



July 2017

Summary Report - The 2016/2017 Influenza Season

Main Findings:

Laboratory Surveillance:

- In the 2016/2017 winter season, the surveillance network numbered 26 clinics distributed throughout Israel. The sentinel clinic network operated from the first week of October 2016 (Week 40) until the second half of April 2017 (Week 15).
- A total of 1,284 specimens for influenza and RSV were collected from the sentinel network. Approximately 36% of the specimens were positive for influenza; 11% of the specimens were positive for RSV.
- The majority of influenza-positive specimens were positive for influenza A (approximately 98%); 99.8% of these were positive for influenza A/H3. 2.1% of the specimens were found to be positive for influenza B.
- The influenza virus isolation rate in the sentinel clinics reached a peak of approximately 56% in Week 52 of the year 2017.
- Molecular characterization of the influenza virus showed three main groups of mutations as compared to the vaccine strain. Data from the surveillance system indicate that the vaccine formulation for the 2016-2017 season was more effective in persons under the age of 65 than in persons aged 65 and over.

Clinical Surveillance:

- In the 2016/17 influenza system, influenza-like illness was observed in the community early in comparison with the multi-annual average, with rates that were lower in comparison with the two preceding winter seasons. Influenza activity in the community in the 2016/17 winter season is defined as medium or lower as per the thresholds calculated using the algorithm developed in the framework of the European influenza surveillance project.
- Similarly to the two previous winter seasons, during this season also influenza-like morbidity rates in the community were highest for infants, children and youths up to the age of 18, and low for the elderly aged 65 and over.



- The rate of visits to "Maccabi Healthcare Services" physicians that concluded with a diagnosis of pneumonia was particularly high among the elderly aged 65 years and over, reaching a peak of 467 visits per 10,000 elderly persons.
- Throughout the season, pediatric emergency room visits due to pneumonia were below the multi-annual average during the 2016/17 winter season.
- Visits to adult emergency rooms due to pneumonia were above the multi-annual average during Weeks 49 in 2016 (beginning of December 2016) until Week 2 of 2017 (beginning of January 2017).
- Throughout the 2016/17 winter season, the average hospital bed occupancy rate in internal medicine departments of general hospitals exceeded 100%.
- In pediatric departments, the average hospital bed occupancy rate exceeded 100% from Week 1 of 2017 (beginning of January 2017) until Week 4 of 2017 (end of January 2017).
- During the 2016/17 winter season, the percentage of deaths due to pneumonia varied around the seasonally expected level.
- The mortality rate among the elderly aged 65 years and over in the 2016/2017 winter season was higher than the multi-annual average between Week 52 of the year 2016 (end of December 2016) and Week 4 of 2017 (end of January 2017). The mortality rate in the population under the age of 65 years varied around the multi-annual average throughout the entire season.

Immunization against Influenza:

- In the 2016/17 winter season, the vaccine chosen was the inactivated vaccine. Two types of inactivated vaccine were in use in Israel: inactivated trivalent vaccine (against 3 strains of influenza) and inactivated quadrivalent vaccine (against 4 strains of influenza).
- The vaccine against 3 strains is recommended for the overall population from age 6 months; infants aged from 6 months to two years may only receive inactivated vaccine while 2-49 year olds may receive live attenuated vaccine or inactivated vaccine. For adults aged 50 and over, only inactivated vaccine is recommended. Inactivated vaccine against 4 strains is intended for those aged 3 years and over.
- During September 2016, second grade pupils received the (trivalent) vaccine against influenza, in the framework of the routine vaccines given in schools via the student health services. Some 55% of second grade pupils were immunized against influenza.



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- In the 2016/17 winter season, some 1,750,000 people were immunized against seasonal influenza (approximately 21% of the total population of Israel). Immunization coverage in persons aged 65 years and over reached approximately 62%. Immunization coverage for infants and children aged 6-59 months reached approximately 21%.



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- **Background:**

The influenza surveillance system in Israel is administered by the Israel Center for Disease Control (ICDC) in the Ministry of Health, and is based on two arms: a laboratory arm and a clinical arm. The laboratory surveillance is based on nasal and pharyngeal swab specimens collected from patients presenting to one of the sentinel clinics with influenza-like illness, and tested for the presence of influenza virus at the Central Virology Laboratory of the Ministry of Health. The clinical surveillance is primarily based upon information regarding patient visits to clinics in the community and to hospital emergency rooms due to influenza-like illness, upper respiratory tract inflammation and pneumonia.

All the information collected from the various information sources is analyzed by the staff of the Unusual Morbidity Surveillance Unit of the ICDC, and summarized in weekly reports during the influenza season and distributed to the management of the Ministry and to specific groups of physicians. The reports may be viewed on the Ministry of Health website in Hebrew and in English¹.

The objectives of the influenza surveillance system are to present an up-to-date picture of morbidity from influenza and its complications, to describe the burden on the health system and to characterize the active influenza strains. The surveillance is usually conducted from October until April of the following year².

1. Laboratory Surveillance

Starting from the winter of 1996/97, the ICDC has been operating a network of sentinel clinics in the community to identify the influenza viruses that are active during the influenza season. In the 2016/2017 winter season, the surveillance network numbered 26 clinics distributed throughout Israel, from Dimona in the South to Akko in the North (Appendix 1 shows the distribution of the sentinel clinics). The medical staff in these clinics have been instructed to take nasal and pharyngeal swabs from patients who are in the first or second day of their illness and meet the definition of influenza-like illness (temperature of 37.8°C or higher accompanied by one or more of the following signs: cough, sore throat, muscle pain, runny nose, chills, etc.). The nasal and pharyngeal swabs are stored under refrigeration, and are transported once per week to the Central Virology Laboratory of the Ministry of Health (Public Health Services), where they are tested for the presence of influenza virus and of RSV (Respiratory Syncytial Virus). In the laboratory, the influenza viruses are characterized at the level of type, subtype and



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strain; genetic and antigenic changes are identified. The degree of correspondence of the influenza viruses to the seasonal vaccine is also assessed.

1.1 Virological Surveillance via the Sentinel Clinic Network: Winter 2016/2017

The sentinel clinic network operated from the first week of October 2016 (epidemiological Week 40) until the second half of April 2017 (Week 15). Table 1 shows the overall number of specimens received in the laboratory for each of the weeks of the surveillance period, for the under-18 and the 18-and-over age groups. The findings of the Central Virology Laboratory's testing of the specimens collected during the above period is shown in Tables 2 and 3. 97.9% of the specimens were found to be positive for influenza A, and approximately 2.1% of the specimens were found to be positive for influenza B. Approximately 99.8% of the specimens positive for influenza A were A/H3 (Table 3).



Table 1: Number of Specimens by Epidemiological Week and Age Group*, Winter 2016/2017^{1,3}:

Week	Year	Total No. of Specimens*	Number of Specimens from Children (under the age of 18)	Number of Specimens from Adults (18 years and over)
40	2016	15	5	10
41	2016	21	9	12
42	2016	22	10	12
43	2016	23	11	12
44	2016	28	18	10
45	2016	36	20	16
46	2016	47	31	16
47	2016	64	33	31
48	2016	63	37	26
49	2016	71	29	42
50	2016	113	50	63
51	2016	97	55	42
52	2016	101	38	63
1	2017	121	48	73
2	2017	99	44	55
3	2017	80	29	51
4	2017	60	26	34
5	2017	56	17	39
6	2017	37	15	22
7	2017	38	12	26
8	2017	29	16	13
9	2017	20	10	10
10	2017	17	8	9
11	2017	5	3	2
12	2017	9	3	6
13	2017	2	0	2
14	2017	4	2	2
Total		1278	579	699

*For 6 specimens, age/date of birth is missing.



Table 2: Distribution of Influenza and RSV Isolations from Nasal and Pharyngeal Specimens Collected in the Sentinel Clinics, Winter 2016/17^{1,3}: Numbers and Percentages

Total Number of Specimens Sent	N=1,284	%
Influenza-positive specimens*	469	36.5
RSV-positive specimens*	140	10.9
Specimens negative for influenza and for RSV	675	52.6

*2 specimens during the current season were found to be positive both for influenza and for RSV.

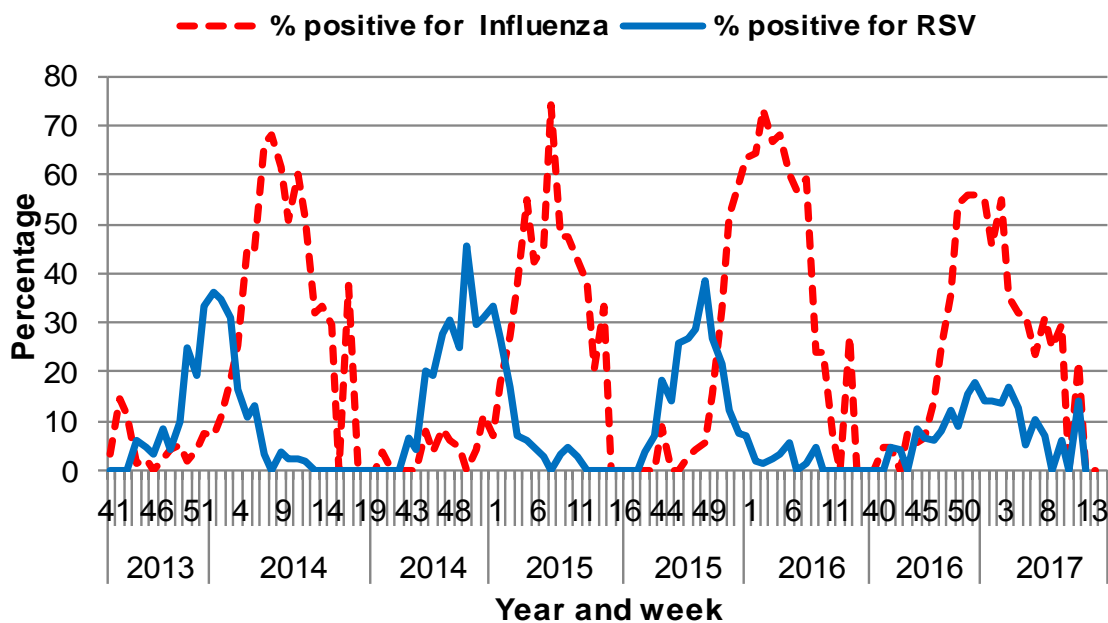
Table 3: Distribution of Influenza Isolations from Nasal and Pharyngeal Specimens By Type, Winter 2016/17^{1,3}: Numbers and Percentages

Type of Influenza Virus	N	%
Type A influenza	459	97.9
A/H1N1 2009	1	0.2
A/H3	458	99.8
A/H1	0	0
Type B influenza	10	2.1
Total no. of influenza-positive isolations	469	100



Figure 1 shows the results of testing by the Central Virology Laboratory of specimens collected from the sentinel clinics during the surveillance season, by week. The percentage of RSV-positive isolations began to rise from the first week of December 2016 (Week 48). The percentage of isolations continued to increase until the last week of December 2016, when it reached a peak of 17.6% of all specimens. From the first week of January 2017, the percentage of RSV isolations declined in the sentinel clinics. The percentage of influenza-positive isolations began to increase in the last week of November 2016 (Week 47), and starting from this Week, the percentage of influenza isolations was higher than the percentage of RSV isolations. In Week 1 of 2017, the percentage of influenza isolations reached a peak of some 56%, after which the percentage of isolations began to decline. Specimens positive for influenza were found throughout almost the entire surveillance period, until Week 14 of 2017 (first week of April 2017). The percentage of specimens positive for RSV declined to a few percent only starting from Week 6 of 2017 (second half of February 2017), and the percentage of specimens positive for influenza declined to a few percent only starting from Week 11 of 2017 (second half of March 2017) ³.

Figure 1: Nasal and Pharyngeal Specimens Positive for Influenza and for RSV Collected at the Sentinel Clinic Network, By Week of Specimen, 2013-2017^{1,3}: Percentages



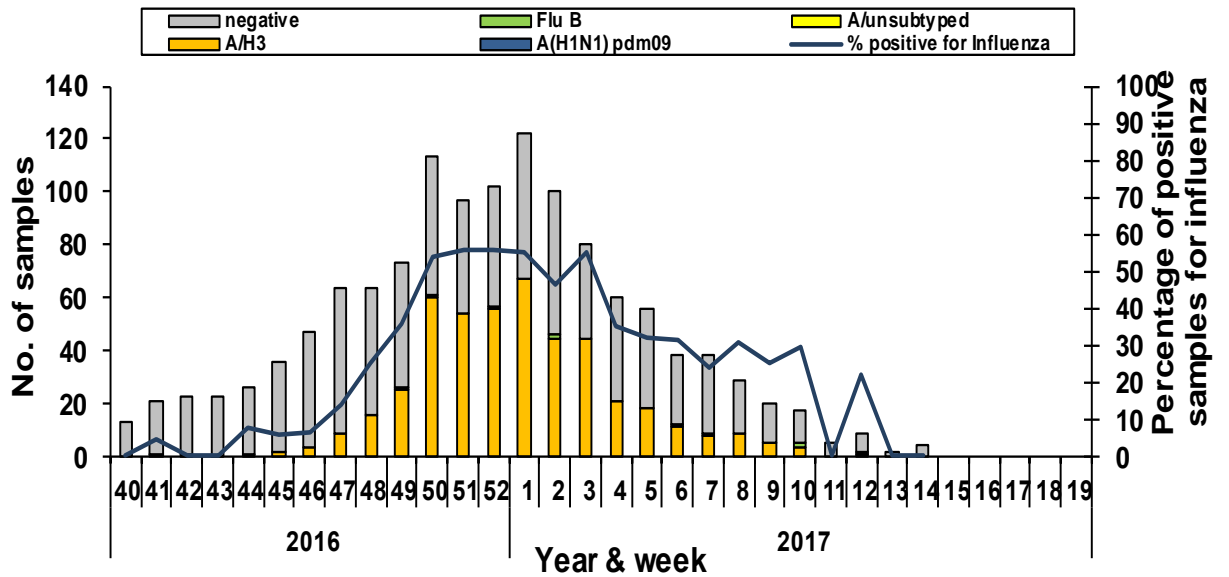


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Figure 2 shows the influenza subtypes isolated from specimens in the sentinel network. A similar pattern of subtype isolations was also identified in hospitalized patients with respiratory illness diagnosed at the Central Virology Laboratory.

Figure 2: Nasal and Pharyngeal Specimens Collected at the Sentinel Clinic Network, By Laboratory Finding and Week of Specimen, Winter 2016/17^{1,3}: Numbers and percentage positive for influenza





2. Clinical Surveillance

The clinical surveillance is based on a number of information sources:

- Data regarding persons insured by the two largest HMOs in Israel ("Maccabi Healthcare Services"⁴ and "Clalit" Health Services⁵) who presented to community physicians and were clinically diagnosed as having influenza or influenza-like illness, acute upper respiratory tract infection or pneumonia. Detailed non-identified information about these patients is conveyed to the ICDC daily, and stored in a dedicated database.
- Daily data regarding the number of patients who presented to the emergency rooms of "Clalit" Health Services' eight general hospitals and were diagnosed with pneumonia.
- Daily data regarding hospital bed occupancy rates in the general hospitals.
- Data regarding deaths in the community and in hospitals.
- Weekly data regarding overall deaths in Israel due to all causes and due to pneumonia, which were reported to the Epidemiology Division of the Ministry of Health.

2.1 Surveillance of Influenza-Like Morbidity in the Community

Figure 3 shows weekly influenza-like morbidity rates, based upon patient visits to "Maccabi Healthcare Services" physicians in the community during the period May 2014 to May 2017. This period includes the three last winter seasons. The average is also plotted, demonstrating seasonal influenza activity in the community in Israel from multi-annual data (2008-2015, excluding the 2009/10 winter season, which deviated from the norm due to the appearance of a new strain of influenza A/H1N1, which caused a pandemic). This season, we have again displayed the baseline level in the figure, which is intended to indicate the beginning of the influenza season and the intensities of influenza activity. The baseline level and the intensities were calculated using an algorithm that was developed in the framework of the European influenza surveillance project (EuroFlu), based on past data accumulated at the ICDC regarding visits to "Maccabi Healthcare Services" clinics due to influenza-like illness. Morbidity rates exceeded the baseline level for the first time in Week 50 of 2016 (second half of December 2016), and remained above it until Week 6 of 2017 (beginning



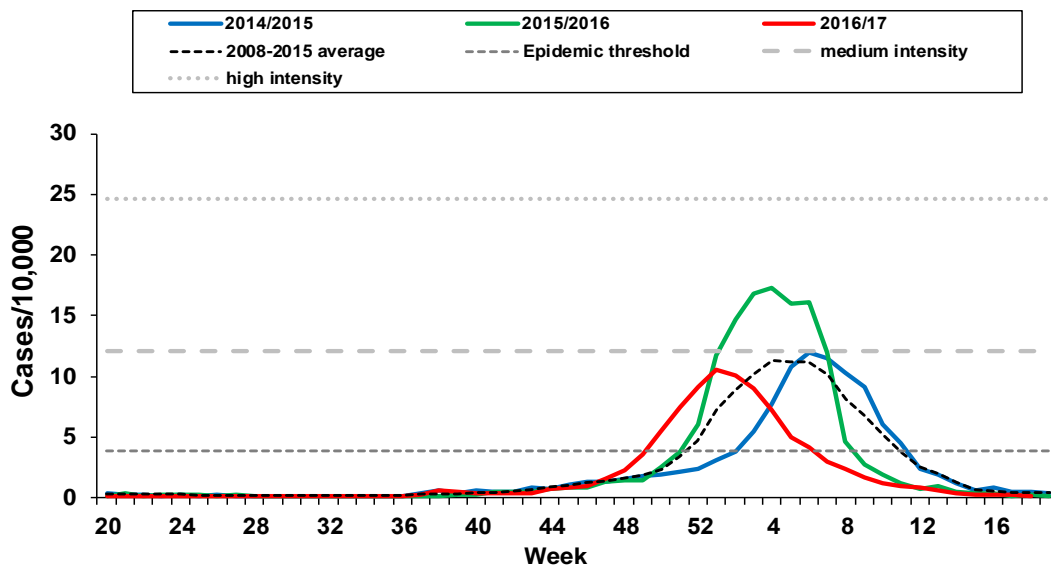
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of March 2017). Influenza activity in the community in the 2016/17 winter season is defined (by peak morbidity) as moderate or lower as per the thresholds calculated using the algorithm developed in the framework of the European influenza surveillance project.

In the 2016/17 winter season, morbidity observed in the community occurred early as regards both the beginning of the season and the peak of the season relative to the multi-annual average, and was at low levels as compared to the two winter seasons that preceded it. The highest morbidity rates observed were for infants, children and youths up to the age of 18 years, similarly to the previous two years (Figure 4).

Figure 3: Visits per Week to "Maccabi Healthcare Services" Clinics that ended with a Diagnosis of Influenza-Like Illness*^{1,4}: Cases per 10,000



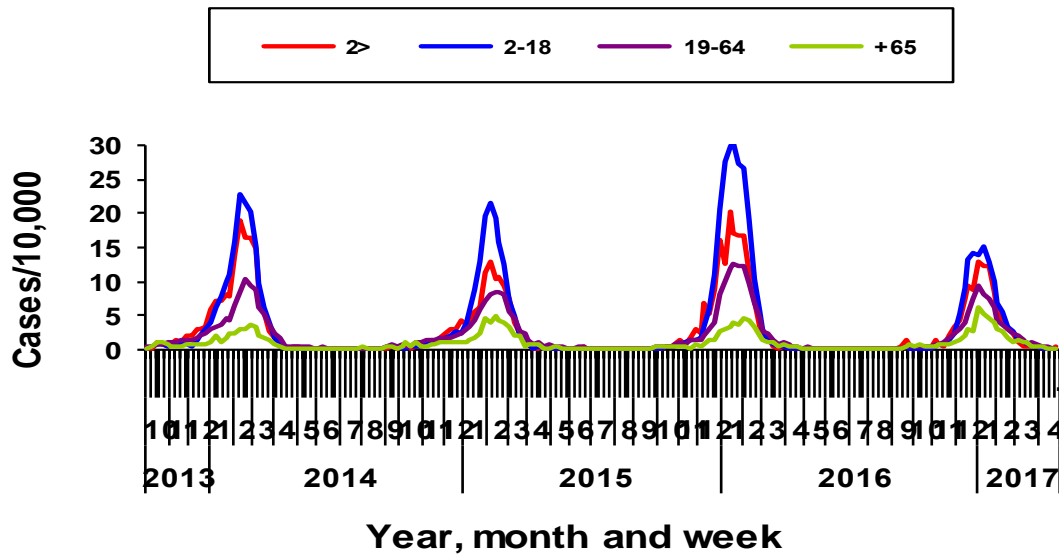
* The multi-annual average does not include the 2009/10 winter season.



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Figure 4: Visits per Week to "Maccabi Healthcare Services" Clinics that ended with a Diagnosis of Influenza-Like Illness, by Age Group^{1,4}: Cases per 10,000



2.2 Surveillance of Pneumonia Morbidity in the Community

Figure 5 shows weekly visit rates to "Maccabi Healthcare Services" physicians that ended with a diagnosis of pneumonia during the period May 2014 to May 2017, as compared to the multi-annual average, excluding the 2009/10 winter season. During Weeks 40-48 of the year 2016 (the first week of October 2016 until the beginning of December 2016), clinic visit rates were below the multi-annual average. During Weeks 49-1 of the 2016/2017 season (the beginning of December 2016 until the beginning of the year 2017), the visit rate was above the multi-annual average, and during Weeks 2-15 of 2017 (the beginning of January 2017 until mid-April 2017), the rates reverted to being below the multi-annual average (Figure 5).

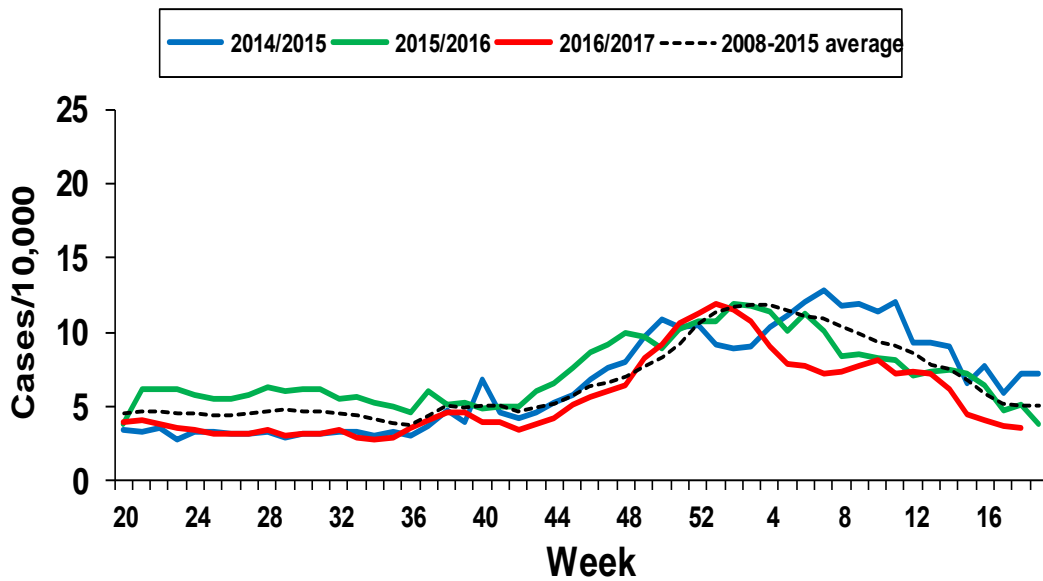
The rate of visits due to pneumonia in the group of infants under the age of two years reached a peak of some 69 per 10,000 HMO members in the 2016/17 winter season; in the group of children and youths aged 2-18 years, the visit rate reached 14 per 10,000 HMO members, and the visit rate for the group of the elderly, aged 65 years and over, reached some 21 visits per 10,000 HMO members. For the 19-64 year old age group, visit rates due to pneumonia were lower than the rates for the remaining age groups (Figure 6).



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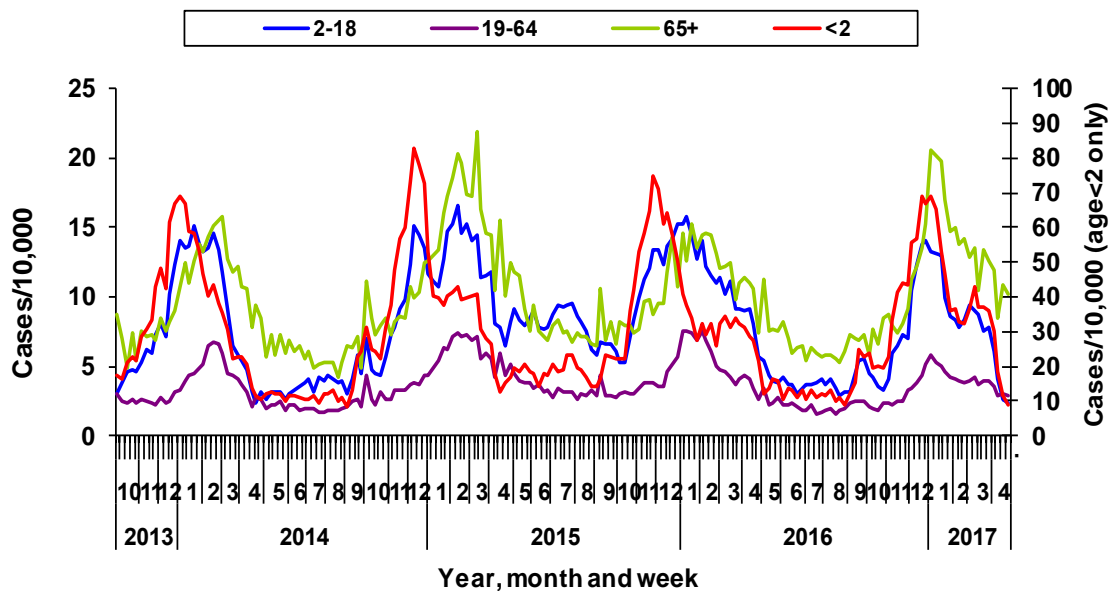
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Figure 5: Visits per Week to "Maccabi Healthcare Services" Clinics that ended with a Diagnosis of Pneumonia^{1,4*} : Cases per 10,000



* The multi-annual average does not include the 2009/10 winter season.

Figure 6: Visits per Week to "Maccabi Healthcare Services" Clinics that ended with a Diagnosis of Pneumonia, by Age Group^{1,4}: Cases per 10,000 (the y-axis for infants up to the age of two years is on the right hand side of the Figure, and the y-axis on the left hand side of the Figure is for all the remaining age groups)

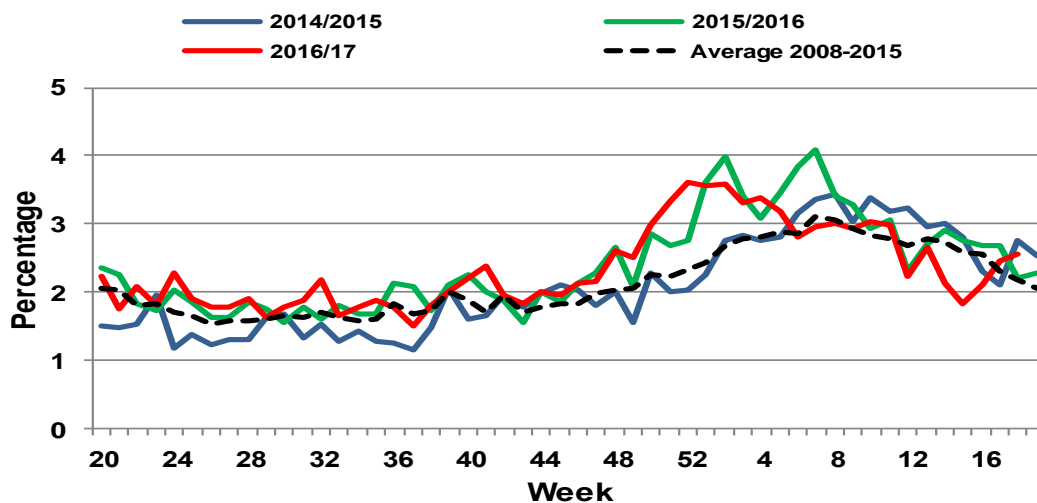




2.3 Surveillance of Emergency Room Visits that ended with a Diagnosis of Pneumonia

Influenza morbidity is generally accompanied by increased emergency room visits due to pneumonia. Figures 7 and 8 show the visits that ended with a diagnosis of pneumonia, as a percentage of all visits that ended with any diagnosis, to adult and pediatric emergency rooms of "Clalit" Health Services' eight general hospitals. From Week 20 until Week 48 of the year 2016 (beginning of December 2016), the percentage of visits to adult emergency rooms diagnosed with pneumonia varied around the multi-annual average. Starting from Week 49 of the year 2016 (beginning of December 2016) until Week 2 of the year 2017 (beginning of January 2017), the percentage of visits was above the multi-annual average (Figure 7)⁵. From Week 3 of 2017 (second half of January 2017) until Week 15 (mid-April 2017), the percentage of visits was below the multi-annual average (Figure 7)⁵. Pediatric emergency room visits due to pneumonia were at a lower level than the multi-annual average throughout the entire season (Figure 8)⁵.

Figure 7: Visits to (Adult) Emergency Rooms in "Clalit" Health Services' Hospitals that ended in a Diagnosis of Pneumonia, May 2014 - April 2017, and the Multi-Annual Average*^{1,5} (expressed as a percentage of all visits that ended with any diagnosis)



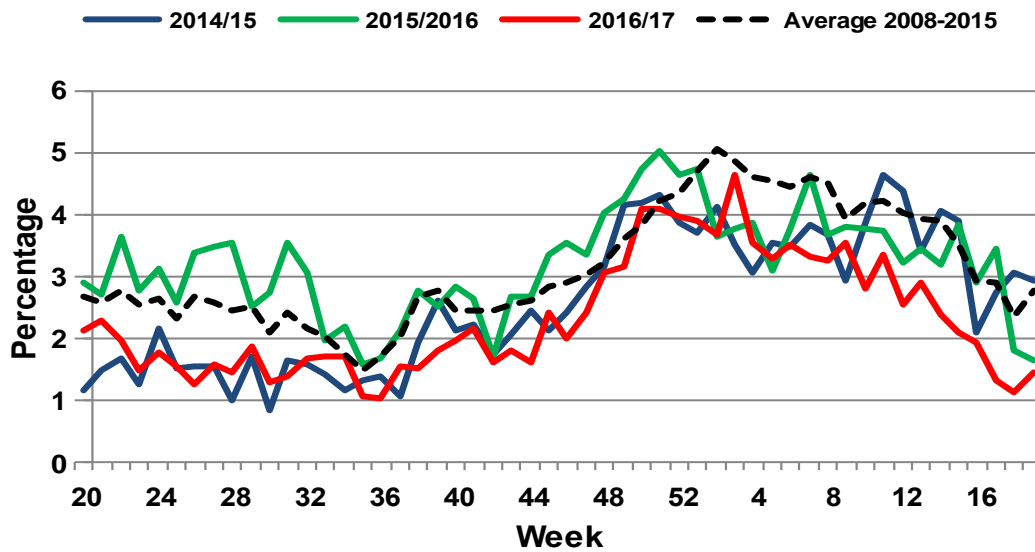
* The multi-annual average does not include the 2009/10 winter season.



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Figure 8: Visits to (Pediatric) Emergency Rooms in "Clalit" Health Services' Hospitals that ended in a Diagnosis of Pneumonia, May 2014 - April 2017, and the Multi-Annual Average*^{1,5} (expressed as a percentage of all visits that ended with any diagnosis)

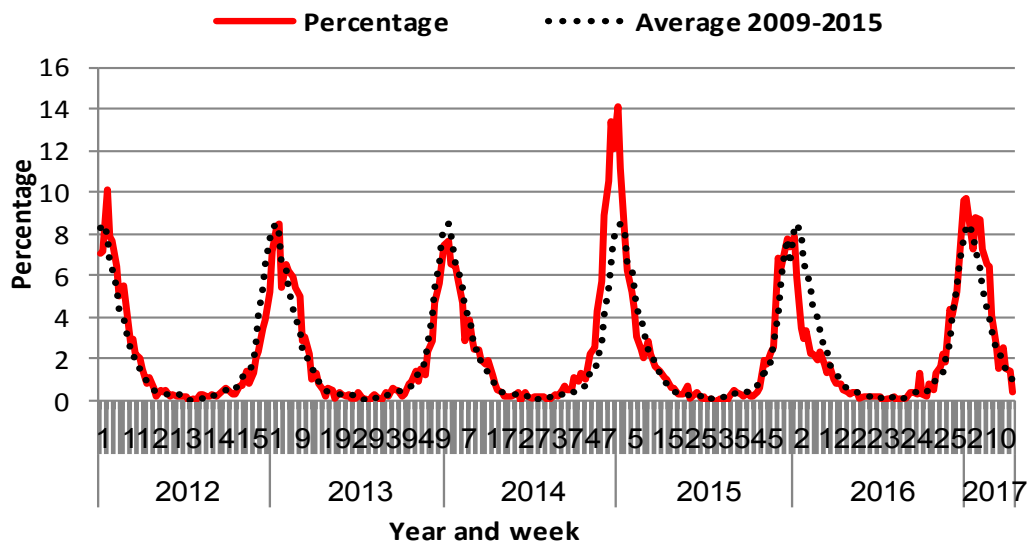


* The average does not include the 2009/10 winter season.

2.4 Surveillance of (Pediatric) Emergency Room Visits that ended with a Diagnosis of Bronchiolitis

Figure 9 shows the percentage of visits of infants under the age of two years to pediatric emergency rooms due to bronchiolitis in the years 2011-2017. It can be seen that the wave of morbidity commenced this year as expected in Week 50 of 2016, and the percentage of visits reached a peak in Week 1 of 2017 (beginning of January 2017). The percentage of isolations positive for RSV during the 2016/2017 winter season matched, as regards timing, the percentage of visits to pediatric emergency rooms due to bronchiolitis for infants aged two years and under (information not displayed).

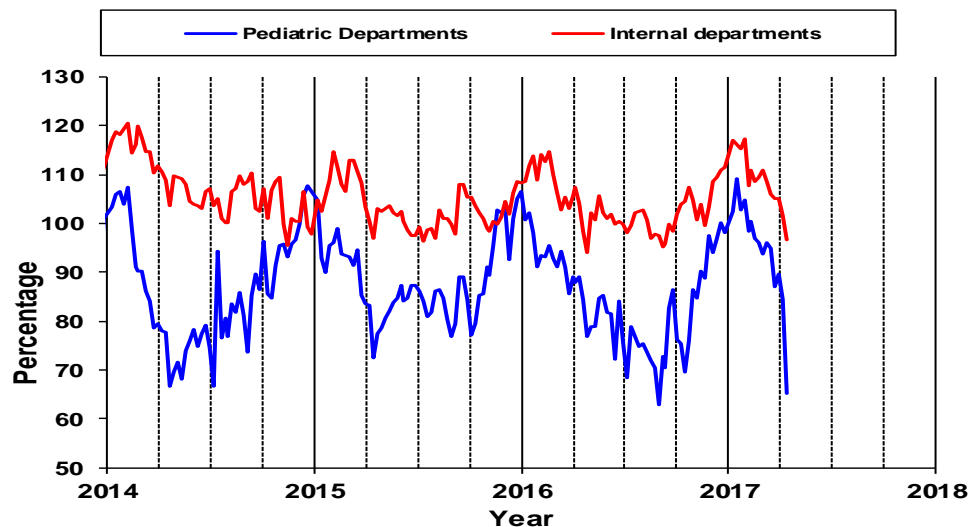
Figure 9: Visits to (Pediatric) Emergency Rooms in "Clalit" Health Services' Hospitals that ended in a Diagnosis of Bronchiolitis, January 2011 - May 2017, and the Multi-Annual Average^{1,5} (expressed as a percentage of all visits that ended with any diagnosis)



2.4 Surveillance of Weekly Hospital Bed Occupancy Rates in General Hospitals

Throughout the entire 2016/2017 winter season, the average hospital bed occupancy rate in internal medicine departments of general hospitals exceeded 100%, and reached a peak of 117% in Week 4 of 2017 (end of January 2017). In pediatric departments, the average occupancy rate was lower than in internal medicine departments. From Week 1 of 2017 until week 4 of 2017 (end of January 2017), the occupancy rate exceeded 100%, reaching a peak of 109% in Week 2 of 2017 (second week of January 2017). In pediatric departments, the peak occupancy rate this year was high compared with the peaks recorded in the two previous influenza seasons. Similarly, also in internal medicine departments, the peak hospital bed occupancy rate was high relative to the peaks recorded in the two previous influenza seasons.

Figure 10: Weekly Hospital Bed Occupancy Rates in Internal Medicine and Pediatric Departments, General Hospitals, 2014-2017¹: Average Percentage



2.5 Surveillance of Mortality

In order to assess the severity of influenza during the winter seasons, two measures of mortality were utilized: mortality due to all causes (Figures 11+12), and mortality due to pneumonia as a percentage of all cases of death in Israel (Figure 13).

The mortality rate among the elderly aged 65 years and over in the 2016/2017 winter season was higher than the multi-annual average from Week 52 of the year 2016 (end of December 2016) until Week 4 of 2017 (end of January 2017) (Figure 11). The mortality rate in the population under the age of 65 years varied around the multi-annual average throughout the entire season (Figure 12).

During the current season, the percentage of deaths due to pneumonia varied around the seasonally expected level, with the exception of Week 10 of 2017 (beginning of March 2017), when the percentage of deaths crossed the epidemic threshold (Figure 13).



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Figure 11: Weekly Mortality Rate Among the Elderly Aged 65 Years and Over, as Compared to the Multi-Annual Average, 2012-2017⁶: Rates per 10,000

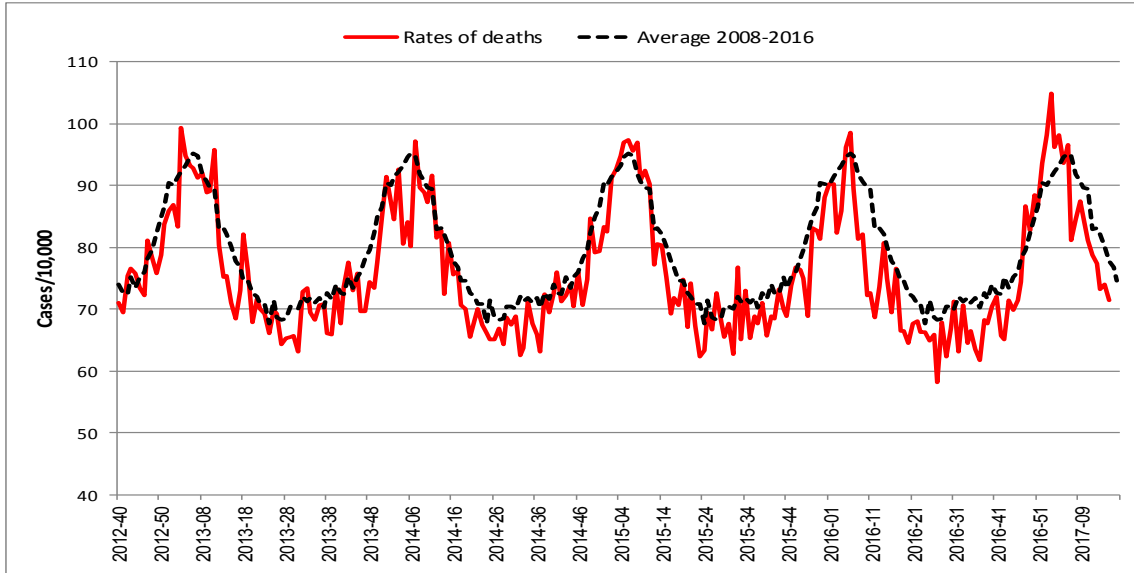
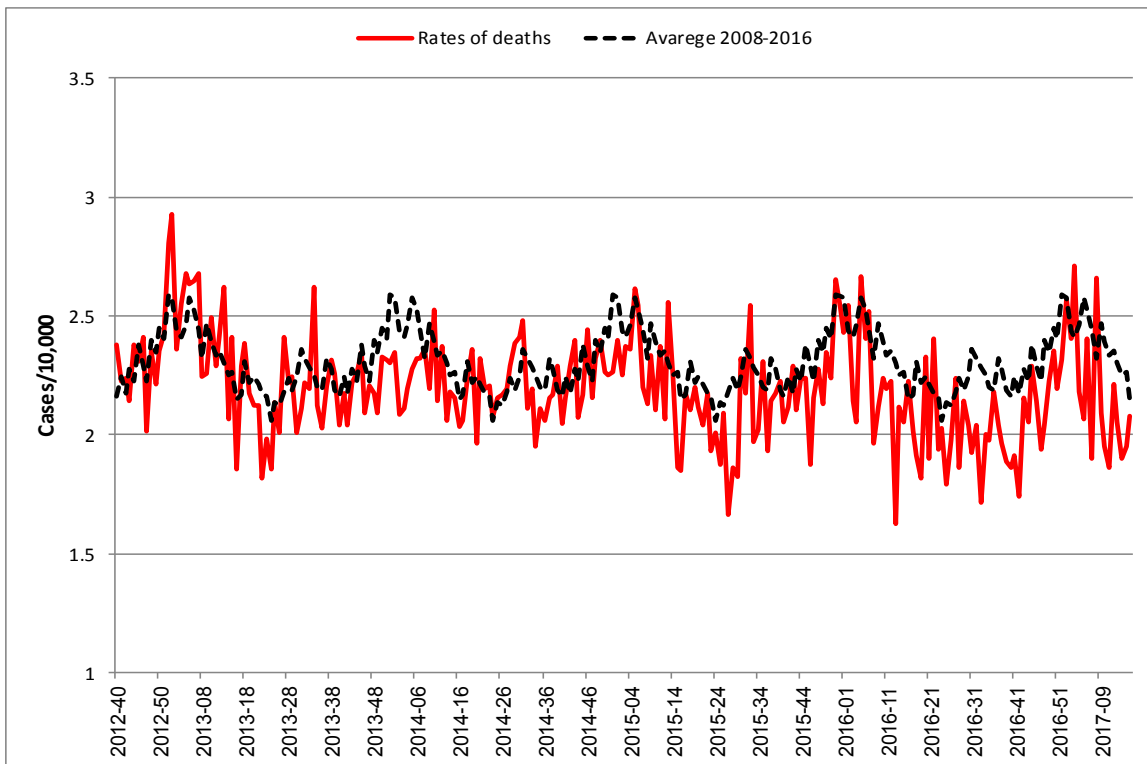


Figure 12: Weekly Mortality Rate Among the Population Below the Age of 65 Years, as Compared to the Multi-Annual Average, 2012-2017⁶: Rates per 10,000

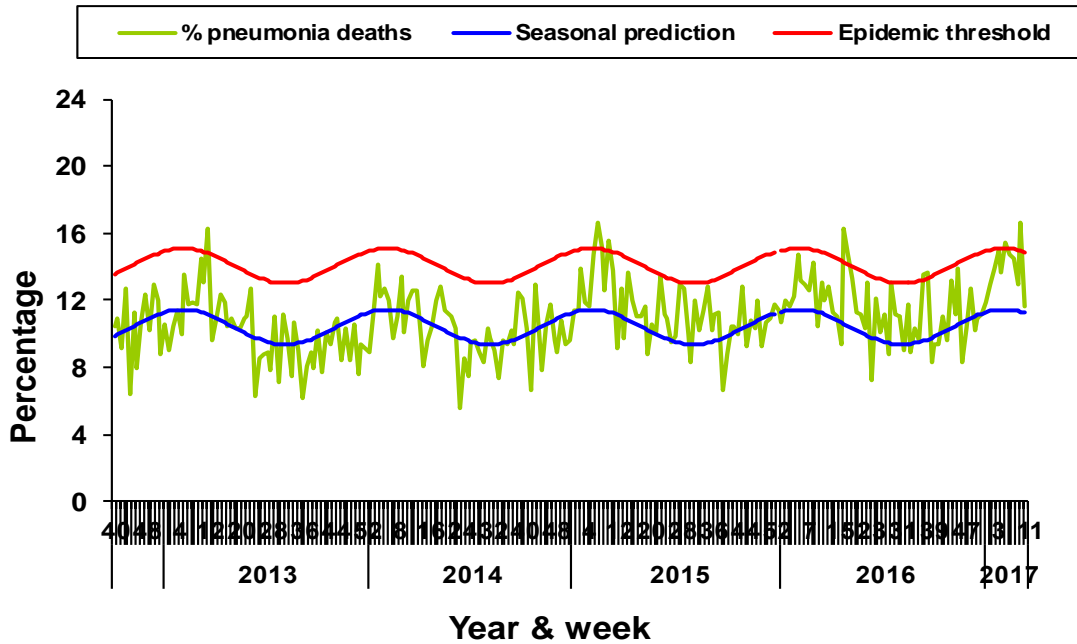




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Figure 13: Deaths per Week due to Pneumonia, as Compared to Seasonal Prediction, 2013-2017⁷: Percentage of Total Cases of Death



3. Immunization Against Influenza and the Degree to which the Vaccine Corresponded to Influenza Viruses Active During the Season

Since 2011, there has been a recommendation for the entire population over the age of 6 months to be vaccinated against influenza. In the Vaccination Guide of the Division of Epidemiology⁸, detailed information regarding the influenza vaccine can be found.

In the 2016/2017 winter season, some 1,750,000 people were immunized against seasonal influenza (approximately 21% of the total population of Israel). Immunization coverage in the elderly group, of persons aged 65 years and over, reached approximately 62%. Immunization coverage for infants and children aged 6-59 months reached approximately 21%.



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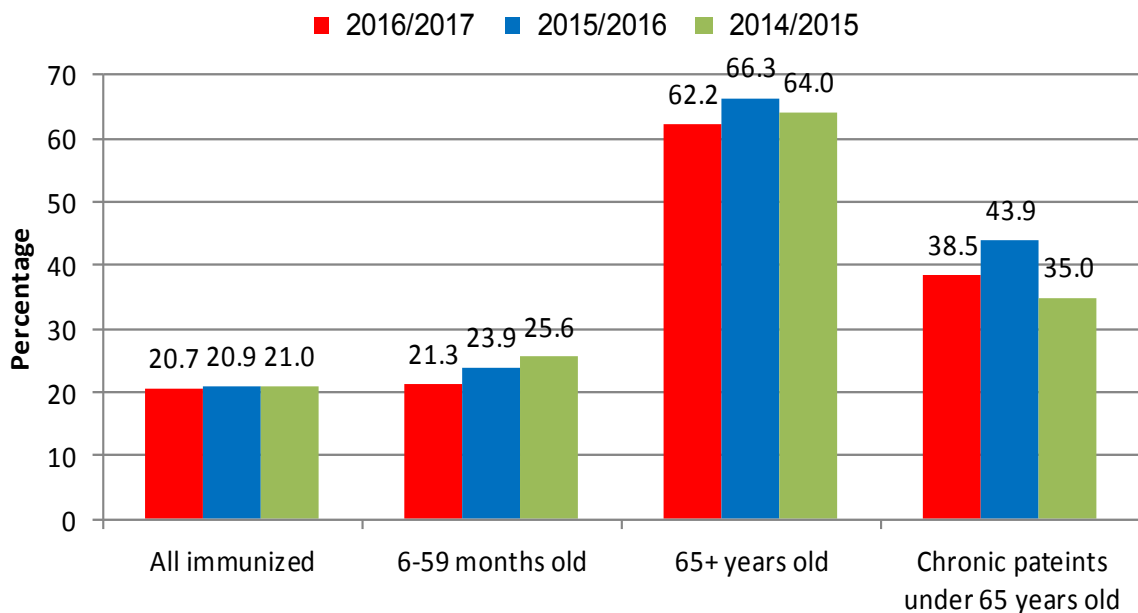
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During September 2016, second grade pupils received (the trivalent) vaccine against influenza, in the framework of the routine vaccines given in schools via the student health services. Some 55% of second grade pupils were immunized against influenza.

Molecular characterization of the influenza virus showed three main groups of mutations as compared to the vaccine strain. It arises from data from the surveillance system that the vaccine formulation for the 2016-2017 season was more effective in persons under the age of 65 than in persons aged 65 and over.

The percentage of persons immunized from all HMOs was similar to the percentages recorded in previous influenza seasons (Figure 14).

Figure 14: Immunization Coverage for the Past Three Influenza Seasons, by Age Group⁹: percentage immunized





4. International Comparison

USA: During the 2016/2017 winter season, A/H3 was the most dominant subtype. 96.5% of specimens of influenza A/H3 that were antigenically characterized were found to correspond to the season's vaccine formulation.

The increase in the percentage of clinic visits due to ILI in the 2016/17 winter season commenced in the second half of December 2016 (Week 50), crossed the national baseline level, and remained above it until Week 15 of 2017 (second half of April 2017). The current season commenced relatively early, and the peak levels were relatively high compared to the 2015/16 influenza season, in which influenza A(H1N1)pdm09 was dominant. The 2014/2015 influenza season, which also had influenza A/H3 as the dominant subtype, also commenced relatively early as compared to the 2016/2017 season.

During the winter of 2016/2017, the hospitalization rate reported as a result of influenza illness was 65.2 per 100,000. The hospitalization rate was particularly high for the elderly aged 65 years and over (291.1 per 100,000). Among hospitalized patients diagnosed with influenza A, 98% were diagnosed with A/H3N2 and 2% were diagnosed with A(H1N1)pdm09.

From Week 40 of 2016 (beginning of October 2016) until Week 20 of 2017 (second half of May 2017), 122 cases of death from pneumonia and influenza were reported throughout the USA.

According to data from public health laboratories, as of Week 15, ending 15-Apr-17, a total of 77,179 specimens had been collected. Of these, 37,992 (49.2%) were found to be positive for influenza, of which 30,778 (81%) were positive for influenza A: of these, 29,601 (96.2%) were found to be positive for influenza H3, 841 specimens (2.7%) were found to be positive for influenza A(H1N1)pdm09 and 336 specimens (1.1%) were not yet subtyped. 7,214 specimens (19%) were found to be positive for influenza B



Europe: The 2016/17 winter season commenced relatively early - in Week 46 of 2016 (second half of November 2016). From Week 40 of 2016 (beginning of October 2016) until Week 10 of 2017 (beginning of March 2017), A/H3 was the most dominant, and starting from Week 11 of 2017 (second half of March 2017), influenza B become dominant. The number of influenza B isolations was still relatively small.

Additionally, in the framework of the EuroMOMO project, excess mortality was reported among adults aged 15-64 years; there was also excess mortality among the elderly aged 65 years and over.

Two thirds of isolations positive for A/H3 were found to antigenically correspond to the strains composing the seasonal vaccine.

5. Sensitivity to Antiviral Preparations:

Both in Europe and in the USA, the influenza viruses were found to be highly sensitive to Oseltamivir and to Zanamivir, and highly resistant to Adamantanes^{10,11}.



Sources of Information:

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Appendix 1: National Distribution of the Sentinel Clinic Network

