Zdravlje u Mađarskoj - Health in Hungary

Case-control study to measure influenza vaccine effectiveness during the 2008-2009, 2009-2010 and 2010-11 influenza seasons in Hungary

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Abstract

Resulting from the constant evolution of influenza viruses, influenza vaccine effectiveness can vary from year to year depending on the matching between the circulating strains and the ones that are included in the vaccine.
Within a European programme to monitor seasonal and pandemic influenza vaccine effectiveness, the Hungarian team conducted case-control studies in 2008-9, 2009-10 and 2010-11. Sentinel GPs swabbed a systematic sample of patients consulting for influenza-like symptoms. Influenza confirmed cases were compared to influenza negative controls. Influenza vaccine effectiveness estimates were obtained using 1- odds ratio. We adjusted estimates for age-group, month of onset, chronic diseases, smoking, previous influenza vaccinations, previous hospitalisations and GP visits in the previous 12 months.
In 2008-2009 50 GPs, in 2009-2010 87 GPs and in 2010-2011 98 GPs participated in the study. In 2009-2010 the adjusted pandemic influenza vaccine effectiveness was 79.1% (95% CI 12.8-95.0%) for 18+ age group, and 80.1% (95% CI: 7.7-95.7%) in the 18-59 age group. According to the preliminary results of the 2010-2011 study the adjusted seasonal influenza vaccine effectiveness was 85.6% (95% CI: 27.0-97.2%). During the pilot study in 2008-2009 the sample was too small to obtain vaccine effectiveness results.
Case control study with the participation of GPs who are involved in the sentinel influenza surveillance system is feasible. Larger sample size is needed to achieve greater precision for subgroup analysis.

Key words: influenza, influenza vaccine, vaccine effectiveness, communicable disease control, case control studies

Background

Influenza is an acute respiratory disease, which is caused by the influenza virus. The most common symptomatic appearance includes sudden onset, fever, muscle ache, sore throat and cough. In most patients the disease is self-limiting and lasts three to seven days. Complications mostly occur among children, elderly people and among those with underlying medical conditions. Influenza is capable of evolving into epidemics rapidly especially if there is antigenic shift or drift such that previous immunity is not cross-protective.

Influenza epidemics occur in almost every year, but the severity and impact of such epidemics vary widely. In temperate climate influenza epidemic usually cause one winter peak. It is estimated that on average 5-10% of the general population gets influenza annually, but during major epidemics or pandemics the attack rates can be even higher. Epidemics generally last for 3-15 weeks depending on the type of the virus and the size and mixing patterns of the affected population. Seasonal epidemics and pandemics are associated with significant excess morbidity and mortality. It is estimated that about 90-95 percent of excess deaths due to seasonal influenza occur among people aged 65 years and older, but in pandemics younger age groups can also be at risk. Many respiratory viruses can cause influenza-like illness (ILI), such as Parainfluenza virus, Adenovirus or Respiratory Syncytial Virus. It is impossible to distinguish between them just with the help of clinical symptoms. Laboratory confirmation of clinical cases is required to make an accurate diagnosis.
Influenza vaccination is a basic preventive method against influenza. In Hungary target population for influenza vaccination is offered free of charge vaccine that is an adjuvanted vaccine containing inactivated whole virus, licensed in Hungary.
Vaccine efficacy studies using serological outcomes are performed before the influenza seasons. Resulting from the constant evolution of influenza viruses, influenza vaccine effectiveness (IVE) can vary from year to year depending on the matching between the circulating strains and the ones that are included in the vaccine. Results of epidemiological studies, which can monitor influenza vaccine effectiveness in a sustainable way, can provide important feed-back for decision makers to measure impact of the intervention and to support public health decision making.

Having annual influenza IVE estimates during and after the influenza season using laboratory confirmed influenza-like illness as an outcome is important, because it provides additional information regarding the impact of current vaccination strategies on the burden of disease. Based on this information decisions can be made to implement complementary public health measures if the vaccine is less effective due to vaccine mismatch.

The results of vaccine effectiveness study can be used to

- provide evidence if current influenza vaccination is effective in preventing laboratory confirmed influenza illness;
- support vaccination campaigns, and response to reports of vaccine failures;
- provide data to support risk-benefit assessment and cost-effectiveness analysis;
- support decision making concerning the strategy of influenza prevention in the future.

It is important to establish networks and systems that are able to provide such data and flexible enough to be adapted to a fast evolving situation that is caused by a newly emerging pandemic influenza virus strain, because such network and a solid expertise cannot be developed within a short time period.

Description of the influenza vaccine effectiveness studies in Hungary

During the 2008-2009 influenza season the European Centre for Disease Prevention and Control (ECDC) funded a pilot case control study in Hungary together with four other EU countries to measure influenza vaccine effectiveness in the elderly. Common protocol was outlined by Epiconcept that coordinated the studies. The Hungarian pilot study was based on GP surveillance network and organized by the National Center for Epidemiology (NCE). The EU-ILI case definition was used. We collected data about exposure and a commonly agreed set of variables to adjust for positive and negative confounding. Two sets of controls were selected: ILI flu negative controls and GP clients not having presented with ILI during the season to test which one is the best, feasible and sustainable to use in our setting. We contributed to the pooled analysis which provided a more precise IVE estimate on European level.
In April 2009 a new Influenza A virus variant emerged causing human infections and began to spread fast across the world. The WHO decided to increase the pandemic alert level at the highest in June 2009. As soon as the new virus was identified by the WHO as a candidate virus for vaccine manufacturing, a number of vaccine manufacturers started to develop a new vaccine against the new strain. As a result, a monovalent pandemic influenza vaccine also became available besides the traditional seasonal influenza vaccine licensed for that season.

Hungary has national vaccine manufacturing capacity, which supplies the country with both pandemic and seasonal influenza vaccines. This capacity made it possible to have enough pandemic influenza vaccine available for the population early, to be able to start the vaccination campaign ten weeks before the start of the pandemic wave in Hungary. The Hungarian study team decided to continue the study aiming to measure IVE in the pandemic situation. We adapted the protocol of the case-control study to measure both seasonal and pandemic influenza vaccine effectiveness during the 2009-10 influenza season among the 18+ population, and to contribute to the European level pooled vaccine effectiveness estimate carried out by Epiconcept.

In 2010-11 vaccine effectiveness study was continued to monitor the trivalent influenza vaccine effectiveness for the vaccine that was licensed for that season, containing also the 2009 pandemic influenza virus strain. Early European level IVE estimate was also calculated based on the pooled analysis of the data that were gathered in a similar way in the contributing countries.

Methods

The aim of the study was to provide estimate on influenza vaccine effectiveness in Hungary during the influenza season with the participation of voluntary GPs that are also involved in the sentinel influenza surveillance network, and to contribute to the European level pooled IVE estimate. The study population consisted of community-dwelling elderly in 2008-2009, and 18+ general population in both 2009-10 and 2010-2011 living in selected sentinel GP practice catchment areas. The age groups included were 60 years and older in 2008-2009, and 18 years and older in the 2009-10 and 2010-11 seasons. Participating sentinel GPs swabbed all elderly and a systematic sample of the 18-59 years old individuals meeting with the selection criteria and consulting for influenza like illness.
Case-control studies were conducted in all the three seasons with cases that were medically attended ILI patients (defined according to EU-ILI case definition) tested positive for influenza, and test negative controls. Voluntary GPs collected clinical samples for laboratory testing and also completed questionnaires about the patients. Samples were transported to the National Center for Epidemiology. Laboratory confirmation was performed with PCR. GPs were contacted if the questionnaire was incomplete to minimize the amount of missing data.
A person was considered vaccinated if he/she had received influenza vaccine more than 14 days before the date of onset of ILI symptoms or of being selected as a control.

The confounding variables that were collected included presence of chronic conditions, pregnancy, morbid obesity, severity measured as any hospitalisation in the previous 12 months, health seeking behaviour measured as number of GP visits in the previous 12 months, smoking history, functional status, and seasonal and/or pandemic influenza vaccination in the previous season.
IVE estimates were obtained using 1- odds ratio with 95% exact confidence intervals (CI). We computed crude IVE and adjusted for confounders, using logistic regression.

Results

During the pilot study in 2008-2009, 50 GPs participated and 280 people above 60 years of age were assessed. The total number of ILI cases enrolled was 141. From these people with ILI 45 was confirmed by laboratory results as influenza. The sample size was too small to provide vaccine effectiveness estimate.
In 2009-10 a total of 87 GPs, contributing to the sentinel influenza surveillance network in Hungary, participated in the study. From them 63 GPs (72.4%) recruited at least one participant. Missing values for the different variables varied from 0 to 4.2% in the database.

Among the 411 medically attended ILI patients swabbed, 50 were excluded (20 – not adhering EU-ILI case definition, 29 – controls after week of last case, 1 – swabbed more than 7 days after ILI onset). Influenza A(H1N1)v was confirmed by RT-PCR in 55 ILI patients, and the remaining 306 patients was tested negative for influenza.

Pandemic IVE estimates were adjusted for age group, sex, presence of underlying conditions, number of GP consultations during the previous 12 months, present seasonal influenza vaccination, region, and month of ILI onset. The study suggested that pandemic influenza vaccination was effective in preventing laboratory confirmed influenza A(H1N1)v illness. The adjusted pandemic IVE was 79.1% (95% CI 12.8-95.0%) for 18+ age group, and 80.1% (95% CI: 7.7-95.7%) in the 18-59 age group. Seasonal influenza vaccination had no effect on the occurrence of laboratory confirmed pandemic influenza illness (seasonal IVE was -53.8%, 95% CI -676.3-69.5%).

Concerning the 2010-11 influenza season, preliminary results are available based on the recruitment from 29 Nov, 2010 to 07 April 2011. 98 GPs from the sentinel influenza surveillance network, covering all regions in Hungary, participated in the study. From them 79 GPs (81%) recruited at least one participant from the start of the study till 07 April 2011. The median number of recruited patients was 9 (IQR 5-17).

Between 29 November 2010 and 07 April 2011 977 patients were assessed and 324 patients were discarded (57 – not adhering EU-ILI case definition, 77 – controls before or after the week of the first or last case, 13 – swabbed more than 7 days after ILI onset, 114 – not adhering to rules of systematic sampling, 19 - other reasons, 44 - under processing and quality control). From the 653 ILI patients Influenza A(H1N1)v was confirmed by RT-PCR in 102 patients, Influenza B was detected in 15 cases. 551 patients were tested negative for influenza.

We adjusted IVE estimates for age groups (18-59, 60+), any presence of underlying conditions, previous pandemic influenza vaccination, previous seasonal influenza vaccinations, and month of ILI onset. The adjusted IVE was 85.6% (95% CI 27.0-97.2%). We found no evidence of effect of the pandemic influenza vaccination in the 2009-10 season on the occurrence of laboratory confirmed influenza in the 2010-11 season (pandemic IVE 23.1%; 95% CI -58.4-62.6%).

Results of the feasibility and acceptability study in the 2009-10 season

In the 2009-10 season we carried out a feasibility and acceptability study among the participating GPs. 86 out of 87 GPs responded with completing the feasibility and acceptability study questionnaire. The GPs opinion about the importance of influenza vaccination studies was measured on a 5 grade scale (1-important to 5-unimportant). The average grade of the responses was 1.36. The self evaluation of their knowledge about the study was also high: good to very good.

During the study, 71% of the GPs filled the study questionnaires by themselves, the others asked the nurse to complete the questionnaires about the patients. The average time spent on filling one questionnaire was 7.7 minutes. They evaluated the time spent on filling the questionnaire on a five grade scale (1-acceptable to 5-unacceptable) at an average 1.9. Most GPs found very easy to fill the questionnaire. 85 GPs responded to the question: would you like to participate in the study in the next season. 62.4% responded yes, 20% not decided yet, and only 17.7% decided not to participate in the study next year.

Discussion, limitations

The result of the 2009-10 study and the preliminary result of the 2010-11 study provided evidence that the 2009 monovalent and the 2010-11 trivalent influenza vaccinations were similarly effective in preventing laboratory confirmed influenza in the given season. This is in line with the data suggesting that in 2009-10 and 2010-11 the match between the influenza vaccine and the predominant circulating strain was good. However, receiving a monovalent pandemic influenza vaccination only in the 2009-10 season provided much less protection against influenza in the 2010-11 season. Low vaccine coverage in the population, low positivity rate among the ILI patients and small sample size in the study population caused some difficulties to provide precise IVE estimates for not only the 18+, but also for the elderly and those with underlying condition.
GP based case control studies using test-negative controls to estimate seasonal IVE against laboratory confirmed medically-attended influenza are feasible on country level. The use of a laboratory confirmed outcome is important to have a valid estimate and may also reduce the magnitude of confounding effects.
Our studies suggest that providing influenza vaccine effectiveness estimate concerning not only seasonal but also pandemic

influenza season is feasible in a small country like Hungary. However, larger sample size is needed to provide IVE estimates for elderly and for those with underlying conditions. The seasonal fluctuation in the attack rates of influenza is unpredictable, which had implications on the sample size of the study, because there is a level of uncertainty, which is difficult to control.

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