VARICELLA VACCINATION IN HUNGARY AND POLAND: OPTIMIZATION OF PUBLIC BENEFITS FROM PROPHYLAXIS TECHNOLOGIES IN THE TIME OF AUSTERITY**

***László Szabó[1, 2], Teresa Jackowska[3, 4], Zoltán Kaló[5, 6] , Andrea Kulcsár[7], Zsófia Mészner[8], Zsuzsanna Molnár[9], Jacek Wysocki[10], Peter Wutzler[11], Judit Kormos-Tasi[2], Christophe Sauboin[12]**

[1]Hungarian Pediatric Association, Budapest, Hungary
President: László Szabó
[2]Department of Family Care and Methodology, Faculty of Health Sciences, Semmelweis University, Budapest, Hungary
Dean: Zoltán Zsolt Nagy
[3]Department of Pediatrics, Medical Center for Postgraduate Education, Warsaw, Poland
Head of Department: prof. Teresa Jackowska, MD,PhD
[4]Department of Pediatrics, Bielanski Hospital, Warsaw, Poland
Director: Dorota Gałczyńska-Zych
[5]Health Economics Research Centre, Faculty of Social Sciences, Eötvös Loránd University, Budapest, Hungary
Dean: Katalin Tausz
[6]Syreon Research Institute, Budapest, Hungary
Director: Zoltán Kaló
[7]Department of Infectology, Joint Hospital Saint László and Saint István, Budapest, Hungary
Director: István Vályi-Nagy
[8]National Institute for Child's Health, Budapest, Hungary
Director: Zsófia Mészner
[9]National Center for Epidemiology, Budapest, Hungary
Director: Márta Melles
[10]Medical University in Poznań, Poznań, Poland
Dean: Grzegorz Oszkinis
[11]Institute for Virology and Antiviral Therapy, Jena University Hospital, Jena, Germany
Dean: Dr. Andreas Sauerbrei
[12]GlaxoSmithKline Vaccines, Wavre, Belgium
Director: Pascal Lizin

Summary
As an international collaboration between the Hungarian Pediatric Society and the Polish Foundation for the Development of Paediatrics, multidisciplinary expert group meeting was organized to analyze the current situation and the results of the work performed on varicella prevention in Poland and in Hungary (ie. burden of disease, public health considerations of primary preventive technologies), and to discuss the possible modification in vaccination practice based on the US and German experience and health economic considerations.
Varicella (chickenpox) is a highly contagious disease predominantly affecting children aged 1-9 years, and approximately 80-90% of children are seropositive for VZV by the age of 15 years. In 2-6% of all cases potentially serious complications can occur in previously healthy children and adults. According to the European surveillance network, European population is highly

**Summary of Expert Working Group Meeting. The members of Expert Working Group Meeting: Z. Kaló, A. Kulcsár, Zs. Mészner, Zs. Molnár, L. Szabó, (Hungary), T. Jackowska, P. Stefanoff, J. Wysocki (Poland), P. Wutzler (Germany) and C. Sauboin (Belgium). The meeting took place in Budapest, on the 26th of September under the title: Varicella Vaccination in Hungary and Poland – Optimization of public benefits from prophylaxis technologies in the time of austerity

infected by VZV, and vaccine uptake is extremely poor. Routine childhood immunization against varicella may be considered in countries where (1) varicella is relatively important public health and socioeconomic problem; (2) vaccine is affordable; and (3) high and sustained vaccine coverage can be achieved. Even in difficult economic periods, when health care budgets are seriously limited, further resources for primary prevention should be found, which would also enable children from all economic backgrounds to receive vaccination on an equal basis. Ideal reimbursement strategy would be full (100%) coverage by giving two doses for one or more cohorts. If it is not feasible second best option would be a partial reimbursement scheme for every child. In case it could not be reached, reimbursement only for risk groups should be implemented in Hungary (this is already available in Poland). As long-term evidence is not available at the time of registration, health economic modelling is required. Modelling with thorough sensitivity analysis can reduce the uncertainty of reimbursement decisions compared to alternative use of public resources.

Key words: varicella, vaccination

INTRODUCTION

Though the problem of the vaccine preventable diseases should be nearly completely solved all over the world, the access to modern immunization possibilities has been challenged.

Fortunately, varicella is a mild infection in most cases. However, in 2-6% of all the cases potentially serious complications can occur in previously healthy children and adults (1). Varicella is a highly contagious disease predominantly affecting children aged 1-9 years, and approximately 80-90% of children are seropositive for VZV by the age of 15 years (2). Varicella and related immediate and long-term complications put a significant medical-economic pressure on national health systems.

Vaccines against VZV infection have been for years available in both Hungary and Poland. Polish and Hungarian experts in vaccinology prepared the recommendation several years ago, varicella infection has been discussed atlocal pediatric conferences, and studies about disease morbidity and complications have been published in local medical journals (3-8). Parents and communities (kindergartens, schools etc.) have been educated in TV programs, web pages, with leaflets; the vaccine uptake, however, is far from optimal. Epidemiology has not changed and the incidence in Europe is still high.

EPIDEMIOLOGICAL BACKGROUND IN EUROPE

European varicella surveillance data isavailable on the website of the European surveillance network for selected vaccine preventable diseases hosted in Sweden by the European CDC (www.euvac.net). This network collects age-specific data including vaccination status, laboratory confirmation, hospitalization and complication rate from 19 countries (fig. 1).

In 2008, 2009 and 2010 almost 900,000 varicella cases were reported from 19 countries. In 2010, 99.5% of all varicella patients were unvaccinated, and patients with breakthrough infection (0.5%) had received at least one dose. These data indicates that Europe seems to have a high prevalence of VZV infections and that vaccine uptake seems to be poor.

Of note, Poland was the country to report most varicella cases of all cases in Europe (n = 183 446 (2010)),

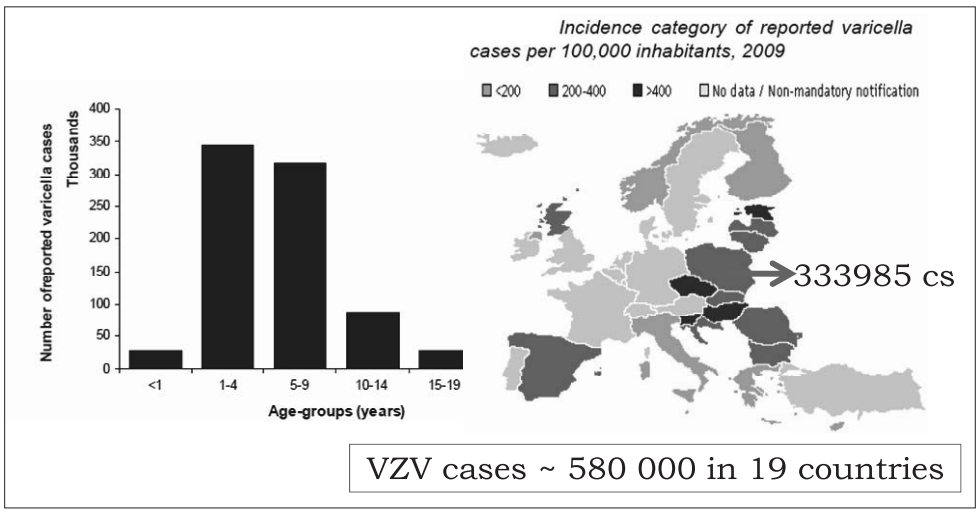

Fig. 1. Varicella Zoster Virus Epidemiology in Europe. Source: www.euvac.net. (Varicella Zoster Virus Epidemiology in Europe) Source: www.euvac.net

with 59% (2008-2009) and 31% (2010) (Varicella surveillance report 2010; www. euvac.net).

VZV prevention in Hungary

In Hungary, the incidence of vaccine preventable diseases has decreased only for those diseases where a compulsory vaccination schedule exists. For decades an age-related vaccination calendar of National Immunization Program (NIP) has been successfully followed in Hungary. Compulsory vaccines get complete reimbursement of the Ministry of Health and have achieved 98% vaccination coverage. Unfortunately, there has not been any modernization in the calendarfrom 2009 to date, whereas in other countries several new vaccines have been introduced as part of the immunization scheme. Vaccines not included in the calendar are optional, and some of them are partially reimbursed. However, the incidence of vaccine preventable diseases as varicella and tick-born encephalitis has not changed significantly in the last few years. These vaccines are available only in the private market with low coverage and consequently no significant epidemiological impact. In the last year (2010) 39.602 varicella cases (with no death) were reported.

Varicella vaccine has beenavailable since 2003, however in the private market only. As a consequence, its vaccination coverage is very poor (about 20%), and only a small percentage of immunized persons have received two shots. In spite of the efforts performed since 2003 (recommendations, continuous professional and parental education) the number of people vaccinated has reached a plateau, so new strategies are needed to further increase the awareness for the disease.

VZV prevention in Poland

After a peak in the early 1990s, the number of new varicella cases has increased since 2006-2007. Meanwhile the number of vaccinated person hadshown a constant increase since 2006 from 8,000 to 30,000 cases in 2010 – mostly financed by parents, except in risk groups, where it has been covered by the government as compulsory vaccination – still with no epidemiological impact.

Poland has a very similar vaccination system to Hungary and other post-Soviet countries. According to the regulation that was introduced in 2008, children below 12 years of age receive mandatory vaccination against varicella if they are part of the following risk groups[9]: (1) immunocompromised, with a high-risk of severe disease; (2) with acute lymphoblastic leukaemia in the remission period; (3) with HIV; (4) before immunosuppressive treatment or chemotherapy; (5) children until 12 years of age from an environment of people described in point 1) who have not developed varicella yet; and from October 2011 (6) children until 12 years of age other than in point 1) to 5) vulnerable to an infection because of environmental reasons, especially those vulnerable because of living in common spaces which enables virus transmission and an outbreak occurrence, including mainly long-term care homes, orphanages, day nurseries and other care institutions.

In both countries, the epidemiological situation which is representative for other European countries shows similar tendencies without improvement using the current prevention methods. To achieve changes, international recommendations and successful programs with varicella vaccination as UMV (universal mass vaccination) are available.

WHO recommendation for VZV vaccination

According to the WHO recommendation, routine childhood immunization against varicella may be considered in countries where (1) varicella is a relatively important public health and a socioeconomic problem; (2) vaccination is affordable; and (3) high and sustained vaccine coverage can be achieved. In addition, vaccination should be offered in any country to individual adolescents and adults without a history of varicella, in particular to those at increased risk of contacting or spreading the infection (10, 11). The United States was the first to follow the WHO recommendation.

The rationale for vaccine control against VZV infection

Varicella is an extremely contagious disease experienced by almost every child or young adult in the world. Four million cases had occurred every year in the United States in 1990-1994 before the introduction of a vaccination; nearly 10,000 patients had required hospitalization and 100 patients had died (10). A cost-benefit analysis in the United States showed that routine varicella vaccination is likely to save 5 times the investment (12). Even when only direct costs were considered, benefits almost balanced the costs (10, 13, 14).

After the general recommendation of one-dose varicella vaccination for routine use for children aged 12 months and above in the United States in 1995, significant improvement has been seen in the number of varicella cases, varicella-related ambulatory visits, hospitalization and deaths. By the year 2000, the incidence of disease had decreased by 75% (coverage rate 84%) and 75-80% reduction of hospital treatment could have been achieved. Varicella-related deaths had decreased by 75-92% in children and adolescents and by 74% in adults (15). However, the problem of breakthrough varicella cases, defined as the appearance of pruritic maculo-papulo-vesicular rash, occurring after more than 42 days after vaccination with no other apparent cause has remained (13). Breakthrough varicella is caused by

primary (PVF) or secondary vaccine failure (SVF) (PVF: the failure to give a protective immune response after vaccination; SVF: the gradual waning of immunity over time).

Several questions are raised on VZV vaccination

Is the safety and efficacy profile of the vaccines adequate for nationwide application? Which vaccination schedules could be preferred? How to fit the schedule chosen into the NIP?

In response to the increasing number of breakthrough varicella cases, several countries have implemented recommendations for a two-dose varicella vaccination schedule (16).

In the current universal routine vaccination (URV) recommendation, the routine childhood schedule includes the first dose at the age of 12-15 months and the second dose at the age of 4-6 years or 15-23 months (minimum interval of 3 months). For adolescents (> 13 years) and adults, two doses are recommended 4-8 weeks apart in those with no evidence of immunity. The second dose should be given for all persons without the history of breakthrough varicella who previously received one dose.

Timing of the second dose varies in different countries from the age of 4-6 years (e.g. Greece, Israel, Saudi Arabia, the United States) to the age of 15-23 months (e.g. Germany, Hungary, Luxembourg).

Besides the epidemiological aspect, the vaccination, as a primary preventive technique, has been analysed from health economic perspective raising further questions.

Health economic considerations: is primary prevention cost-effective or cost-saving?

In the long-term, health care expenditure grows faster than GDP (as a result of growing expectations with income growth, aging population, easier access to health care due to insurance coverage etc.). In challenging economic periods, governments tend to implement cost-containment measures in the health sector. Even in those periods, when health care budgets are seriously restricted, further resources for primary prevention should be found.

Primary prevention programmes improve the efficiency of health care programmes by different means. They may improve the equity of health care provision, especially if certain screening or vaccination programmes are mandated or targeted for those subpopulations with greater health needs. Preventive programmes positively influence the health behaviour of patients, and consequently can lead to patients taking a more active part in their health care, reducing their moral hazard. Moral hazard means that, as patients have zero or minimal personal financial contribution when accessing health care services related to their own disease, they do not pay attention to the price and quantity of health care technologies, they rely too much on the solidarity of the community (i.e. payers of health insurance premiums). Preventive services, including vaccination programmes can help societies to reassess the solidarity principle, as they emphasise the importance of personal investment into people's own health, and the adherence to guidelines and therapeutic advice.

Clinical opinion leaders and policy-makers have to understand that primary prevention is mostly cost-effective without being cost-saving. Credible and methodologically solid health economic analyses can increase the social priority of primary prevention including vaccination programmes. However, in order to facilitate cooperation with policy-makers and payers, clinicians have to accept that registered indication is not equal to reimbursed indication, and not every innovative therapy is available for every patient immediately.

A general objection of payers is the lack of long-term experience with a new innovative preventive or therapeutic technology. It should be kept in mind, however, that it is impossible to present these long-term data at the launch of preventive health care programs. In preventive medicine, we cannot wait for confirmatory evidence (e.g. cannot investigate what happens if in one-year influenza is not controlled vs. the next controlled year), so we have to accept a reasonable health economic modeling approach. Of note, uncertainty for vaccines is still less than for many other health technologies (e.g. surgical interventions, medical devices etc.) or food products. The immunological response and safety of vaccines have to be tested in clinical trials. There are no mandatory clinical trial criteria for new surgical methods, medical devices or food ingredients. For varicella vaccination, however, real-world experience is available to validate our approach.

Health economic considerations: modelling techniques to estimate the benefits of vaccines

To estimate the benefits of vaccines, modelling is required, since vaccine clinical trials are in some cases limited to immune efficacy; duration of protection is usually unknown (induction and duration of immunological memory); epidemiology of disease is often not known, and we cannot wait for evidence on real pandemics; the efficacy measured from randomized controlled trials (RCTs) is subject to different transmission settings, as we cannot control the spread of disease; long-term benefits are not directly captured; and population effectiveness could be different from individual efficacy, especially due to herd immunity.

The optimal vaccination strategies (routine, at risk, versus epidemiological barrier, etc.) should also be determined by modelling techniques.

A general objection by payers is that modelling is only hypothetical extrapolation. Considering only short time horizon may underestimate the real value of investment into health, and this is especially true for vaccines. Therefore we have to choose such time horizon that enables all consequences in terms of costs and outcomes to be taken into account (e.g. lifetime benefits). Health economic modelling, with thorough sensitivity analysis, reduces the uncertainty of reimbursement decisions compared to alternative use of public resources.

Moving towards universal varicella vaccination: the German experience

In the pre-vaccination area, the incidence of VZV infection was about 760,000 varicella cases per year in Germany. Vaccines became available in 1995[1] and 2004[2]. The goals of varicella vaccination strategy were declared: (1) to reduce the rate of morbidity, complications, hospitalizations and mortality; (2) to protect susceptible high-risk patients by herd immunity; (3) to eliminate varicella in the long-term; and (4) to save medical and societal costs.

The health economic project to calculate clinical benefits and cost-effectiveness of a universal vaccination program consisted of seroprevalence and epidemiological studies, as well as health economic modelling (to assess the potential clinical and economic effects of a universal varicella vaccination program vs. no vaccination).

The possible vaccination strategies are: (1) children strategy (universal vaccination of children at the age of 15 months; (2) adolescent strategy (vaccination of susceptible persons at the age of 11-15 years; and (3) combined strategy (vaccination of children at the age of 15 months and of susceptible persons at the age of 11-12 years). Economic analyses have shown that universal mass vaccination of infants using a one-dose schedule is cost-saving in Germany) (17). According to a 10-year follow-up, two doses of varicella vaccine have been shown to be more effective than one dose and to reduce varicella breakthrough rates (18). Basingon the newly available data, the German Standing Committee on Vaccination (STIKO) modified its recommendations for varicella vaccination in July 2009. The recommendation for varicella vaccination now includes a routine two-dose schedule with the administration of the first dose at the age of 11 to 14 months and the second dose at the age of 15 to 23 months, with a minimum interval of four to six weeks between these doses.

CONCLUSIONS

1. Varicella causes a significant medical and economic burden. Improving the present unfavorable epidemiological situation is needed in both countries. Many limiting factors for data collection exist (varicella is currently underreported), more focus on prevention and proper infrastructure is needed. Vaccine uptake seems to be mainly limited by the lack of broad health-consciousness of general public, the lack of reimbursement and parents' financial capabilities.
2. The role of health economics is important. Assessment of cost-effectiveness and budget impact can facilitate the match of optimal vaccination strategy with efficient and sustainable health care financing. Before implementing a new vaccination strategy, hypotheses and assumptions have to be made, and all of them need economic modelling. At present, broad access to the vaccines seems to be limited mostly for budgetary reasons, besides the scarcity of information on the part of doctors and patients. Partial reimbursement could also be satisfactory after modelling possible scenarios – if full reimbursement could not be achieved.
3. Reimbursement could not only give parents financial support to access the vaccine but also help them consider varicella vaccine as important, as reimbursement is an explicit indicator of public health priorities. It is expected to lead to higher vaccine uptake and consequently decrease theburden of disease. As the first step, the best vaccination schedule that fits into the national vaccination calendar should be defined. The most appropriate recommendation would be to vaccinate children in their second year of life.
4. There are several options for the improvement of the access to vaccines:
   a) Full reimbursement of two doses of varicella vaccine for one or more cohortswould bean ideal situation.

   If this is not feasible, other options could be:
   b) Partial reimbursement scheme for one or more cohorts:
      – the same reimbursement rate for both doses (e. g. 50%);
      – the first dose with no reimbursement, the second dose with full reimbursement.
   c) Reimbursement for high-risk groups or persons from an environment of risk groups (this is already available in Poland).
5. Whichever solution is chosen, significant education of the health care workers, parents and patients is crucial. □

[1]Varilrix is a registered trade mark of GlaxoSmithKline group of companies.

[2]Varivax is a trade mark of Sanofi Pasteur MSD.

ACKNOWLEDGEMENTS

The authors thank Dr Ildikó Simonfalvi for medical writing services.

DISCLOSURE STATEMENT

CS is an employee of the GlaxoSmithKline group of companies.

PW has been a consultant to GlaxoSmithKline and Sanofi Pasteur MSD, and has served on advisory boards for vaccine manufactures.

AK is in relationship with GlaxoSmithKline, Pfizer, Merck & Co., Novartis, she is regular lecturer and consultant on different vaccination topics.

TJ has been receiving support for travel to meetings from GlaxoSmithKline; receiving payment for lectures from GlaxoSmithKline, receiving travel, accommodations, meeting expenses from GlaxoSmithKline; principal investigators for clinical studies from GlaxoSmithKline.

JW has been paid for lecturing and received travel grants for participation in scientific congresses from GlaxoSmithKline.

ROLE OF THE FUNDING SOURCE

This meeting and the preparation of the manuscript, was funded by GlaxoSmithKline.

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Received: 04.08.2013
Accepted: 08.09.2013

Correspondence to:
*László Szabó
Department of Family Care and Methodology
Faculty of Health Sciences
Semmelweis University
1085 Budapest, Vas u. 17, Hungary
tel.: +36 30 965-72-65
e-mail: szabo.laszlo.md@gmail.com