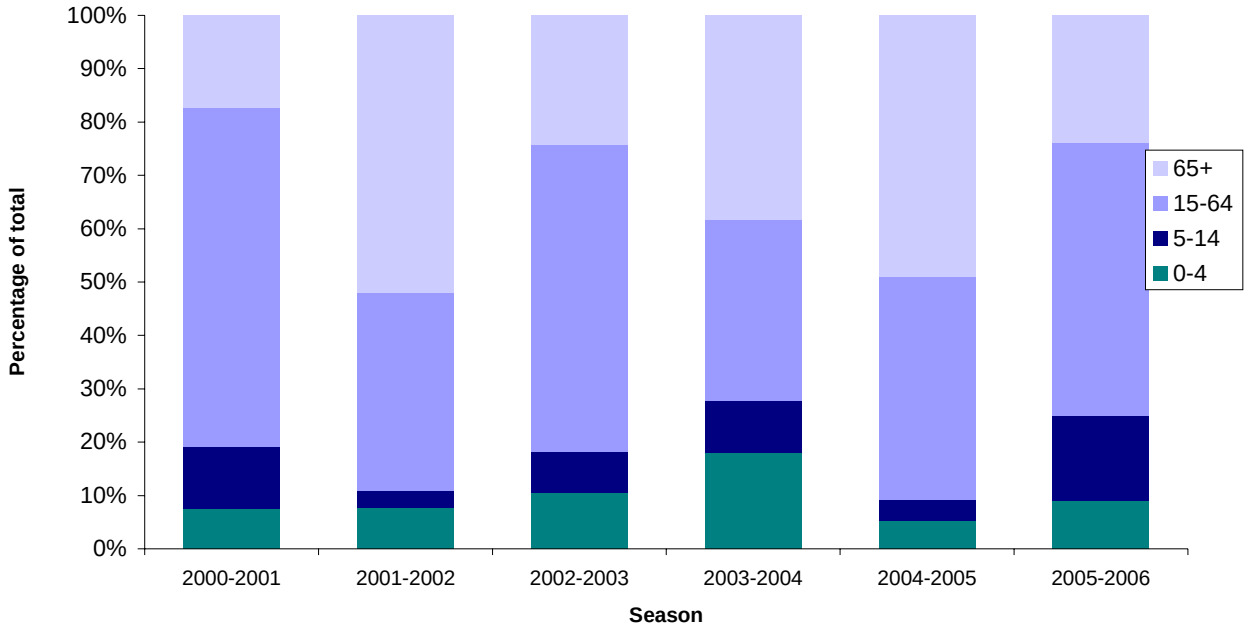
***4:2:1)*** Age distribution of sentinel ILI cases and laboratory verified cases 2005-2006



***4:2:2)*** Age distribution during the last six seasons for sentinel cases

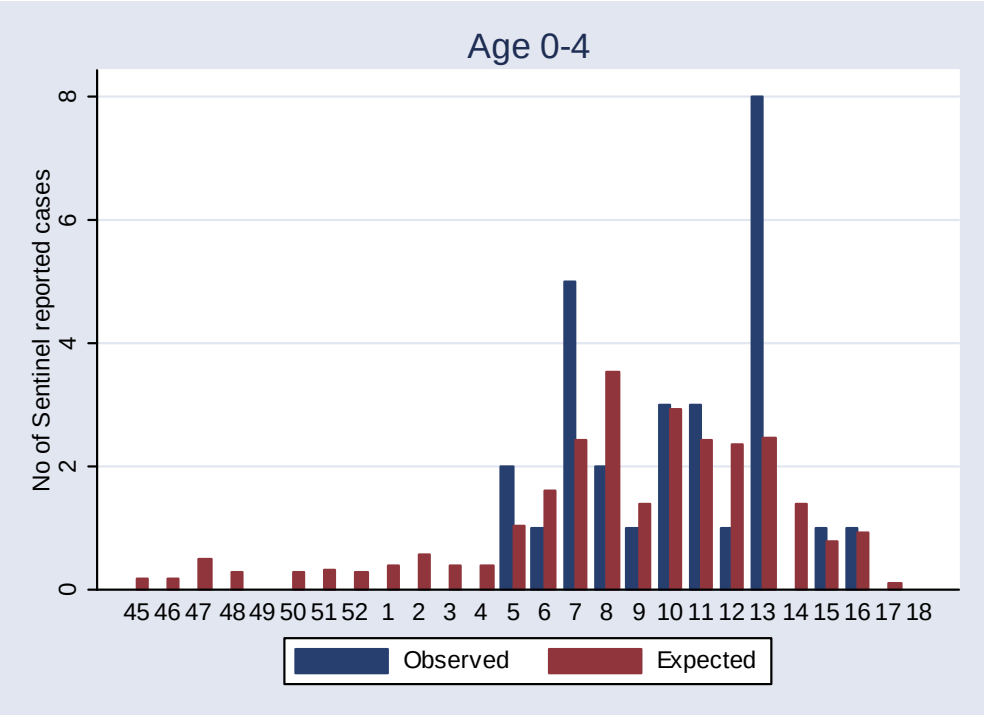


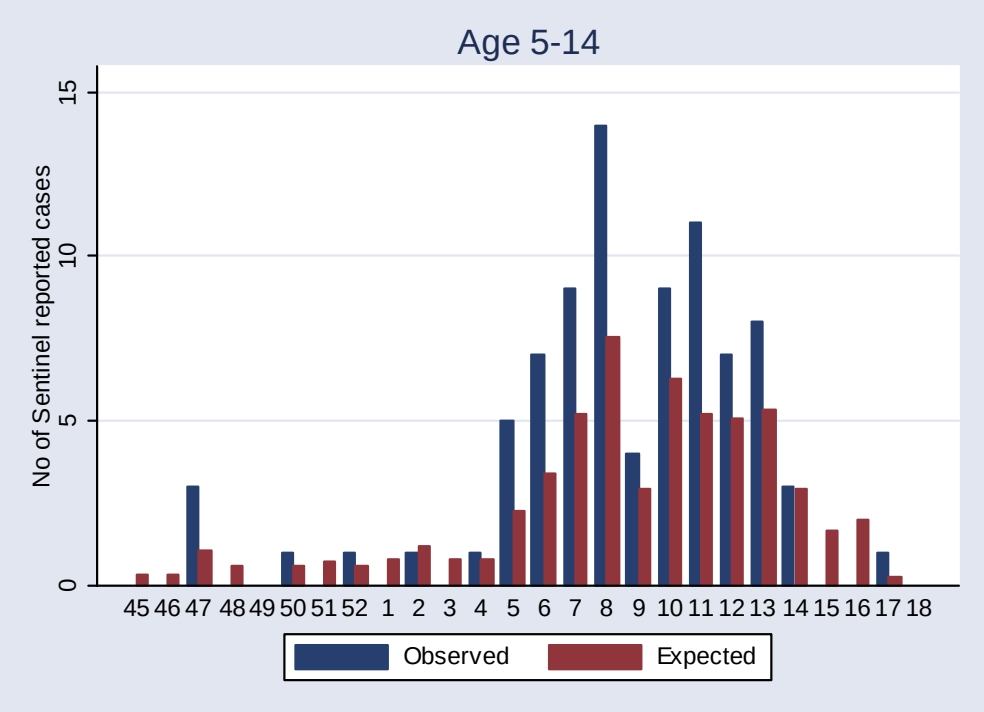

***4:2:3)*** Age distribution during the last six seasons for laboratory cases

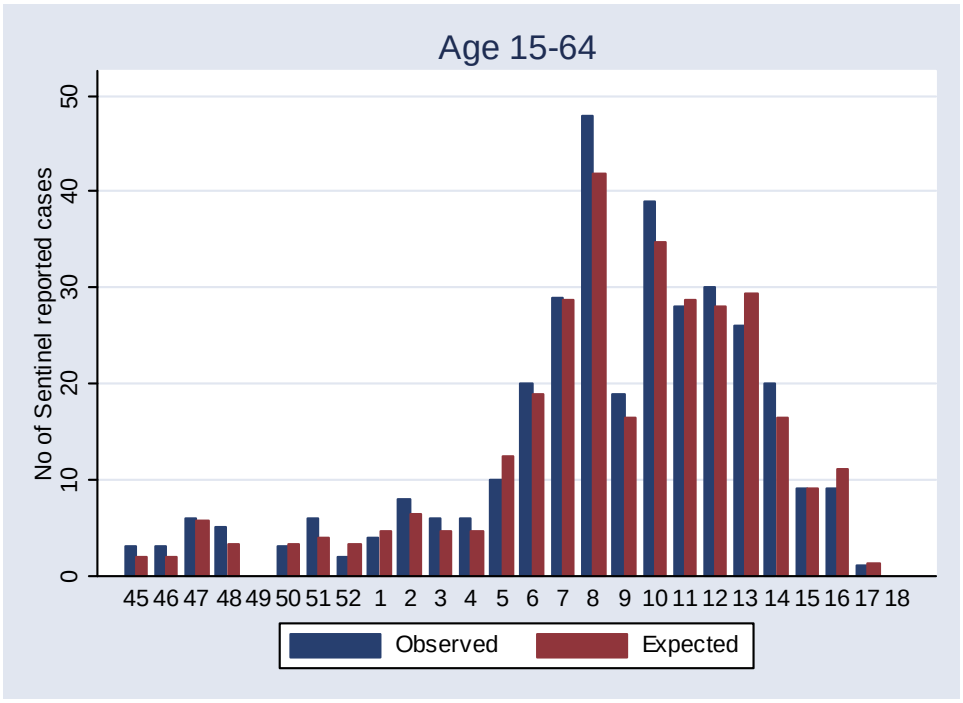


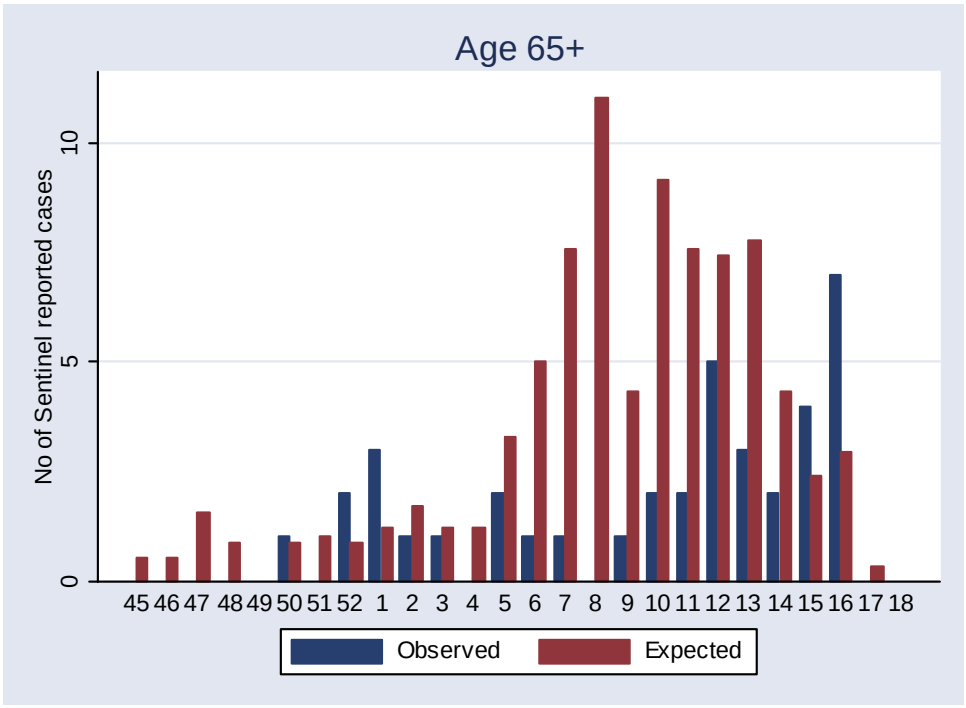
***4.3:1***) Age distribution of ILI cases during the season 2005-06

*"Expected "is the number of cases that would have occurred if the cases were evenly distributed in relations to the population of the respective age groups.*



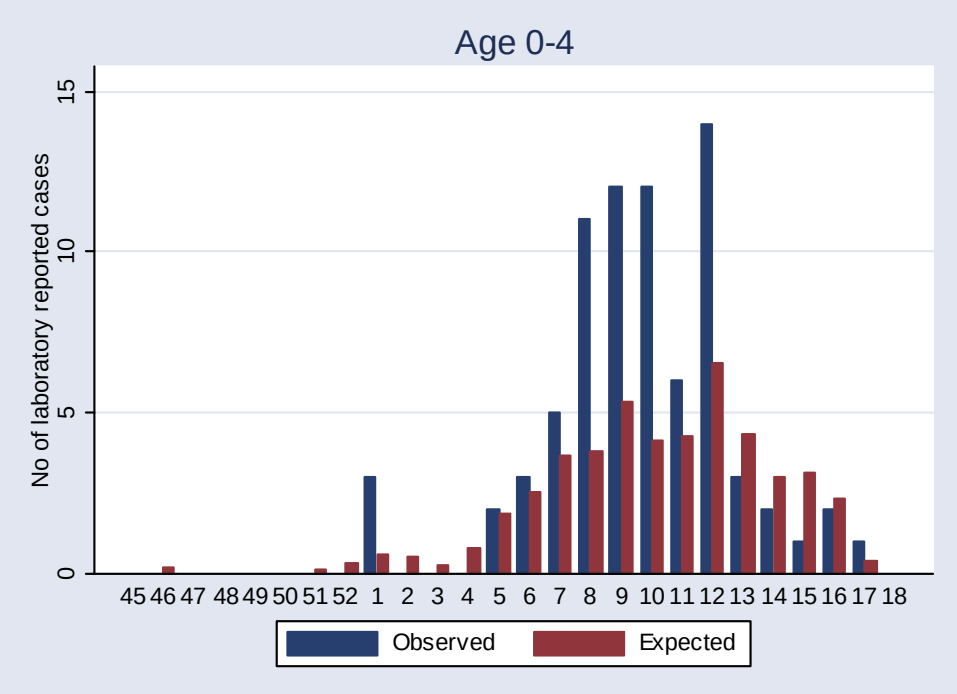



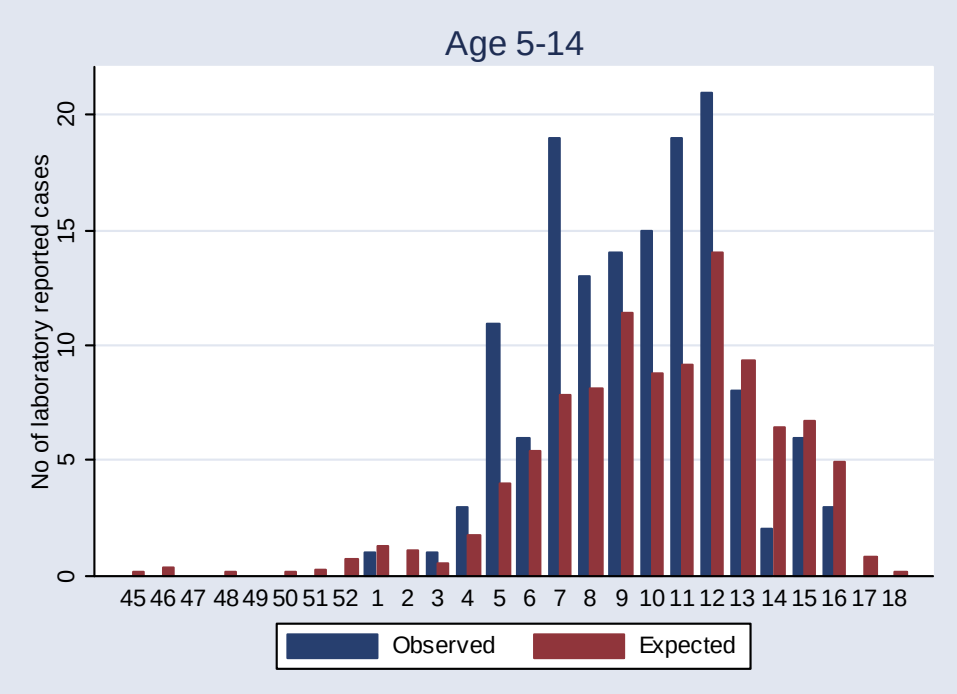

Age 15-64
No of Sentinel reported cases
0
10
20
30
40
50
45 46 47 48 49 50 51 52 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Observed
Expected

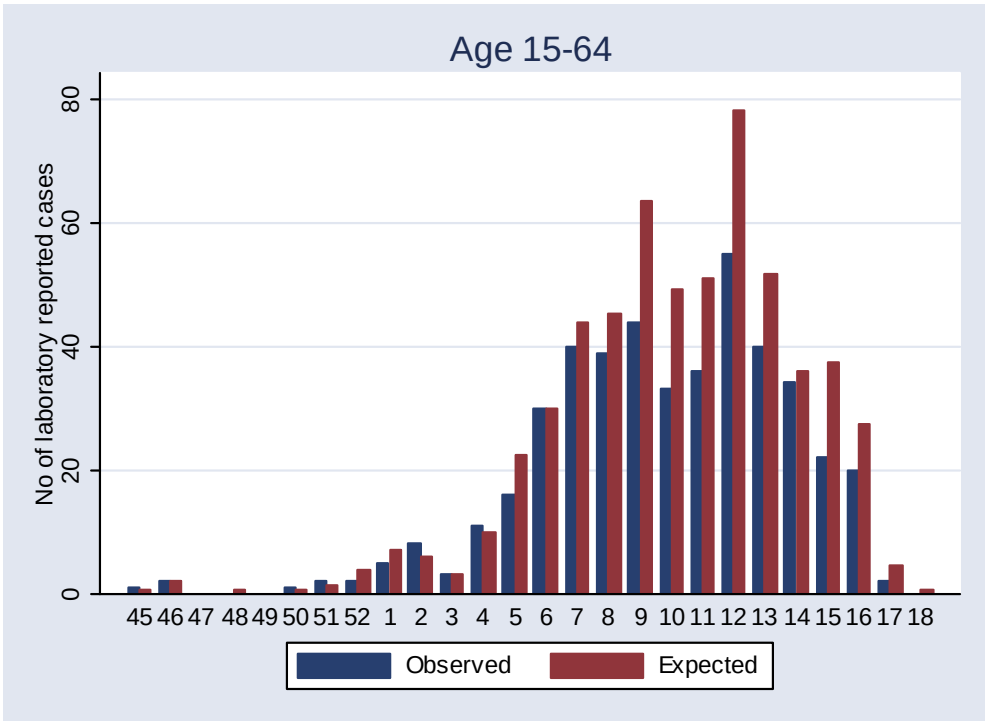

Age 65+
No of Sentinel reported cases
0
5
10
45 46 47 48 49 50 51 52 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Observed
Expected

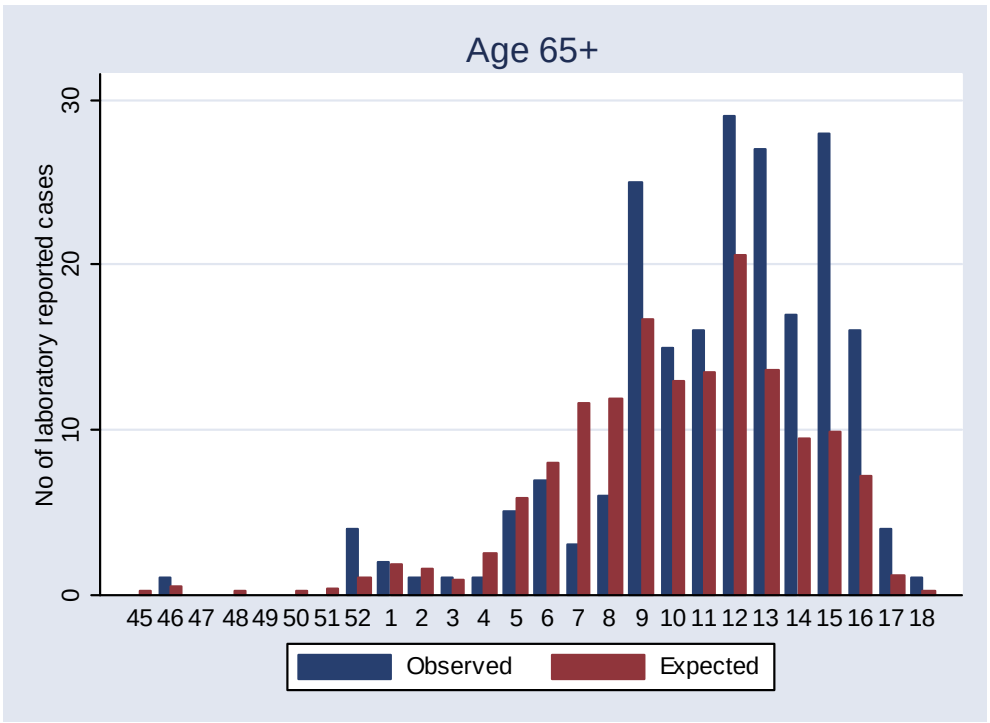
***4.3:2***) Age distribution of laboratory verified cases during the season 2005-06

*"Expected "means here the number of expected cases in relation to the whole population.*

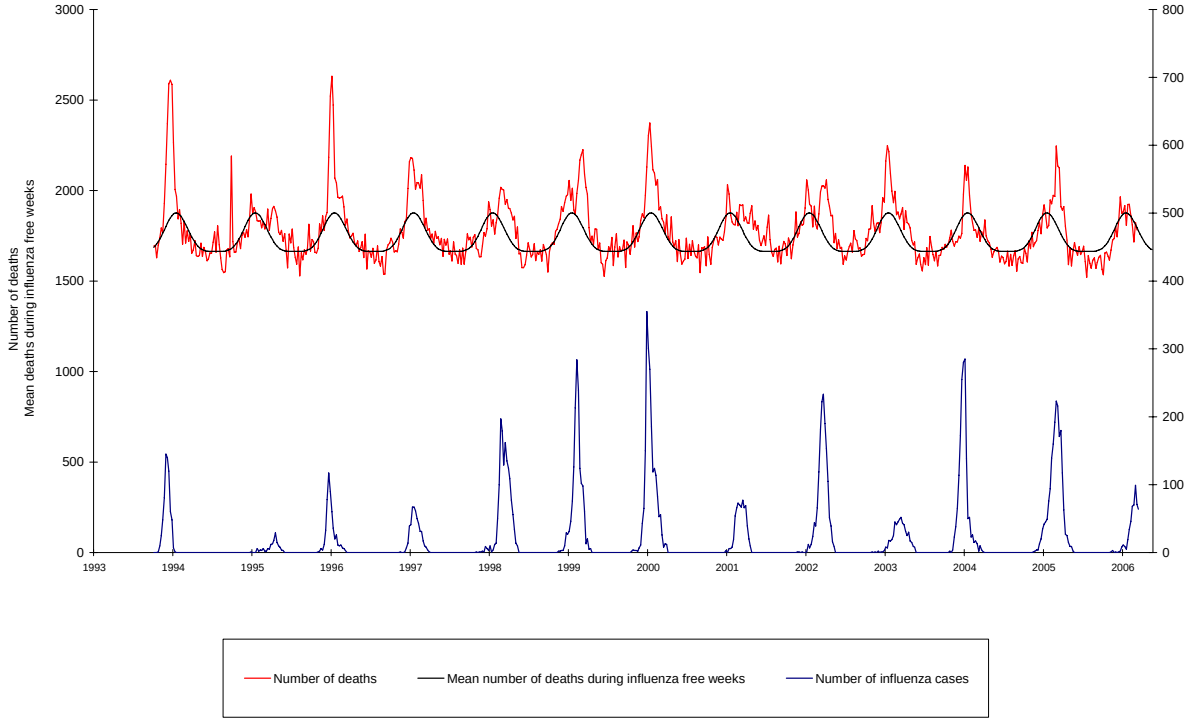



Age 15-64
No of laboratory reported cases
0
20
40
60
80
45 46 47 48 49 50 51 52 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Observed
Expected


Age 65+
No of laboratory reported cases
0
10
20
30
45 46 47 48 49 50 51 52 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Observed
Expected

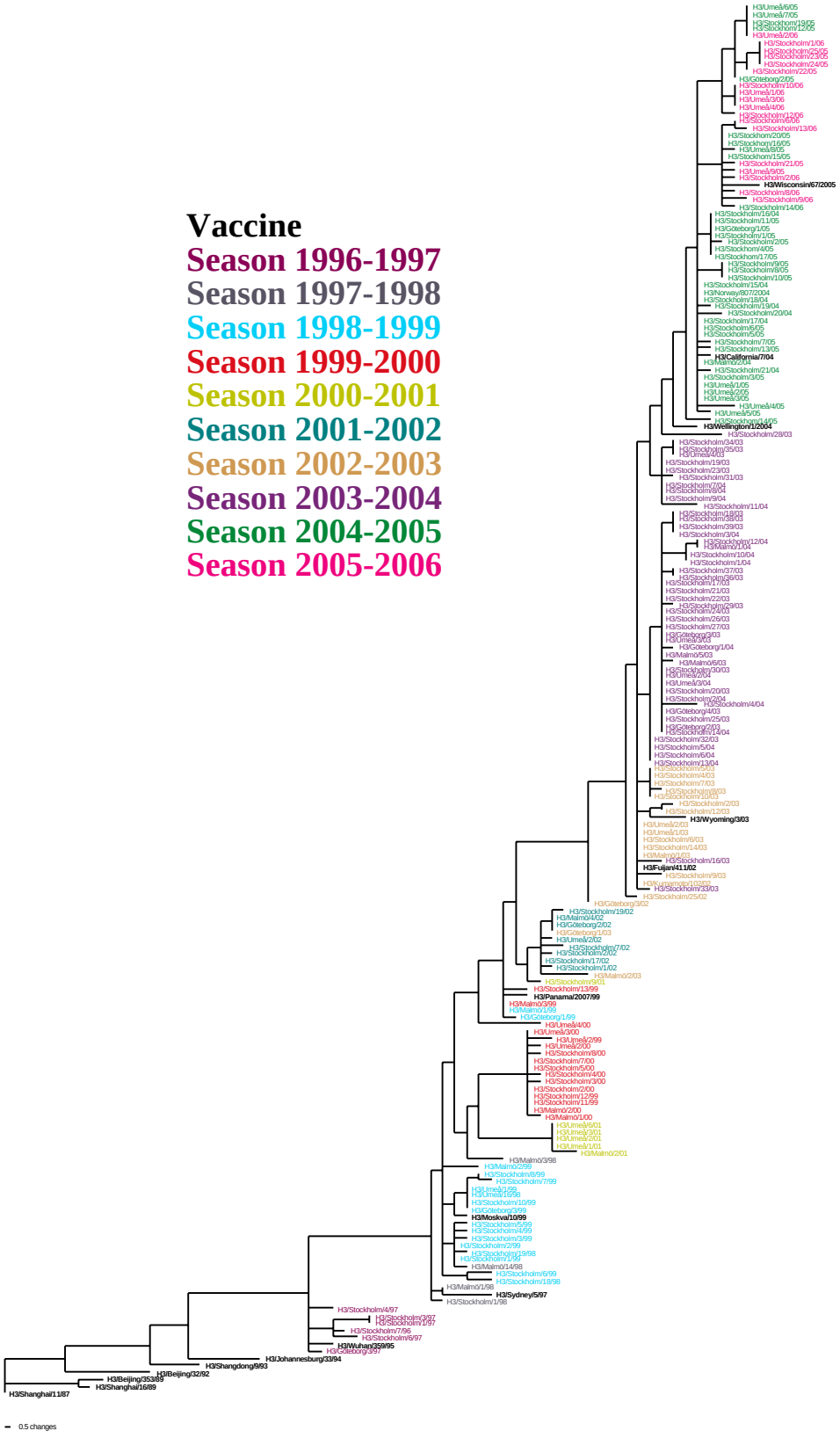
**4:5)** Diagram of the weekly number of deaths in Sweden from week 40 1993 to week 20 2006, and the number of laboratory verified influenza cases during the same period. (The peak of mortality in September 1994 reflects the Estonia ferry catastrophe). Adjusted mean for corresponding influenza-free weeks is also included.



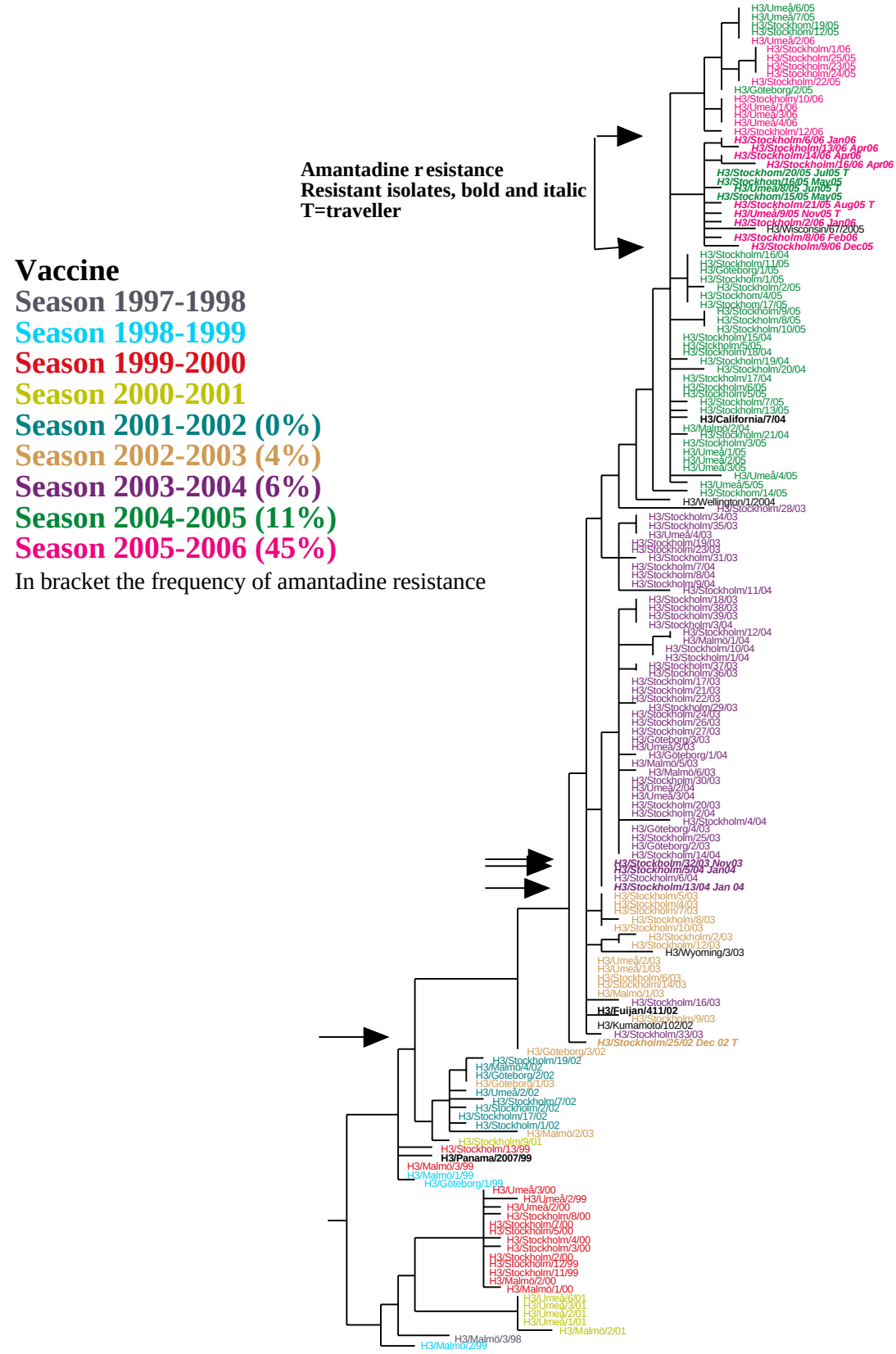
**4:6)** Table of isolates for which extended feno- and genotypings were performed.

| Name: | Genically similar to: | Comments: | M2 mutations: |
|---|---|---|---|
| Influenza B | | | |
| B/Stockholm/11/05 | B/Yamagata/16/88 | | |
| B/Stockholm/1/06 | B/Victoria/2/87 | | |
| B/Stockholm/2/06 | B/Yamagata/16/88 | | |
| B/Umeå/1/06 | B/Yamagata/16/88 | | |
| B/Stockholm/3/06 | B/Victoria/2/87 | | |
| B/Stockholm/4/06 | B/Victoria/2/87 | | |
| B/Stockholm/5/06 | B/Yamagata/16/88 | | |
| B/Stockholm/6/06 | B/Yamagata/16/88 | | |
| B/Stockholm/7/06 | B/Victoria/2/87 | | |
| B/Stockholm/8/06 | B/Yamagata/16/88 | | |
| B/Stockholm/9/06 | B/Victoria/2/87 | | |
| B/Stockholm/10/06 | B/Victoria/2/87 | | |
| Influenza H1N1 | | | |
| A/Stockholm/3/06 | A/New Caledonia/20/99 | | No mutation |
| A/Stockholm/4/06 | A/New Caledonia/20/99 | Traveller from Nairobi | No mutation |
| A/Stockholm/5/06 | A/New Caledonia/20/99 | | No mutation |
| A/Stockholm/7/06 | A/New Caledonia/20/99 | | No mutation |
| A/Stockholm/11/06 | A/New Caledonia/20/99 | | No mutation |
| A/Stockholm/15/06 | A/New Caledonia/20/99 | | No mutation |
| A/Stockholm/17/06 | A/New Caledonia/20/99 | | No mutation |
| Influenza H3N2 | | | |
| A/Stockholm/21/05 | A/California/7/04 | Traveller from south of China | S31N |
| A/Stockholm/22/05 | A/California/7/04 | Traveller from Thailand | No mutation |
| A/Umeå/9/05 | A/California/7/04 | Traveller from Thailand | S31N |
| A/Stockholm/23/05 | A/California/7/04 | Infected by traveller from Singapore | No mutation |
| A/Stockholm/24/05 | A/California/7/04 | Infected by traveller from Singapore | No mutation |
| A/Stockholm/25/05 | A/California/7/04 | | No mutation |
| A/Stockholm/1/06 | A/California/7/04 | | No mutation |
| A/Stockholm/2/06 | A/California/7/04 | | S31N |
| A/Stockholm/6/06 | A/California/7/04 | | S31N |
| A/Umeå/1/06 | A/California/7/04 | | No mutation |
| A/Umeå/2/06 | A/California/7/04 | | No mutation |
| A/Umeå/3/06 | A/California/7/04 | | No mutation |
| A/Umeå/4/06 | A/California/7/04 | | No mutation |
| A/Stockholm/8/06 | A/California/7/04 | | S31N |
| A/Stockholm/9/06 | A/California/7/04 | | S31N |
| A/Stockholm/10/06 | A/California/7/04 | | No mutation |
| A/Stockholm/12/06 | A/California/7/04 | | No mutation |
| A/Stockholm/13/06 | A/California/7/04 | | S31N |
| A/Stockholm/14/06 | A/California/7/04 | | S31N |
| A/Stockholm/16/06 | A/California/7/04 | | S31N |

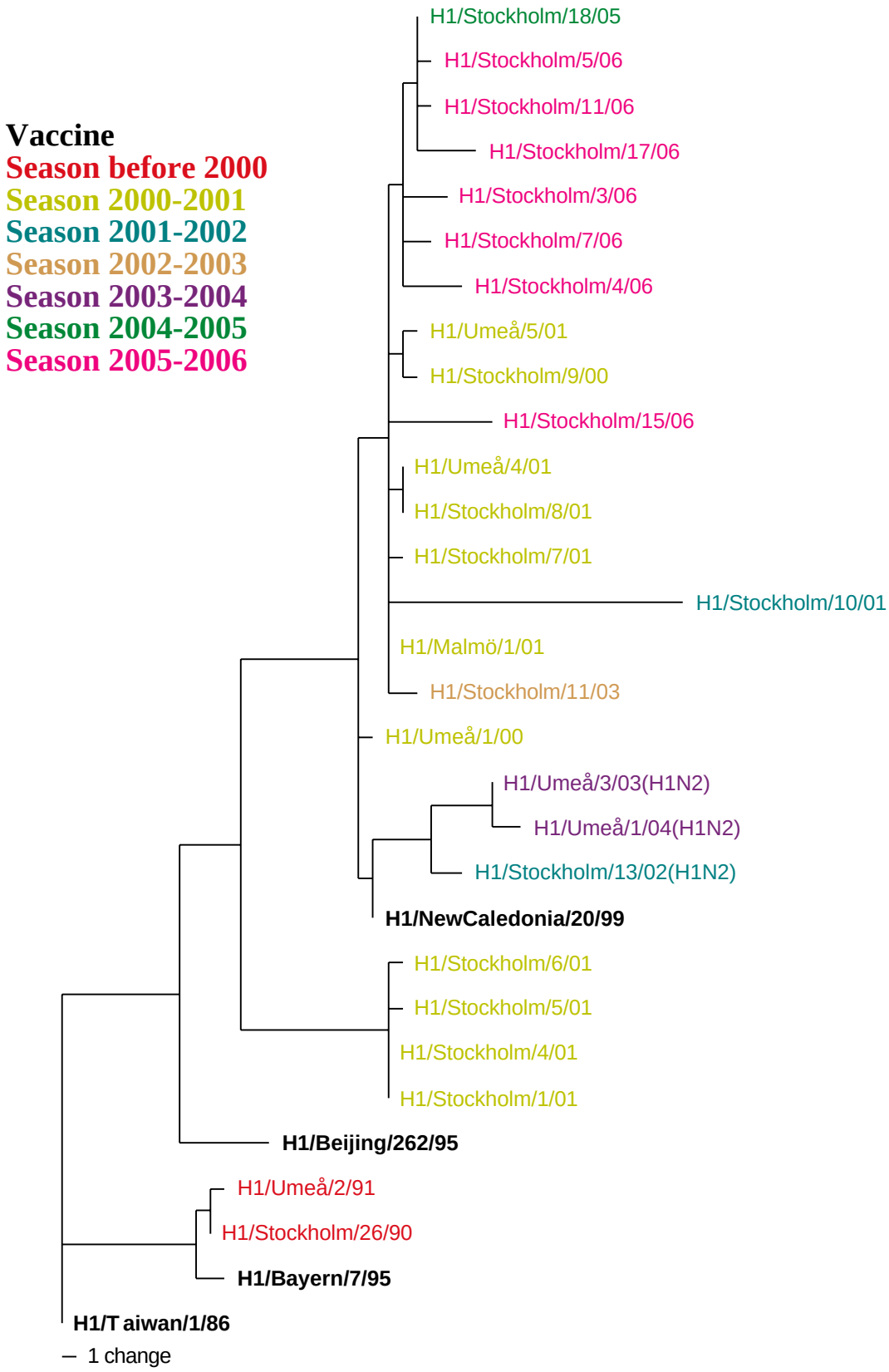
**4:7)** The phylogenetic tree of the amino acid sequences of HA of influenza A/H3 strains isolated in Sweden 1996-2005 compared to the vaccine strains.



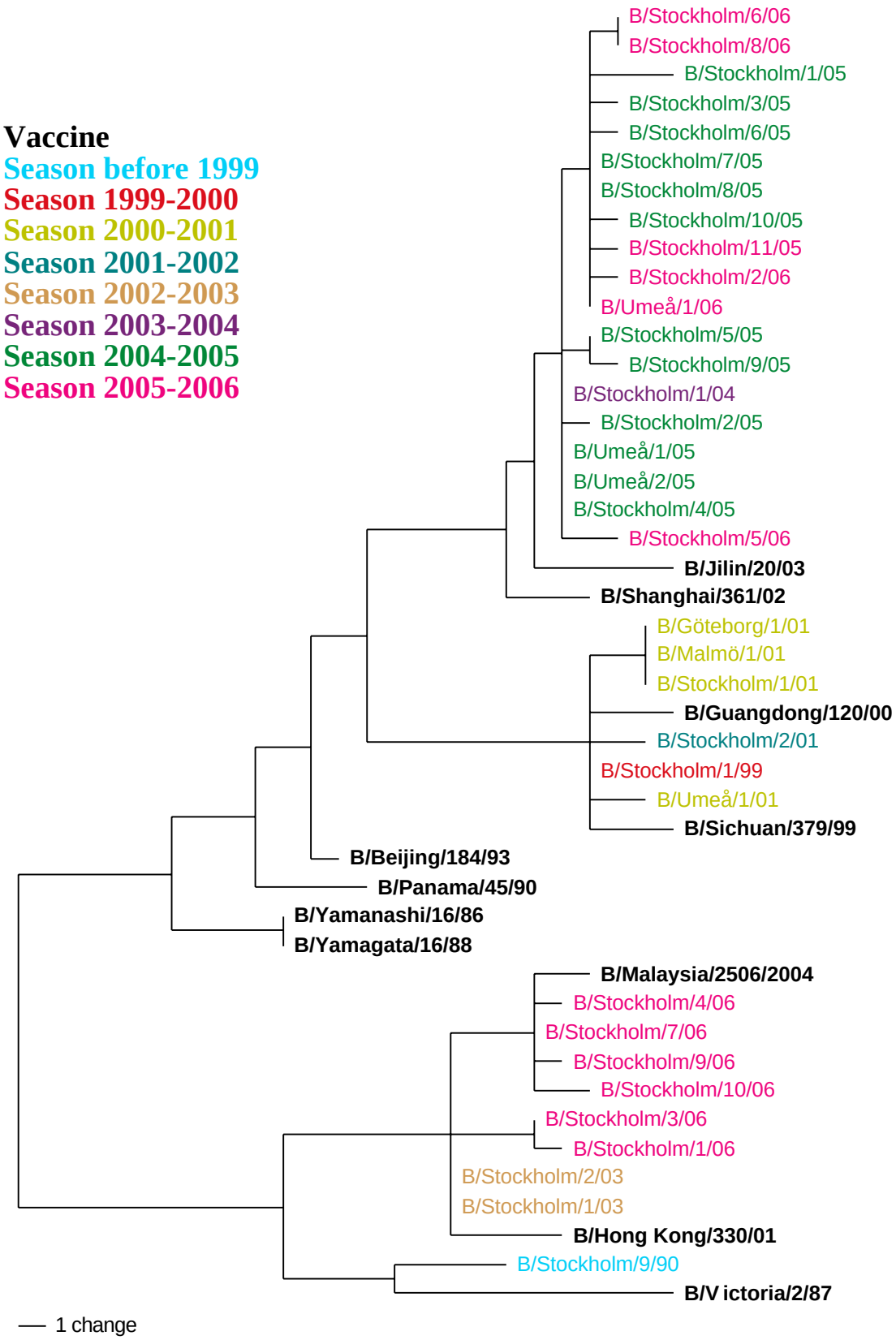
4:8) The phylogenetic tree of the amino acid sequences of HA of influenza A/H3 strains isolated in Sweden 1998-2005. Amantadine resistant strains are indicated with bold and italic name. A T indicate that the isolate derived from a patient travelling in Asia before sampling.



**4:8)** The phylogenetic tree of the amino acid sequences of HA of influenza A/H1 strains isolated in Sweden compared to the vaccine strains



**4:9)** The phylogenetic tree of the amino acid sequences of HA of influenza B strains isolated in Sweden compared to the vaccine strains.



## 5) QUALITY CONTROL OF LABORATORY DIAGNOSIS OF INFLUENZA

In collaboration with the organisation for External Quality Assessment in Sweden (Equalis), panels for quality control of antigen detection with IFA or ELISA and PCR and for virus isolation, were sent to laboratories performing this types of diagnostic assays in Sweden. The influenza panel for IF consisted of 8 different acetone fixed preparations of the influenza strains expected for the season, grown in MDCK cells, and mixed with different proportions of uninfected cells from a lymphoblastoid cell line. Twenty-four laboratories reporting altogether 31data sheets participated. Most of the participating laboratories answered the panel correctly (221/248 analyses). The results of the External Quality control from 1994-2005 related to methods is presented (Table 5:1)

**Table 5:1)** External Quality Control Assessment in Sweden (Equalis).
Results of panels for influenza antigen detection from 1994-2005. The number (%) of reported correct results related to total number of examinations performed with the methods.

| **Panelresultat 1994-2005** | **Influensa A/H1** | **Influensa A/H3** | **Influensa B** |
|---|---|---|---|
| **Imagen** | 215/257 (84%) | 195/225 (87%) | 171/234 (73%) |
| **DPC-PathoDx** (2000-2005) | 102/123 (83%) | 103/110 (94%) | 76/86 (88%) |
| **Chemicon indirekt IF** | 96/98 (98%) | 84/89 (94%) | 87/91 (96%) |
| **WHO** | 33/35 (94%) | 30/31 (97%) | 29/30 (97%) |
| **Chemicon direkt IF** (2000-2005, not 2004) | 19/24 (79%) | 17/18 (94%) | 12/14 (86%) |
| **Biotrin** (1994-2005, not 1999) | 15/16 (94%) | 15/16 (94%) | 12/12 (100%) |
| **Real-time PCR** (2003-2005) | 14/14 (100%) | 15/15 (100%) | 10/10 (100%) |
| **Binax NOW** (2004-2005) | 7/8 (88%) | 8/9 (89%) | 2/6 (33%) |
| **Becton-Dickinson** (2001-2003) | 8/10 (80%) | 8/8 (100%) | 2/6 (33%) |
| **Biosoft/Argene** (1994-1999) | 5/6 (83%) | 6/6 (100%) | 5/7 (71%) |

## 6) METHOD DEVELOPMENT AND RESEARCH

**6:1.** The frequency rate of admantane resistant influenza A, H3 and H1 strains, circulating in Sweden during season 2001-2002 to 2005-2006 was investigated. No resistance among subtype H1 isolates was found. The first resistant H3 strain was collected from a traveller from Asia during season 2002-2003. The frequency of resistance among H3 isolates increased from 4% during season 2002-2003 to 45% during this season (Table 4:6 and 6:1).
The most common mutation was serine-to-asparagine at position 31 (S31N) in M2.
One isolate (Stockholm/16/05) contained a valine-to-alanine change at amino acid position 27 (V27A), in combination with the S31N mutation.
The resistant strains were collected from patients with or without travelling history from Asia. During the last two seasons resistant strains were collected during the whole seasons, however, all the resistant strains clustered together in the phylogenic analyse of hemagglutinin (Figure 4:8).

Table 6:1) Frequency rate of admantane resistant influenza A, H3 and H1 strains, circulating in Sweden during season 2001-2002 to 2005-2006.

| Adamantane resistance among Swedish influenza | | | | |
|---|---|---|---|---|
| Season | No analysed | H1 | H3 | Resistance among H3 |
| 2001-2002 | 31 | 1 | 30 | 0/30 (0%) |
| 2002-2003 | 24 | 1 | 23 | 1/23 (4%) |
| 2003-2004 | 51 | 2 | 49 | 3/48 (6%) |
| 2004-2005 | 38 | 1 | 37 | 4/37 (11%) |
| 2005-2006 | 24 | 5 | 20 | 9/20 (45%) |

### 6:2. Sentinel sampling.

New founding from the Swedish Government has allowed initiation of sentinel sampling from Swedish sentinel units. Some infectious clinics and sentinel units will also be included. The systems will be dimensioned for 200 samples/week, to be examined by PCR, and cultivations upon positive PCR result.

## 6:3. Modelling and prediction.

6:3.1. Sentinel and laboratory data have been used by a group of statisticians to evaluates models for epidemic predictions.

The reports are available on www.smitskyddsinstitutet.se, under the following headings:

**Exploratory analysis of spatial aspects on the Swedish influenza**

Smittskyddsinstitutets rapportserie 3:2006. Författare David Bock och Kjell Pettersson. Statistical Research Unit, Göteborg University.

**On statistical surveillance of Swedish influenza incidence. Peak detection**

Smittskyddsinstitutets rapportserie 2:2006. Författare David Bock, Eva Andersson och Marianne Frisén. Statistical Research Unit, Göteborg University.

**Exploratory analysis of Swedish influenza data**

Smittskyddsinstitutets rapportserie 1:2006. Författare Eva Andersson, David Bock och Marianne Frisén, Research Unit, Göteborg University.

A special analysis on the possibility of prediction based on the timing of laboratory diagnoses will be performed separately.

6:3.2.In a study founded by the Swedish Emergency Management Agency, detailed modelling for prediction of spread of influenza in the society is performed by PhD Lisa Brouwers and collaborators.

## 6:4. Death rates.

In collaboration with the demographic unit at Sweden statistics a study to identify a possible role of influenza vaccination for the sudden decrease of death rates in Sweden. The fluctuations of death rates in the Nordic countries will further be studied in a collaboration lead by Ann Mazick, Statens Seruminstitut, Copenhagen.

## 6:5. Population-based surveillance.

Since sentinel reporting by GPs only reveal a part of the true spread of influenza in the society, a study of self reporting of disease has started. The prerequisites for recruiting at least 1% of the population for self reporting of influenza via SMS, automated telephone requests and the webb is being studied. In a pilot study, self reporting was compared to personal interviews. The results were rather discouraging concerning the automated techniques, and analyses for the reasons for the failure, and renewal of the recruitment program are being conducted. A pilot study for recruitment and optimal technique will be conducted during September, and a population-based study of one Swedish county is planned to start during the next influenza season.

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