CHANGES IN SURVEILLANCE OF ACUTE RESPIRATORY INFECTIONS INCLUDING INFLUENZA IN THE SLOVAK REPUBLIC DURING 1993–2008

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SUMMARY

The authors evaluated surveillance of acute respiratory infections (ARI), influenza and influenza-like illnesses (ILI) in the Slovak Republic (SR). They analyze morbidity, age-specific morbidity, complications, mortality, number of influenza viruses isolations and vaccination coverage rates in the SR in the years 1993–2008. They focus mainly on the analysis during the epidemic. Most epidemics have been caused by influenza virus A subtype H3N2. The age group mostly affected by morbidity during the year were children at the age of 0–5, while during the epidemic, the highest morbidity was recorded among school children at the age of 6–14. A complicated clinical course of the disease was reported in 1,422,836 patients (5.1%). Since the 2002/2003 influenza season, the sentinel physicians have participated in taking biological material, which ensures monitoring of influenza viruses circulating in the SR. As of the 2006/2007 season, the ARI/ILI have been reported separately in the SR in accordance with the monitoring requirements set by the European Influenza Surveillance Scheme (EISS) project, and the calculation of morbidity is done from the number of persons, who are in care of the reporting physicians: Vaccination coverage in SR is still very low in comparison with other European Union (EU) countries.

Key words: surveillance, acute respiratory infections, influenza, influenza virus, vaccination

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INTRODUCTION

ARI for their high incidence and a regular annual occurrence rank are socially, medically and economically the most serious communicabe diseases. ARI are the leading cause of morbidity. Clinically, the most serious illness is influenza.

A notable characteristic of the influenza virus is a high frequency of its antigenic changes. These changes are referred to as antigenic variation. A pandemic, which is always caused by influenza virus A, occurs always following an antigenic shift (1). A virus, which generates during this shift, has one or both antigens different from the previous virus. In the interpandemic period, the epidemics occur, when only the antigenic drift in the influenza virus occurs. The antigenic drift is generated through the multiply localized changes in the hemagglutinin and neuraminidase gene. However, no exchange of genetic information occurs.

These changes are responsible for annually recurring more or less epidemic (2).

Because influenza viruses change constantly and epidemics occur annually the need for permanent surveillance of influenza is of prime importance. Regular supervision and organized surveillance is one of the most important methods of controlling the spread of influenza. It focuses on early detection of virus with epidemic or pandemic potential, e.g.early detection and identification of new variants or subtypes of influenza virus circulating in human population. These data then enable the authorities to take immediate and effective measures in preventing and reducing health and social impacts (3).

The most effective prevention against influenza, from health and economic point of view, is definitely vaccination. Influenza vaccination is the most important part of the anti-epidemic as well anti-pandemic measures (4). Influenza vaccination has a good legislative support in SR, and health insurance companies fully reimburse for the influenza vaccination in accordance with recommendation by public health authorities. In spite of these facts, vaccination coverage is still very low.

MATERIALS AND METHODS

Until 2006, data were obtained from the Information System of Hygiene, Epidemiology and Microbiology (ISHEM) program. Since 2006, relevant data has been collected from the "Influenza" program was implemented, which is a part of the Epidemiological Information System (EPIS), available through a web portal also to the reporting physicians.

In the SR ARI/ILI are monitored and reported all year round. Influenza in the areas with a temperate climate, where also the

SR belongs, occurs in the winter months from the 40th calendar week (CW) of the actual year until the 18th CW of the following year. This period is referred to as the "Influenza season". Until the 2005/2006 influenza season, all newly detected cases of ARI/ILI had to be reported together. The calculation of morbidity was done for 100,000 inhabitants. As of the 2006/2007 season, the ARI/ILI have been reported separately in the SR in accordance with the monitoring requirements set by the EISS project, and the morbidity calculation is based on the number of persons who are registered with the reporting physicians:

- ARI – any acute infection of the respiratory system with or without fever such as: cold, rhinopharyngitis, tonsillitis, sinusitis, otitis media, laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonia and bronchopneumonia.

- ILI – an illness with a sudden onset, fever, with a presence of at least one of the overall symptoms, such as headache, myalgia, arthralgia, chills and with a presence of at least one of the respiratory symptoms, such as cough, sore throat, cold.

Reports on occurrence are sent by the general practitioners for adults (GP) and paediatricians according to a prescribed model on a weekly basis all year round to a respective Regional Public Health Authority (RPHA). During a mass outbreak, a time interval of reporting is set by RPHA. The reporting is done by phone, fax or e-mail. Reports include number of new cases reported in the period of 7 days starting on Friday and ending on Thursday of the following week. They are marked with a calendar week, in which the collection is completed.

The weekly reports are submitted to the respective RPHA which should receive them on Friday by 8 a.m. at latest. The reports are gradually processed and analyzed at the district, regional and national levels. Then they are sent to the EISS.

Monitoring of the age-specific incidence and complication incidence is done in five age groups:

- 0–5 years old, pre-school children
- 6–14 years old, school children
- 15−18 years old, adolescents (monitored as of the 2006/2007 season)
- 19–59 years old, work force
- 60 and more years old, work force and pensioners.

As to the complications, 6 complications were monitored in 2006/2007 season. Currently, however, only the first three of the listed ones are monitored:

1. bronchopneumonia and pneumonia
2. otitis
3. sinusitis
4. diarrhea, vomiting, haematemesis
5. Reye's syndrome, encephalitis, paresis, aphasia, encephalopathy, meningoencephalitis, myelitis, Guillain-Barre syndrome
6. other

When assessing the epidemiological situation, also data on the number of patients treated with ARI/ILI by first aid services and data on ratio of children's school absence are used. If more than 30% of the collective members were absent due to the ARI/ILI, the situation is assessed as an epidemic.

With respect to an epidemic occurence, the following criteria are applied regarding the size of the affected area:

Local epidemic – a double increase in morbidity in town or village during two consecutive weeks, or if there are the epidemics in the collectives attended by more than 50% of the town/village's inhabitants; laboratory detection of influenza virus circulation.

District epidemic – a double increase in morbidity in the district's territory during two consecutive weeks, or if there are the local epidemics in the territory, where more than 50% of the district's inhabitants live; laboratory detection of influenza virus circulation.

Regional epidemic – a double increase in morbidity in the region's territory during two consecutive weeks, or if there are the district epidemics in the territory, where more than 50% of the region's population live; laboratory detection of influenza virus circulation.

National epidemic – a double increase in morbidity in the whole SR during two consecutive weeks, or if there are the regional epidemics in the territory, where more than 50% of the SR population live; laboratory detection of influenza virus circulation.

Besides surveillance of morbidity, mortality, complications with ARI/ILI, there is sentinel surveillance of influenza virus circulation in the population implemented in every county. The selected sentinel physicians, approximately 1–2 paediatricians and 1–2 GPs for adults regularly take nasopharyngeal swabs from patients with suspected influenza and send them to a laboratory.

Nasopharyngeal swabs are collected and placed into containers with viral transport medium – (Medium 199 with 0.5% BSA and antibiotics Penicillin G, streptomycin, amphotericin, gentamicin) supplied by the laboratory (5, 6). To confirm the diseases, direct or indirect laboratory diagnosis is used. Direct diagnosis includes:

1. An attempt to isolate influenza viruses in MDCK cell cultures (2–6 days) and in 10-day-old chicken embryos (10–20 days).

2. A direct detection of influenza virus antigens by the ELISA method (detection in 24 hours). From 2005, the methods under 1 and 2 were not used any longer in the SR.

3. Direct detection of influenza virus antigens by a rapid screening method (within 20 minutes). This test is intended for an informative mostly outpatient use.

4. Molecular biological test – the polymerase chain reaction (PCR) and Real-time PCR (result in a few hours) (7).

Indirect diagnosis – retrospective serological examination is done by a complement fixation reaction and hemagglutination-inhibition reaction. The examination result is assessed using antibody titre levels from two blood samples of a patient. The first sample is taken in an acute phase, followed by the second one in 2–3 weeks. Only the significant increase in antibody titre determines a positive result (8, 9). The examinations are carried out in 3 virological laboratories in the SR, namely in the laboratory of NRC for influenza in Bratislava and in the laboratories of the RPHA Košice and Banská Bystrica. Further identification of the isolated influenza virus strains is carried out in the NRC, which at the same time cooperates with the WHO international laboratory in London (10). Here they confirm the results of identification done in the NRC. The laboratory results from the above laboratories are reported to the NRC once a week during the influenza season, and once a month out of the season.

Vaccination against influenza in the SR is carried out in accordance with MoH SR Decree No. 585/2008 Coll. stipulating the details on prevention and control of communicable diseases. The outputs on the percentage of vaccination coverage of the SR population are obtained annually from the distributors and pharmacies.

RESULTS

From 1979 to 2008, a total of 52,750,944 ARI/ILI cases were reported in the SR. An average of 1,758,365 diseases were reported per year. The number of reported diseases in individual years ranged from 1,018,692 in 1979 to 2,527,662 in 1997. The overall morbidity per 100,000 inhabitants ranged from 20,620.4 in 1979 to 47,089.4 in 1997. Morbidity exceeding 40,000 cases/100,000 inhabitants was reported in this 30-year period in six calendar years: in 1986 – 46,964.6, in 1989 – 44,813.1, in 1995 – 40,880.6, in 1997 – 47,089.4, in 1998 – 44,522.1 and in 1999 – 43,894.6: morbidity over 40,000 cases occurred two times from 1979 to 1990, four times from 1991 to 2,000 and from 2,000 to 2008 not in a single year.

Morbidity below 30,000 cases/100,000 inhabitants was reported in 8 calendar years. Morbidity per year ranged most frequently from 30,000–40,000 cases per 100,000 inhabitants (Fig. 1). ARI/ILI morbidity curves used to have at the beginning of the season towards the end of the calendar year almost identical developments with a gradual increase and decrease during the Christmas season. This phenomenon was observed practically every year except for the year 1995, when the epidemic culminated in 51st calendar week with morbidity of 6,159.8/100,000, so just before the Christmas season. However, early in the following year, a gradual increase in morbidity can be seen. In recent years, the increase ARI/ILI morbidity was reported several times during the season, i.e., one before Christmas and second one in February or March.

From 1993 to 2008, the epidemics were reported 2 times in December, 1 time in January, 9 times in February (56%) and 4 times in March. They lasted 4–9 weeks, 5.8 weeks on average. The highest morbidity per week and outbreak ranged from 1,065.8/100,000 in 2006 to 6,159.8/100,000 in 1995. Morbidity reached over 2,000/100,000 inhabitants in 10 from 16 monitored years (Table 1). There have not been any typical epidemics recorded in recent years, mostly we had to deal with rather minor outbreaks. The number of ARI/ILI cases in the epidemics ranged from 259,247 in 2006 to 934,086 in 1999, affecting 4.7–17% of the overall population.

Throughout the analyzed period, the age group mostly affected during the influenza season were pre-school children, i.e. 0–5 years old. From 1993 to 2006 morbidity ranged from 48,953 to 110,286.9/100,000. Morbidity in 2007 was 158,199.4 and in 2008 146,812.6.

Contrary to the previous years, morbidity in 2007 and 2008 was not calculated for the overall population, but for the number of persons who were registered with the reporting physicians. Due to specific conditions for the transmission of causative agent prevailing in schools, the incidence of disease among school children exceeded during epidemics incidence in other age groups.

From 1993 to 2008, a complicated clinical course of the disease was reported in 1,422,836 diseased (5.1%). The most frequent complications (46.8%) were bronchopneumonia and pneumonia. They complicated the course of 665,962 (2.4%) of all reported diseases.

Moreover, 305,489 of sinusitis were reported, which is 21.4% out of all complications and 1.1% out of all diseases, 135,936 otitis, which represents 9.7% of the complications and 0.5% of all reported diseases. Further more, there were 315,449 of other complications reported representing 22.4% of the total complications registered.

Most complications were reported in the years 1997–1999, which corresponds with the highest number of diseases reported during these years (Fig. 2). As of 2007, the attention has been paid to the following major diagnosis only: bronchopneumonia and pneumonia, sinusitis and otitis.

Table 1. *Month of epidemic, duration and highest weekly morbidity in seasons 1992–2008*

Season	Duration epidemics in weeks	Month with highest morbidity	Highest weekly morbidity /100,000/ inhabitants
1992/1993	5	february 1993	3100.4
1993/1994	6	february 1994	2441.7
1994/1995	4	february 1995	1150.7
1995/1996	4	december 1995	6159.8
1996/1997	6	february 1997	2585.1
1997/1998	6	march 1998	2669.3
1998/1999	7	february 1999	4155.1
1999/2000	5	february 2000	2821.3
2000/2001	9	february 2001	3373.1
2001/2002	5	february 2002	1203.1
2002/2003	9	march 2003	2568.3
2003/2004	5	january 2004	1896.8
2004/2005	5	march 2005	1515.9
2005/2006	5	march 2006	1065.8
2006/2007	7	february 2007	2544.1
2007/2008	5	december 2007	1258.1

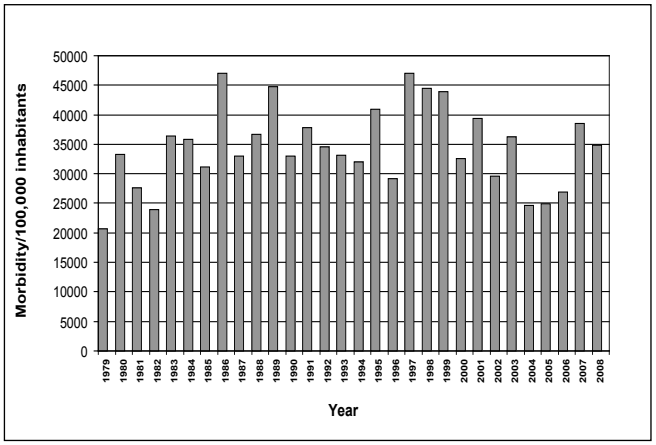

Fig. 1. *The acute respiratory infections, influenza and influenza like illness morbidity, SR, 1979–2008.*

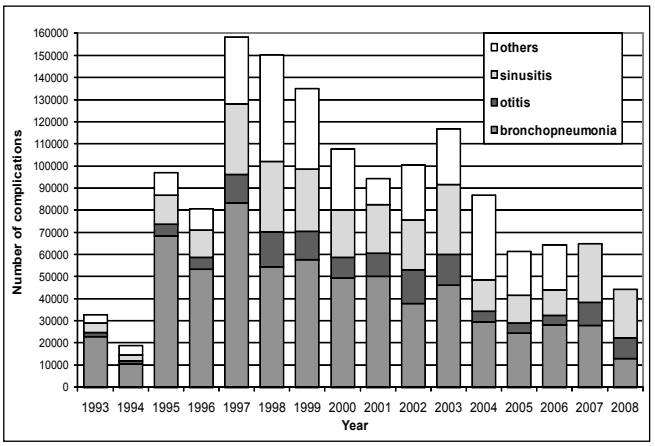

Fig. 2. *Number of complications of acute respiratory infections, influenza and influenza like illness, SR 1993–2008.*

From 1993 to 2008, 55 deaths due to influenza were reported, their number ranging from 1–16. There were no deaths related to ARI/ILI cases reported in 1997, 2002, 2005–2008. The age of the patients was: 2 x 0–1 year, 1 year old, 16 months old, 2 years old, 2 x 3 years old, 6 years old, 9 years old, 2 x 10 years old, 2 x 17 years old, 23 and 25 years old, 31, 32, 33 and 37 years old, 3 x 39 years old, 43, 44 and 2 x 45 years old, 53 and 55 years old, 56 and 57 years old and 25 patients (45% of total number of deaths) were more than 60 years old. The oldest patient was 90 years old. In one case, an 83 years old vaccinated women became ill. Influenza virus A (H3N2) was isolated from a nasopharyngeal swab. Results of laboratory examination of death cases were as follows: 7 by detection of antigen from lung tissue: 6 of influenza virus A and 1 influenza virus A and B, 4 by isolation of virus (3 from post-mortem materials and 1 from nasopharyngeal swab): influenza virus A (H3N2) Johannesburg/33/94-like, A (H1) New Caledonia/20/99, A (H3N2) Panama/2007/99-like, B/Hong Kong/330/01-like and 1 influenza virus A from liquor by the PCR method. All death cases were reported during the influenza epidemic.

To isolate influenza virus, the materials were collected from the diseased subjects during the monitored years. As of 2003, when the SR was integrated into the sentinel system of influenza reporting, an increase in the number of examined biological material and thus also in influenza virus isolations can be observed. Before the implementation of the sentinel in 1993–2002, the number of isolations was 0–45 per season. After the implementation, the number of influenza virus isolation ranged from 109 to 260 (Fig. 3).

For an attempt to isolate influenza virus, the nasopharyngeal swabs were taken every year. They were taken from the outset of the season. Their number gradually increased in connection with increasing morbidity.

From 1993 to 2008 the influenza virus was isolated altogether in 1298 cases: 1005 (77.4%) influenza virus A and 293 (22.6%) influenza virus B. Evidence of influenza virus antigen confirmed infection in 119 cases: 72 with influenza virus A and 47 with influenza virus B and 1 by PCR influenza virus A. The influenza viruses were isolated in the influenza seasons only. Occurrence of the influenza viruses by year of monitoring was as follows: influenza virus A dominated in the years 1993–2001, 2004 and 2007 (isolated in 100 to 75% of the total number of isolations). Influenza virus B dominated in 2002 (isolated in 94% of the total number of isolations) and in 2006 (isolated in 88% of the total number of isolations). The isolation of both A and B of influenza virus was reported in 2003, 2005 and 2008.

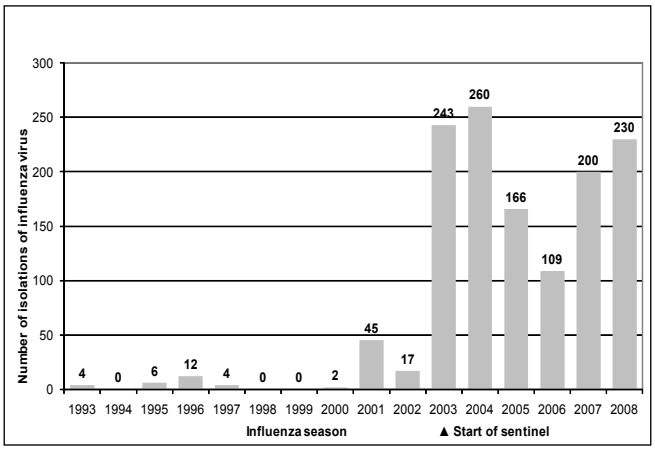

Fig. 3. *Number of isolations of inluenza virus, SR 1993–2008.*

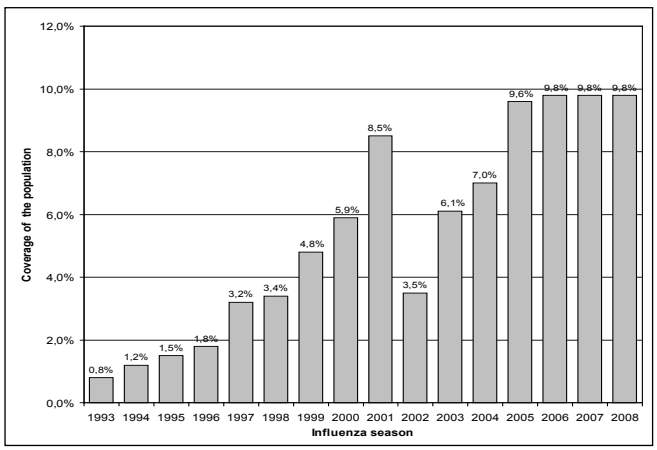

Fig. 4. *Vaccination coverage of the SR population (in %).*

The H3N2 subtype was mostly detected in the isolations. This one was prevailing in 1993–2000, 2004 and 2007. In 2001, only the H1N1 subtype was isolated. In the years when the mixed infections were recorded, both H3N2 and H1N1 subtypes were isolated.

In 2003, for the first time influenza virus A (H1N2) was also isolated in the SR. The virus was isolated from 3 children attending the Special Primary Boarding School in Nitra, where 27 of 71 children vaccinated against influenza became ill. The diseases had a mild course. The viruses were confirmed by the WHO international laboratory in London. This virus was detected and described for the first time in the world during the 2001/2002 influenza season in Great Britain.

From 1993 to 1998, influenza vaccination coverage was minimal in SR, it ranged from 1–3% of the overall population (about 50,000 up to 150,000 persons). Only in 1999 some health insurance companies decided to buy the influenza vaccines for a group of people at risk of influenza infection, which increased vaccination coverage to 4.9%. As of 2000, all health insurance companies (HIC) have begun to reimburse the influenza vaccines to groups of people at risk. The groups of people to whom the HIC fully reimburse influenza vaccines are annually extended. The reimbursement by the health insurance companies is set by the indicative limits of the Ministry of Health of the SR. The HIC currently reimburse influenza vaccines to all children from 6 months to 12 years of age and to all persons aged 59 years and older. Furhter, to all persons irrespective of age with serious chronic respiratory diseases, cardiovascular diseases, metabolic, renal and immune disorders. Vaccination is compulsory for the persons living in social service facilities and is underpinned by legislation for all healthcare workers and people working in the areas with a risk of infection. In 2007 and 2008, the HIC fully reimbursed influenza vaccination to the general population. Even despite the existing legislation and good will of the HIC that are fully aware of the health and economic importance of influenza vaccination, influenza vaccination coverage is still very low in SR.

It stagnates in the last 3 years and objectively it did exceed 10% (Fig. 4). The groups of people with the lowest vaccination coverage are children under 15 years of age – 4% and persons aged 16 to 59 years – 7%. The highest vaccination coverage is in the group of persons aged 60 years and older – 32%. These alarming numbers are caused on the one hand mainly by low awareness of citizens who do not know about this possibility of protection, because of their insufficient information, and on the other hand, it is lack of interest on the part of the GPs and the anti-vaccination, non-expert media performances. Vaccination coverage of SR population is below the limits recommended by WHO experts.

DISCUSSION

Influenza is an infection that accompanies the humankind for a very long time, it is constantly present in the population and it is the most frequent human disease. It occurs annually with a greater or lesser strength, in the form of the epidemics or pandemics. It causes high morbidity and the enormous health and economic damages. In 1933, Sir Christopher Andrewes isolated with his colleagues an influenza virus (4). Further study of the virus revealed a connection of the epidemics with the virus variability. A definition of influenza epidemic is very complex. The general rule is that the epidemic occurs, if the number of disease cases exceeds the expected numbers. Individual countries have different criteria for a definition of influenza epidemic. In the SR, influenza epidemic is announced according to the incidence rates based on a weekly ARI/ILI monitoring. ILI are recorded mainly in January (10).

The influenza epidemic is announced, if a double increase in morbidity is observed during two consecutive weeks or if the disease spreads over the territory, where more than 50% of the population live in. In the Czech Republic (CR) it is announced, if the ARI/ILI incidence is higher than 2,000 cases/100,000 inhabitants (11). In England they monitor the number of the persons examined due to ARI/ILI. If the number of ARI/ILI patients reaches 400/100,000 of all health services contacts, the epidemic spread is considered. In the US, influenza activity is monitored on the basis of the surveillance of influenza-associated deaths and the associated pneumonias. However, there have not been any typical winter epidemics recorded in SR in recent years (12). The influenza epidemics occur in the countries with a temperate climate in 1–3 year cycles (13). It can be seen in the present analysis that the epidemic outbreaks occur at irregular time intervals. During the period 1993 to 2000 there were 7 outbreaks and from 2001 to 2008 only three outbreaks reported. Even though the influenza affects annually about 10% of the world's population, it is still underestimated to a great extent and perceived by expert and general public as a trivial and benign disease. Between the years 1979–2008, ARI/ILI affected from 1,018,692 to 2,527,662 persons, which is about 18–45% of the overall SR population. Most diseases were reported during the epidemic. The number of ARI/ILI in the epidemics ranged from 259,247 in 2006 to 934,086 in 1999, 4.7–17.0% of the overall population. Havlík states that during an epidemic, 10–20% of the population may be affected (11). Despite the ever expanding range of scientific knowledge on influenza, we are still unable to stop its epidemic spread. Declining role of national borders calls for a coordinated approach to surveillance of ARI/ILI (14, 15, 16). Many authors state that actual influenza morbidity and mortality recorded during epidemics is in fact much higher than that reported officially. Mostly affected are the so called risk groups. These are mainly the elderly or persons with primary chronic disease (e.g. chronic respiratory, cardiovascular or metabolic disease). At the same time, the persons older than 65 years have significantly weakened immune protection against influenza infection. In these persons, the serious complications occur more frequently and very often lead to death. In our analysis, from 55 death cases, 45% of persons were older than 60 years. The other risk group consists of small children, mainly at the age of 0–5. These children are in general most affected by morbidity every year during the influenza season.

The influenza epidemics hit the SR annually from December to March, mostly with its peak at the end of February. The largest epidemic was reported in December 1995 with the incidence reaching its peak of 6,159.8 cases/100,000. Laboratory detection of influenza illnesses is one of the major problems in the confirmation of influenza illnesses and subsequent adoption of anti-epidemic measures. The clinical symptoms of influenza do not have to be distinct. Majority of patients treat themselves at home. They do not consult the GPs. And even if the patient visits the GP, material for laboratory confirmation of diagnosis is taken only exceptionally. More frequently the GPs are consulted by the

patients already suffering from bacterial infections. In recovery, however, the tests on direct virus detection (isolation, antigen detection, PCR) are already negative.

During the monitored years, the epidemics have been caused in turns by the H3N2 and H1N1 subtypes. From 1993 to 2000, only the H3N2 subtype was isolated also in Europe (8).

From 2001 to 2008, both subtypes circulated and alternated with influenza virus B (17). These strains have circulated also in the CR (7). The year 2003 is an exception, when the rarely circulating new H1N2 subtype was isolated. It suggests that influenza surveillance in the SR is well performed. The results show the need for sustained and organized influenza surveillance.

The only way of prevention is vaccination. Vaccination may protect not only the persons mostly endangered with a complicated course of the disease, but also the healthy persons, because if they become ill, their incapacity to work would lead to great economic losses. Attainable vaccination coverage is also ill-effected, for instance, by the interventions of our physicians, who appear in popular media with unverified and unconfirmed anti-vaccination statements as happened for example in 2002. This had subsequently a profound negative impact on vaccination coverage, which decreased to 3.5% and affected the vaccination morale in the following years as well. The groups of people with the lowest vaccination coverage are children under 15 years of age and persons aged 16 to 59 years. SR markedly falls in influenza vaccination behind the developed countries of the world and EU countries, where vaccination coverage of the overall population is about 30% and that of the risk population reaches even 70 up to 90%. We have been therefore promted to assume a responsible approach in order not only to protect the SR population, but also prevent transmission within EU countries.

The HIC fully reimburse all influenza vaccines required for protection of the population at risk with respect restriction set up by public health authorities of SR. (18). Medical market is sufficiently supplied with influenza vaccines suitable for all ages. For the persons, who for any reason cannot be vaccinated, there are anti-influenza antivirotics.

CONCLUSIONS

From our analysis follows:

- Number of ARI diseases reported during 1979–2008 ranged from 1,018,692 to 2,527,662, an annual average of 1,758,365 diseases
- Course of ARI morbidity was nearly identical in every and each year with a gradual increase and decrease during the Christmas season
- Epidemics occurred annually in recent years, especially during the spring months
- Since 2001 recorded epidemic of small-scale morbidity hardly reached epidemic level
- Since 2003, SR joined the influenza sentinel reporting system which will improve the monitoring of surveillance of influenza viruses circulating in the population
- Influenza viruses were isolated only in the flu season. Influenza virus A subtype H3N2 was isolated in 13 influenza seasons
- In accordance with the requirements of the monitoring program EISS since the 2006/2007 season, the SR monitor ARI/ILI morbidity separately and calculate the morbidity per number of persons registered with GP in question
- Vaccination uptake is stagnating, coverage not exceeding the level of 10% due to the low awareness of citizens, lack of interest in influenza prevention by GPs and incongruous media statesments with regards to vaccination.

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