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Dear Colleagues

THE FOURTH JHPOR EDITION IS LARGELY DEVOTED TO VACCINES. WE PRESENT SOME ISSUES OF VACCINATION AGAINST INFLUENZA, WE SHOW THE AVAILABILITY AND FUNDING MECHANISMS OF COMBINATION VACCINES FROM 33 EUROPEAN COUNTRIES, AND COST-EFFECTIVENESS ANALYSIS OF HUMAN PAPILLOMAVIRUS (HPV) VACCINATION AS AN EXTENSION TO THE CERVICAL CANCER PREVENTION.

Despite the campaign for vaccination against influenza, its coverage is steadily falling, and last season it was below 5% in Poland . The reasons for varying effectiveness of influenza vaccines are complex, but nowadays it is believed, that role of genetic and environmental factors should be emphasized. Some point to the need to monitor the post-vaccination adverse events. Additionally, approach to vaccination should be personalized.

The increasing cost of clinical trials of vaccination cause the increased interest in solutions based on public-private partnership. The current and planned in the near future research projects conducted by IMI (Innovative Medicines Initiative) acting jointly with the EFPIA (European Federation of Pharmaceutical Industries and Associations) are showed in the article of A. Wittelsberger and M. Goldman.

Two articles in this issue relate to schizophrenia. The first shows the methodology of the project titled "Burden of Disease in Seven Central and Eastern European (CEE)", and the second was the analysis of the cost effectiveness of injectable atypical antipsychotics long-acting for chronic schizophrenia in Poland.

As for disease cost we present to you 2 articles. The first one shows clinical and economic analysis of non-medical technology in Russia, and the second one written by colleagues from Military Institute of Medicine in Warsaw presents assessment of direct costs of hospitalization caused by drug-induced skin reactions. Both works were presented during the earlier Russian-Polish ISPOR meetings.

Also, an analysis of rationalization, which refers to solutions in the Polish Reimbursment Act, was presented on the example of hypertension drugs.

It should be noted, that in the framework of the Polish Pharmacoeconomic Society a Polish glossary of Quality of Life related terms is currently in progress. The glossary's methodological assumptions were presented in the form of a short communication.

The next edition of JHPOR will be dedicated to the challenges in monoclonal antibody-based therapies. At the same time I cordially invite all interested to the 1st JHPOR Conference titled "Safety Aspects of Monoclonal Antibodies and Fusion Proteins Treatment", which will be held on March 15th, 2014, in Warsaw.

We wish you pleasant reading of our journal

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JHPOR – ISSUE 3

Influenza – the greatest master of metamorphosis – constant puzzle

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ABSTRACT

Influenza is a disease in which the continuous evolution of the virus is essential for the occurrence in the human population with seasonal epidemic, and from time to time also pandemic. According to information from WHO, between 330 million and 1.575 billion individuals suffer from influenza and influenza – like virus every year throughout the world, with deaths of between 0.5 and 1 million individuals. The evolution of the influenza virus is most apparent in the case of surface glycoproteins of the virus, but it also relates to each of the eight viral gene segments, both type A and B. Modular construction of the genome of influenza virus is also responsible for the huge variation in both genotype and phenotype. According to the Recommendations of the Advisory Committee on Immunization Practices (ACIP) recommended vaccination should we all willing ranging from 6th month until the ripe old age and instill the highest percentage of the population in each country. Vaccinated against influenza we should due to clinical indications and epidemiological indication not only ACIP recommends vaccination against influenza but also 14 International Scientific Societies. In the last epidemic season - 2012/2013 instilled only 3.75% of the population, in spite of that in Poland for many influenza seasons in many regions local authorities allocate a certain amount of funds to offer free flu vaccination to people 50 – 65 years of age who are not once in the high-risk group.

Flu decimated the human population from time immemorial. It was and still continues to be the cause of many human tragedies. Statement by Dr Kevin Sullivan of the USA quoted Influenza is defined as an uncontrolled scourge of humanity remains constantly up to date, because of our irreverent relation to the fight against this pathogen [1]. According to information from WHO, between 330 million and 1.575 billion individuals suffer from influenza and influenza – like virus every year throughout the world, with deaths of between 0.5 and 1 million individuals [2].

Influenza is a disease in which the continuous evolution of the virus is essential for the occurrence in the human population with seasonal epidemic, and from time to time also pandemic. For example, 9 may 1997, the avian influenza virus A/H5N1/ broke the barrier of species and became pathogenic to humans [3]. Almost 60% of people infected with A/H5N1/ die, and therefore was labeled as Highly Pathogenic Avian Influenza (HPAI). Influenza A virus infects not only humans, but also horses, pigs, minks, aquatic mammals such as seals, whales, and birds especially aquatic birds. The all subtypes were found among birds, but only a few of them also among the people [5,6].

In the peer for years, the number of influenza virus hemagglutinins HA [H1-18] and neuraminidase NA of influenza virus NA N11 is increasing due to the isolation of influenza virus from some species of bats [7,8]. The evolution of the influen-

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za virus is most apparent in the case of surface glycoproteins of the virus, but it also relates to each of the eight viral gene segments, both type A and B. This difference results from the accumulation of the molecular changes in the eight RNA segments that may occur by various mechanisms, which may contribute to the evolution of influenza viruses [5,6].

Modular construction of the genome of influenza virus is also responsible for the huge variation in both genotype and phenotype. The ancient Greek philosopher who lived in 540 – 480 BC, Heraclitus of Ephesus wrote: Nothing is permanent except change, and in the case of influenza virus works. In the XX century there were three pandemics: 1918-19 - Spanish flu – A/H1N1/ 50-100mln caused the victims death, Asian flu -A/H2N2/, caused 1-4 million victims of death, Hong Kong flu -A/H3N2/ led to 1-4 million victims of death. From this period in the epidemic season generally revolve two types of influenza virus type A (subtype A/H1N1 and subtype A/H3N2/) and type B [1,5,6].

The cornerstone, which caused the development of researchmultifaceted influenza virus was the isolation of influenza virus from humans by three British researchers Ch. Andrewes, W. Smith and P. Laidlaw at the National Institute for Medical Research in London. The next step is the multiplication of viruses in eggs in 1937 (which is currently used) resulted in the ability to produce influenza vaccine, as the only effective method of preventing illness, as well as post-influenza

complications and death. In 1941, the first permit for the use of vaccines in humans. They were sponsored by the United States Armed Forces. In 1967 initially inactivated vaccine was purified containing the gradient of gravity. Then, in 1968, receiving the vaccine split and in 1976 subunit vaccine, in 1996 vaccine with oil adjuvant MF59, and in 1997 virosomal vaccine [1,2]. Next year resulted in various modifications of inactivated influenza vaccine as well as live-attenuated recommending influenza vaccine [LAIV] by ACIP in 2011, currently influenza virus strains used for the production of influenza vaccines. Thanks to the latest molecular biology techniques turn out to be almost 100% compatible with those that appear in the next epidemic season [9].

It's hard not to mention that in Poland in the years 1983-1984 in the National Centre for Influenza in the Department of Virology, National Institute of Hygiene in Warsaw in cooperation with the Military Institute of Epidemiology obtained inactivated influenza vaccine [1]. One of them was inactivated vaccine chromatographic purity, containing whole virions. The second one, which also had a purity of chromatographic, was vaccine subunit type, i.e. contain only the hemagglutinin and neuraminidase. These vaccines were obtained on a laboratory scale. Evaluation of the results of their application in animal and controlled human studies showed improved quality and effectiveness in comparison with conventional inactivated vaccine, manufactured by the Serum and Vaccine Production Plant in Krakow.

A total of 1,215 people were vaccinated, and made a comparative study of four different groups of people vaccinated three-component vaccine against influenza with different levels of purification, indicating both the level of antibodies antihaemagglutinin and antineuraminidase. The resulting vaccine had called a state control. Was tested by the Department of Sera and Vaccines at the National Institute of Hygiene in Warsaw. The results of these studies suggested the possibility of production of modern vaccines do not deviate from the standards of the World Health Organization. The authors of this study was three-person team: Professor Lidia B. Brydak Ph.D., Professor Wiesław Gall MD., and not living now Romuald Semkow MD. This work was pioneering in Poland regret it should be noted that the development is not implemented for mass produced. It is the only development of technology vaccine against influenza in Poland [10]. In 1980-1990 the research was conducted on the adaptation of influenza viruses A/H3N2/ antigenic formula for low temperature replication, and then analyze their antigenic and biochemical characteristics necessary to determine the possibility of using them as donor genes using recombinant method for producing vaccine strains. Such designation indicators - genetic markers necessary for this type of research for output strains and cold adapted, that is adapted to low temperatures. As a result of these studies yielded two polish mutants A/Pol/L/71 / H3N2/ and A/Pol/79/85 which can be used as donor genes using a method for producing recombinant influenza vaccine strains, as was confirmed by Professor L. Döhner Ph.D., of the University of Greifswald in Germany. This work was the subject of dessertation thesis of Professor Lidia B. Brydak PhD. For several epidemical influenza seasons doctors of all specialites have to the disposal many kinds of influenza vaccines, ranging from different types of inactivated - to live-attenuated influenza vaccine (LAIV) produced in eggs and various tissue culture.

Table 1 shows the vaccine registered in Poland. In the epidemics seasonal 2013/2014 are available vaccine written by slash. According to the Recommendations of the Advisory Committee on Immunization Practices (ACIP) recommended vaccina-

Table 1. Influenza vaccines registered in Poland in 2011

Tab.1. Influenza vaccines registered in Poland in 2011
Influenza vaccine received in cultured chick embryos:
Inactivated influenza vaccine split virion with:
- VAXIGRIP *(Sanofi Pasteur SA, F)*
- Fluarix (GlaxoSmithKline, B)
- Begrivac (Novartis Vaccines and Diagnostics, D)
- ID Flu * *(Sanofi Pasteur SA, F)*
Subunit vaccines containing isolated surface antigens, hemagglutinin and neuraminidase, ie:
- Influvac *(Abbott, USA)*
- Agrippal (Novartis Vaccines and Diagnostics SRL, I)
Vaccines wirosomalne:
- Inflexal V (Berna Biotech I, S.r.I)
Influenza vaccine received in the MDCK cell culture:
Inactivated subunit influenza vaccine, containing isolated surface antigens, hemagglutinin and neuraminidase, ie:
- Optaflu (Novartis Vaccines and Diagnostics, D)
Influenza vaccine received in the Vero cell culture:
Inactivated influenza vaccine with split virion
Preflucel (Baxter ,A)
*Vaccine administered intradermally
....Brydak L.B. 2011

Table 2. Recommendations of the International Scientific Societies for influenza vaccination

Tab. 2. Recommendations of the International Scientific Societies for influenza vaccination
- Advisory Committee on Immunization (ACIP)
- American Academy of Pediatrics (AAP)
- American Academy of Family Practice (AAFP)
- American Academy of Family Physicians (AAFP)
- Working Party on Preventive Services (USPSTF U.S.)
- American College of Internal Medicine
- American Society of Internal Medicine, U.S.
- American Society for Infectious Diseases (IDSA)
- Canadian Working Group on Periodic Health Research
- American Cancer Society
- American College of Obstetrics and Gynecology
- Executive Director of the Department of Health UK
- American Heart Association / American College of Cardiology
- Global Initiative on Chronic Obstructive Lung Disease (GOLD)
- Global Strategy for Recognition, Treatment and Prevention of Asthma (GINA guidlines)
(Develop summary: Brydak LB., 2007)

tion should we all willing ranging from 6th month until the ripe old age and instill the highest percentage of the population in each country [2.12]. Vaccinated against influenza we should due to clinical indications and epidemiological indication not only ACIP recommends vaccination against influenza but also 14 International Scientific Societies as shown in Table 2 [1].

As Director of the National Influenza Center, Head of the Department of influenza Research at the National Institute of Public Health-National Institute of Hygiene in Warsaw in the nineties to the present time I have started working with clinicians concerning research on the immune response after vaccination with influenza-risk children and adult patients resulted in numerous publications in journals of national, international, reports at international congresses and conferences of national [14-34]. These studies were designed to increase influenza vaccination, evaluation of the humoral response and to provide specific examples will be helpful in promoting molding and encourage health professionals to protect not only patients but also their loved ones. As a result to carry out research in the following high-risk groups [Table 3].

The results of our studies of influenza vaccination in patients with acute cardiovascular events were included in the recommendations of the European Cardiac Influenza Vaccination [12]. There are hundreds of clinical studies published in reputable scientific journals documenting

A TOTAL OF 1,215 PEOPLE WERE VACCINATED, AND MADE A COMPARATIVE STUDY OF FOUR DIFFERENT GROUPS OF PEOPLE VACCINATED THREE-COMPONENT VACCINE AGAINST INFLUENZA WITH DIFFERENT LEVELS OF PURIFICATION, INDICATING BOTH THE LEVEL OF ANTIBODIES ANTIHAEMAGGLUTININ AND ANTINEURAMINIDA

Table 3. Studies conducted in the Research Department of influenza viruses, the National Influenza Center, NIPH in collaboration with clinicians in the groups at risk and evaluated the humoral immune response to influenza vaccination

Tab.3. Studies conducted in the Research Department of influenza viruses, the National Influenza Center, NIPH in collaboration with clinicians in the groups at risk and evaluated the humoral immune response to influenza vaccination

Children

Children aged 6-35 m.ż, 3-8 years of age, 9-12 r.ż 0.13-20 years of age
Children with acute lymphoblastic leukemia (ALL), vaccinated at different times after treatment.
Children with severe haemophilia and mild.
Children with bronchopulmonary dysplasia.
Children with glomerulonephritis.
Children with chronic renal failure subjected to continuous ambulatory peritoneal dialysis, hemodialysis and chronic renal failure vaccinated once and twice.
Children infected with HIV.
Children vaccinated after splenectomy in age groups 0-5 years of age, 6-10 years of age, 11-15 years of age, *(dissertation, MD.,PhD)*
Children with aplastic anaemia
Children with asthma
Children with inflammatory bowel disease

Adults

Adults aged 21-30 years of age, from 31 to 40 years of age, from 41 to 50 years of age, from 51 to 64 years of age > 64 years (2 *dissertations, MD.,Ph.D*)
Billeted students of the Military Medical Academy
Patients chronically ill
Patients with acute lymphoblastic leukemia
Patients with chronic renal failure
Patients after renal allograft resipients
Patients infected with HIV at various levels of CD4, with symptoms of AIDS and asymptomatic
Patients with breast cancer
Patients with cancer of the thyroid
Patients with asthma *(part of MD.,PhD thesis)*
Patients with chronic obstructive pulmonary disease (COPD) *(part of PhD thesis)*
Patients with a group of young and elderly *(dissertation MD.,PhD)*
Patients with acute cardiovascular events *(some of the habilitation thesis, MD.)*
Patients with malignant lymphomas-Hodgkin's *(MD.,PhD thesis)*
Patients with lupus (*dissertation MD., PhD*
Patients with primary systemic vascular inflammation: Wegner's granulomatosis *(part of the habilitation thesis MD)*

Brydak L.B. 2010

that influenza vaccination prevent multisystem post-influenza complications, I regret to say that Poland is on the penultimate place in Europe regarding the percentage of vaccinated population [2]. The epidemic season 2012/2013 instilled only 3.75% of the population, in spite of that in Poland for many influenza seasons in many regions local authorities allocate a certain amount of funds to offer free flu vaccination to people 50 – 65 years of age who are not once in the high-risk group. Figure 1 shows the percentage of the population vaccinated against influenza in Poland [13].

The age range which offers a free flu vaccination depends only on the decision of Health and Social Affairs of the City and is different depending on the region. According to the Act of 5 December 2008, Article 51 of the Act of 5 December 2008 on preventing and combating infections and infectious diseases in humans - Acts. U. No. 234, item. 1570, which entered into force dn.1 January 2009, the doctor is obliged to inform the patient about resulting from the provision of the Act, requiring a protective vaccinations listed in the relevant ordinances. Failure to comply with this requirement may result in legal consequences (adjudication shall follow the provisions of the Act dated. August 24, 2001 - Code of Conduct

misdemeanor cases Coll. Laws of 2008, No. 133 and No. 214 poz.848, item. 1344).

Please be aware that multi-organ post-influenza complications due to influenza infection may occur from persons at high risk, pregnant women, infants, small children of the adults and the elderly, and also in young people who were previously healthy. Multi-organ post-influenza complications often should also be considered in terms of human tragedy is not computable for money and very serious economic costs incurred by our Country.

Already in 2008, I suggested to develop and implement the National Programme for Prevention of Influenza in order to protect the population against the Polish extremely dangerous pathogen. I described it in my book: FLU, flu pandemic myth or real threat? in the chapter on public health (pp. 437-465). In 2012, the Working Group was established Influenza and developed such a program, which now has the name of National Programme for Influenza Prevention and was presented at the conference Vaccinations in NIPH-NIH on 16 April 2013 is available on the websites of www.opzg.pl. According to studies, Ernst & Young, which is contained in the Nation-
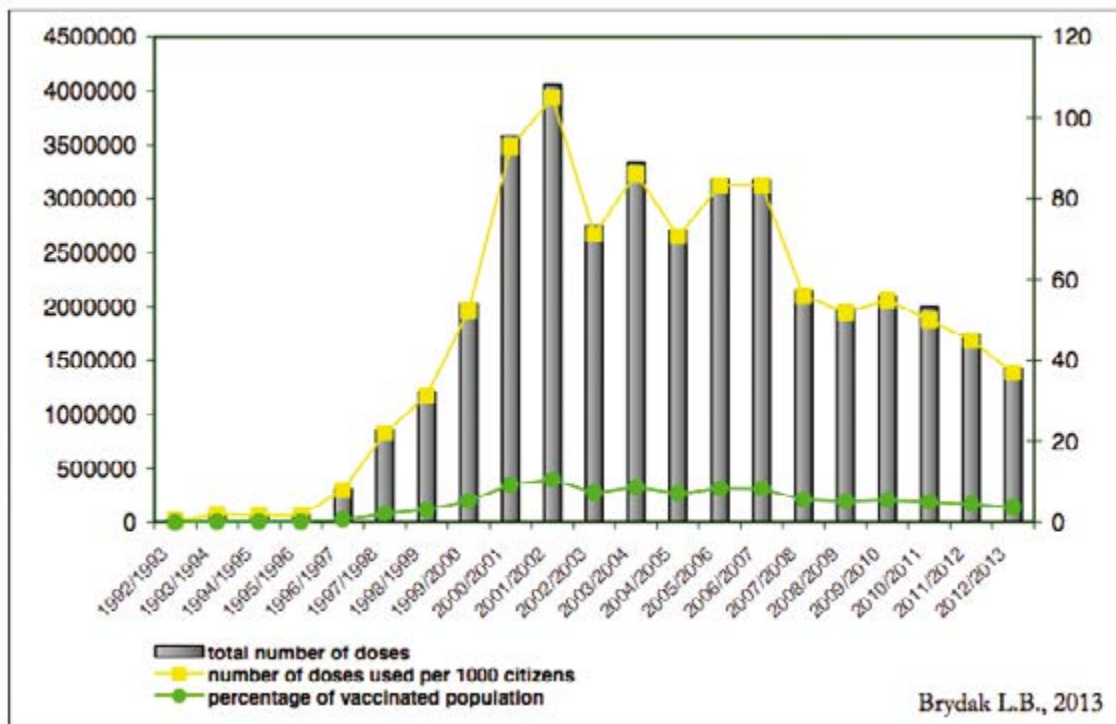
Figure 1. Usage of inactivated vaccine against influenza in Poland in the epidemic season 1992/1993 – 2012/2013

al Programme for Influenza Prevention and Influenza costs in Poland should take into account the direct costs of treatment and indirect costs of influenza. The direct costs of treatment of influenza: ie expenditure on drugs, visits to doctors, treatment of post-influenza complications, specialized tests, hospitalizations, and represent only a small part of the total costs borne by society as a result of illness from the flu and its complications, and is approximately PLN 730 million in the year epidemic [approximately PLN 43.5 million a year without epidemic].

Indirect cost: that reflect the loss suffered by the economy as a result of staff sickness absence or long-term absence from work due to illness or caring for the sick, the decline in labor productivity sick, but not being on sick leave, severe post-influenza complications, which can lead to partial or total incapacity, severe post-influenza complications, which can lead to the death of the employee. The indirect costs of influenza in Poland amount to approximately PLN 4.3 billion in the year of the epidemic [approximately PLN 836 million a year without an epidemic].

Costs difficult to classify in economic terms: for example, reduced quality of life due to pain, loss of free time, reducing the possibility of functioning such as social activity.

Marcus Aurelius, Roman emperor who lived from 121-180, said: Man is worth so much, how many things are matters coming before it. These words are also valid in the XXI century. ■

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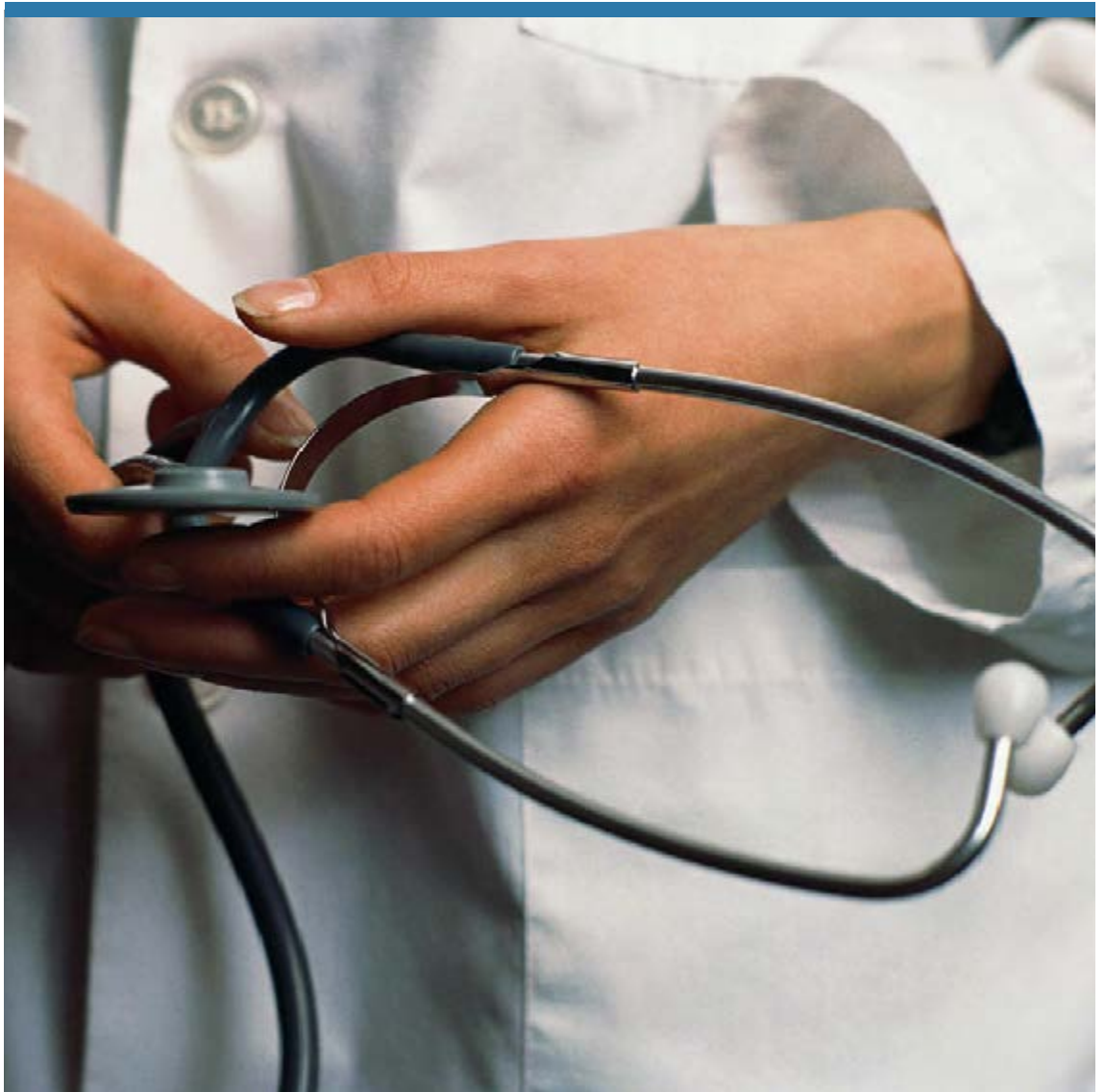
Public-private collaboration to advance the development and benefit-risk assessment of vaccines: The Innovative Medicines Initiative

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ABSTRACT

The true value of vaccines to public health remains to be fully exploited. Many of the challenges associated with vaccines, such as public distrust in the overall safety of vaccines, or finding standardised approaches to measure vaccine effectiveness, require the involvement of a number of different stakeholders in order to be successfully addressed.

Public-private partnerships such as the Innovative Medicines Initiative (IMI) provide a neutral platform that facilitates collaboration on an unprecedented scale between industry, academia, regulators and other actors in the field of vaccine research.

INTRODUCTION

Vaccines are one of the most effective preventative health measures we have. Many infectious diseases that caused millions of deaths in the 20th century are either completely or close to eradication now. Infectious diseases like smallpox or poliomyelitis no longer pose a fatal threat to mankind. For other diseases, such as diphtheria, haemophilus influenza, measles, mumps, pertussis, rubella, and tetanus, the number of deaths per year has been drastically reduced. More than 70 vaccines have been licensed to date, for use

Public-private collaboration to advance the
development and benefit-risk assessment of
vaccines: **The Innovative Medicines Initiative**

against approximately 30 microbes, and there are many more in the development pipeline. The global vaccine market is estimated at $32.05 billion in 2013 and is expected to reach $84.44 billion by 2022 [1]. As of 2010, 79% of vaccines were still produced in Europe, 13% were produced in the US, and 8% were produced in Asia [2]. Half of the investment of Vaccine Europe members is still made in Europe[2], but a trend away from Europe and towards Asia is observed and feared to continue for both sales and investment.

Numerous initiatives have promoted global collaboration in vaccine development, including those by the Bill & Melinda Gates Foundation, the Global Alliance for Vaccines and Immunization (GAVI), the World Health Organisation (WHO), and public-private and product development partnerships. Furthermore, the past decades have seen significant advancement of novel technology and newer generations of vaccines [3]. In reverse vaccinology, genomic information of an organism leads to the identification of novel antigenic targets [4]. Gene-based delivery using DNA or viral vectors and prime-boost combinations have successfully been used to elicit enhanced immune responses [5-7]. Computational and technological advances in the capacity to study genes, proteins and cells have resulted in the field of systems vaccinology that aims at understanding the mechanisms by which vaccines stimulate immunity and at predicting the efficacy of vaccines [8].

Yet significant challenges are still associated with vaccines. Efforts are being made to shorten the time lag that has historically existed in the introduction of new vaccines between high- and low-income countries, but important gaps in vaccination coverage remain. WHO recently estimated that 1 in 5 of all children who die before the age of five, that is more than 1.5 million children, lose their lives to vaccine-preventable diseases [9]. Coverage gaps exist not only between countries, but also within countries. For example, in a recent study by WHO and UNICEF, some countries experience a measles vaccine coverage rate which is 58% higher for the richest fifth of the population than for the poorest fifth [10].

Furthermore, scientific challenges in novel vaccine development still exist. For viral pathogens, such as influenza viruses or malaria, antigenic variation poses a scientific conundrum in vaccine development. It is also becoming increasingly clear that environmental and genetic factors play a role in the effectiveness of vaccines. More personalised approaches to vaccination have therefore been proposed [11,12].

Finally, vaccines face a societal challenge – there is a real risk of low uptake due to perceived safety issues. Since vaccines are given to healthy people, safety is ranked high, and any scare about vaccine safety sensitively impairs public acceptance of immunisation programs, both in high-income and in lower-income countries. Accurate assessment of the link between vaccination and rare adverse events requires large sample sizes. The same is true for vaccine effectiveness. In addition, proper information systems are required for broader assessment of vaccine impact and vaccination coverage, as well as background distribution of adverse events, and the burden of preventable disease before and after vaccination was implemented.

To address these challenges, different stakeholders need to play a role. The vaccine industry is essential for their know-how in vaccine development and production; public health organisations are key for their epidemiology, surveillance data and recommendations on vaccination; small specialist companies and academic groups need to bring in novel technologies and knowledge management approaches. There is a need to align the decision-making of reimbursement agencies and national government vaccination committees with the development goals of the scientific community, as shows the recent example of the UK MenB case [13]. Successful collaboration among such a diverse set of stakeholders often requires the adoption of a different mind-set by the different parties, and this is why a neutral trusted platform is useful to facilitate exchange and interaction. The Innovative Medicines Initiative (IMI) offers such a platform with the facilitation of genuine partnerships between public and private players as one of its key missions.

FURTHERMORE, SCIENTIFIC CHALLENGES IN NOVEL VACCINE DEVELOPMENT STILL EXIST. FOR VIRAL PATHOGENS, SUCH AS INFLUENZA VIRUSES OR MALARIA, ANTIGENIC VARIATION POSES A SCIENTIFIC CONUNDRUM IN VACCINE DEVELOPMENT.

Founded in 2007 by the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA), IMI is the largest public-private partnership worldwide with the aim to facilitate the development of better and safer medicines for patients. With a total budget of €2 billion, 42 IMI projects are now up and running and a further 9 projects are in the preparatory phases. IMI projects have traditionally addressed bottlenecks in early phases of drug development, such as the identification and validation of novel biomarkers and models, or they deal with knowledge management and learnings that can be generated by pooling data. Some of the more recent IMI projects are of broader relevance to public health and deal with later phases in the drug development pipeline as well as post-market benefit-risk assessment [14].

VACCINATION BENEFIT-RISK ASSESSMENT

There is an increasing amount of data available on vaccine-preventable diseases, vaccination coverage and adverse reactions to vaccines, mostly due to a greater use of electronic health records, and robust infectious disease surveillance systems which are now in place. However, the information is currently largely fragmented into geographically-limited and non-standardised databases, and access to data is sometimes restricted.

The pioneering work under the Vaccine Safety Data Link project in the US [15] and the first European experiences gathered by the Vaccine Adverse Event Surveillance and Communication (VAESCO) and I-MOVE projects [16-18] have paved the way for a broader and sustainable, readily-available framework for combined benefit/risk measurements that are based on standardised, automated and validated processes.

The IMI project ADVANCE launched in October 2013 in response to IMI's 7the Call topic 'Developing a framework for rapid assessment of vaccination benefit/risk in Europe' recognises the need to be able to address concerns about the risk associated to vaccination in a timely and commonly accepted manner. The goal of ADVANCE is to review, develop and test methods, data sources and procedures which should feed into a blueprint of an efficient and sustainable pan-European framework that can rapidly deliver robust quantitative data for the assessment of vaccine benefits and risks. It is hoped that such a framework will allow regulators and public health authorities to make fast, informed decisions regarding vaccination strategies, and help to restore public confidence in vaccines. A key step in making this work will be to link up the data that is available in different places and different countries, in order to make it possible to analyse it. This step must resolve not only the inter-operability of the different data sources, but also the associated ethical and legal issues and variations thereof within different countries.

Of note, ADVANCE brings together different stakeholders as full partners, i.e. the vaccine developing industry, major public health and regulatory organisations including the European Center for Disease Prevention and Control (ECDC), the European Medicines Agency (EMA), a number of national public health and regulatory bodies, and academic experts in data mining and data linkage. In addition, the consortium is built around an open participation concept fostering contributions by institutions invited to contribute on an ad-hoc basis under a Memorandum of Understanding throughout the lifetime of the 5 year project but without having to officially adhere to the contractual framework established by the consortium partners at the beginning of the project. This is essential to ensure that the ultimate goal of the project, a blueprint of an efficient and sustainable vaccination benefit-risk assessment framework, will be implementable and acceptable to all stakeholders. One focus of the ADVANCE project will therefore be the definition of 'best practice' and a code of conduct, including the definition of rules for interactions between the public and private stakeholders.

The project will run a number of proof-of-concept studies to ensure the platform meets the needs of its users. In order to cover the most common situations, these studies should ideally cover different age groups (e.g. infants / children, adolescents and adults / the elderly), different risk groups (e.g. pregnant women, peo-

ple with other underlying health problems), and different vaccination scenarios (e.g. annual flu vaccinations, or vaccines introduced into routine immunisation programmes).

In all aspects of its work, ADVANCE will exploit synergies with related projects. For example, the team will work closely with IMI's EMIF project on data frameworks [19], and draw on the PROTECT project's expertise in analysing and visualising the benefits and risks of medicines [20].

DEVELOPMENT OF INFLUENZA VACCINES

While ADVANCE is dealing with challenges faced by vaccines post-licensure, clinical development of novel vaccines faces another set of difficulties. The effectiveness of vaccines needs to be demonstrated in clinical efficacy trials. For a pharmaceutical company, the process is often too costly, long and risky to provide sufficient incentives for engaging in vaccine development, in particular for diseases of the poor where limited return can be expected from low-income countries. Therefore, initiatives incentivising vaccine development have been warmly welcomed. For example, the European Vaccine Initiative (EVI) or the PATH Malaria Vaccine initiative have both helped advance novel malaria vaccine candidates with one novel vaccine each in later stages of clinical development [21].

As for influenza vaccines, the situation is complicated by the fact that an effective vaccine needs to be produced each and every year, based on the actual relevant viral strains identified. Vaccines developers produce the inactivated or life attenuated vaccine consisting of the strains of influenza virus recommended by the WHO. They run assays to analyse the effectiveness of a new vaccine, or to expand the use of existing vaccines to other age groups or categories. Public health and academic laboratories are involved in investigating how a vaccine performs in different target groups, and make recommendations on the ways the immunogenicity and efficacy of influenza vaccines should be evaluated.

The issue here is that there is no standardised correlate of protection and that the assays used to evaluate vaccines vary between laboratories. Each laboratory uses its own assay protocols that are reviewed every year to adapt to the change in strain. As a result, it is challenging to compare studies and to agree on the effectiveness of a vaccine.

Furthermore, due to the yearly change in strains, any effort to achieve standardisation must consider the question whether the priority should be to implement a strain-specific consensus protocol, an effort that will need to be repeated every year, or whether harmonisation of more generic procedures and standards should be prioritised.

The need for standardisation of serological assays is broadly recognised by public health, academic and industry investigators. The currently best validated and commonly used assay for regulatory submissions is the haemagglutination inhibition (HAI) assay. However, rigorous standardisation is lacking, and it is largely recognised that the HAI assay is inherently quite variable and labor-intensive. A higher throughput and more robust test would be very welcome. Another commonly-used test is the virus neutralisation assay (VN), but here too no standardised assay and protocol exists, nor was a clear correlate of protection ever established.

With the event of the 2009-2010 influenza pandemic, numerous efforts to optimise comparability and align interpretation of influenza serological studies have been put in place. For example, the Global Consortium to Standardize Influenza Seroepidemiology to Inform Public Health Policy (CONCISE) includes a number of public and government institutions working together with the aim of generating best practices for flu seroepidemiologic investigations.

The EMA is currently finalising new guidelines on influenza vaccines with the intention to develop a single, harmonised guidance for both seasonal and pandemic influenza vaccines. A draft concept paper issued in 2011 as well as several meetings and workshops leading to the revised guidelines highlighted the need for assay standardisation [22,23]. There have been international

Figure 1. Overview of IMI project ADVANCE dealing with vaccination benefit-risk assessment and IMI 10th Call for proposals on serological assay standardisation for influenza vaccines

IMI project: ADVANCE
Accelerated Development of Vaccine Benefit-Risk Collaboration in Europe
Total budget: EUR 10.7 million
Project start date: 1 October 2013
Project duration: 5 years
Coordinator: Erasmus Medical Center
Managing entity: University of Basel/Children's Hospital Basel
Leading EFPIA company: GSK Biologicals

IMI 10th Call: Immunological assay standardisation and development for use in assessments of correlates of protection for influenza vaccines
Total budget: EUR 12.2 million
Call launch: 29 October 2013
Anticipated project start date: end 2014/early 2015
Project duration: 5 years
Leading EFPIA company: Novartis

collaborative studies involving several laboratories to evaluate assay reproducibility, using candidate standard serum preparations or sera panels from clinical vaccine trials [24-28]. A recent collaborative effort by the Paul-Ehrlich Institute and the National Institute for Biological Standards and Control in association with the EMA analysed assay variability for the HAI and VN assays in different laboratories. A marked inter-laboratory variation of up to 5.8-fold for the HAI assay, and of up to 7.0-fold for the neutralisation titres was found [24]. Importantly, the variation was drastically reduced when calibrated antibody standards were used, indicating that the reproducibility of immunogenicity results can be improved through standardisation. The IMI held a consultation workshop prior to the launch of its 10th Call 'Immunological assay standardisation and development for use in assessments of correlates of protection for influenza vaccines'. Since the objective of that workshop was to receive expert input for the optimisation of the IMI 10th Call topic, no formal report has been published, but many of the recommendations are reflected in the IMI 10th Call text, published online on 29 October 2013 [14]. All these studies and meetings resulted in the recommendation that further research was much needed into the standardisation of serological assays, on correlates of protection and how serology is predictive of vaccine efficacy, and on vaccine efficacy end-

points. Achieving standardisation of serological assays is considered a necessary first step in any effort towards clinical validation of a correlate of protection.

IMI's 10th Call for proposals (deadline for submission of Expressions of Interest January 28, 2014) aims to address the need for standardisation of serological assays. The main focus of the €12.2 million effort is to achieve a common agreement on the way to perform HAI and VN assays, with the expectation that vaccine manufacturers, public health and regulatory laboratories all adhere to and implement the collaboratively-developed standardised protocols. In addition, work to advance our understanding and usefulness of less validated assays for the evaluation of influenza vaccine performance, such as cell-mediated immunity and NA assays, are invited in the Call. Although the scope of the current Call is standardisation of serological assays, it is anticipated that the existence and acceptance of standardised assays will then spur the establishment of correlates of protection to be tested in future clinical trials.

CONCLUDING REMARKS

Vaccines have a great value to society, but it remains a challenge to fully exploit that. Innovative models of multi-stakeholder collaboration

have arisen that bring together the vaccine industry, academic teams, regulatory bodies and public health institutions. Collaboration between these public and private groups is innovative and requires an open mind-set. A neutral platform such as the IMI helps to facilitate exchange and, as a result, should improve the general acceptance and impact of the project outcomes.

DISCLAIMER

The opinions expressed in this article do not necessarily reflect the positions and opinions of the European Commission or the EFPIA.

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The prevalence of combination vaccines for children in Europe. Analysis of the availability and funding

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ABSTRACT

The article presents an analysis of data from 33 European countries on combination vaccines against diphtheria (D), tetanus (T), pertussis (P), polio (IPV), Haemophilus influenzae type b (Hib), hepatitis B (HBV). The purpose of this article is to present the availability and funding mechanisms of vaccinations which represent pharmacological innovations.

The performed analysis included 5 approved combination vaccines marketed in Europe (5-in-1 DTaP-IPV-Hib vaccines, and 6-in-1 DTaP-IPV-Hib--HepB vaccines). Although in the vast majority of countries the analysed vaccinations are not mandatory, the vaccination rate remains very high. Significant differences between the European countries can be seen in vaccination schedules or the types of available combination vaccines in the national childhood immunisation programmes. Despite the different rules and regulations regarding the funding of combination vaccinations from public resources, countries systematically seek to provide patients with the latest generation formulations.

INTRODUCTION

Combination vaccines representing pharmacological innovations are not commonly used. Combination vaccines are vaccines comprising two or more microbial agents or their antigens combined in a single dose. They are administered at the same time at the same anatomical site and provide combined immunity against at least two diseases. Combination vaccines reduce the need for multiple injections, which are necessary to prevent infectious diseases.

In Poland and in the European Union/European Economic Area (EU/EEA) countries, 5 in 1 against diphtheria, tetanus, pertussis, polio and Hib vaccines (Infanrix IPV + Hib, Pentaxim) and 6 in 1 vaccines against diphtheria, tetanus, pertussis, polio, Hib and hepatitis B (Infanrix hexa, Hexacima) are available. These diseases have been largely eliminated or reduced owing to actions taken by the European countries in providing access to vaccinations. This article aims to analyse the differences in the planning, organisation and funding of combination vaccines for the population of children in Europe.

METHODS

In this article we present information that allowed us to compare the availability, funding mechanisms, and how and where combination vaccines are purchased in the European countries. The information collected was based primarily on data collected from experts in each country.

The analysis of the solutions adopted in the field of immunisation against diphtheria (D), tetanus (T), pertussis (P), polio (IPV), Haemophilus influenzae type b (Hib), hepatitis B (HBV) vaccines was performed for both pentavalent and hexavalent vaccines in the paediatric population. Analysis of the existing legal regulations, organisation and funding mechanisms for vaccinations covered 33 [1] countries in Europe.

Data on the epidemiology of vaccination published by the European Centre for Disease Prevention and Control (ECDC) and Eurostat were used in the analysis. The publicly available information was supplemented by collecting additional data directly from the analysed countries. The recommendations and guidelines for vaccination are from the Web sites of the Centre for Disease Control and Prevention (CDC) or the European Office of the CDC (ECDC), and the World Health Organization (WHO).

EPIDEMIOLOGY

In 2010, 14 cases of diphtheria were reported in the EU countries; the incidence rate was below 0.01/100,000 for the European population. The majority of cases were women over 45 years of age. Diphtheria has been almost completely eliminated in Europe; however, it is still present in the former Soviet Union countries (especially in Ukraine and Russia), and therefore there are cases of sporadic epidemics in the world, especially when the vaccination rate is insufficient. This situation points to the need for vaccination in all age groups [1].

Tetanus is a very rare disease in the EU/EEA countries, caused by the bacterium Clostridium tetani, mainly due to effective vaccination programmes in all countries and generally good standards of hygiene. The incidence rate is very low at 0.02/100,000 for the European population. Vaccinations against tetanus are included in the immunisation schedules of all EU countries for the youngest age groups; however, it is suggested that there is a need for additional vaccination in adults, especially those who have not been vaccinated in their childhood [1].

In 2010, 13,964 confirmed cases of pertussis have been reported in the 28 EU/EEA countries [2] giving an average incidence rate of 3.87/100,000. Data from Germany and Liechtenstein are not shown in the cited analysis. However, this rate varies between countries, being the highest in Estonia (95.55/10,000) and the lowest in Spain (0.66/100,000). Most cases involved groups of children aged 5 to 14 years, and adolescents. Consequently, countries such as: Austria, Belgium, France, Finland, Germany, Norway and Italy have introduced additional vaccinations in adolescents in their immunisation programmes. It should be noted that pertussis is often misdiagnosed in adolescents and adults, and as a result, they can infect younger children [1].

In 2002, the World Health Organization (WHO) announced European a polio-free region. In 2010, 478 confirmed cases were reported in Tajikistan (460 cases), Turkmenistan, Russia and Kazakhstan. In most cases, the disease was caused by a wild strain of the WPV1 virus. The virus was

probably brought to these countries from India. However, in spite of an epidemic outbreak in Tajikistan, there were no cases of illness caused by the WPV1 virus over the next 12 months in the European countries. There was only one case of acute epidemic post-vaccination paralysis in Poland in 2010, which has no effect on the above figures [1].

In 2010, 14,745 confirmed cases of hepatitis B have been reported in the 27 EU/EEA countries (except for Belgium, Italy and Liechtenstein, which did not provide data), giving an incidence rate of 3.43/100,000. The disease usually occurs in people aged 25 to 34 years (33.2% of all cases), more often in men (8.79/100,000 of the male population) than in women (7.42/100 000 of the female population) [1].

Haemophilic bacteria type b (Haemophilus influenzae [Hib]) is a common bacterium that causes inflammation of the respiratory tract (e.g., bronchitis, sinusitis) and otitis media, as well as more serious, life-threatening diseases: meningitis, sepsis, epiglottitis, pneumonia. In the years 1990–2009, all EU member states have implemented mandatory vaccination of young children against Hib; as a result, the incidence of this bacterial infection has become very rare. In 2010, there were only 1,970 confirmed cases of Hib infections (data from 29 countries [3]).

Invasive Hib infection are most common in children under 5 years of age (incidence rate 1.014/100,000), and in adults over 65 years (1.17/100,000). The incidence is dependent on the season of the year, with an increase in the winter months [1].

GUIDELINES AND RECOMMENDATIONS

The Advisory Committee on Immunization Practices (ACIP) guidelines for vaccination schedules against diphtheria, tetanus and pertussis indicate the need to start vaccination at 2, 4, 6 months of age, and then in months 15–18 and at 6 years of age, but not earlier than at 6 weeks of age. Children older than 7 years, which have not been previously vaccinated, should be vaccinated at the age of 11–12 years, and then every 10 years.

Hepatitis B vaccination is recommended for all children aged 0–18 years; ideally, the first dose should be given to the newborn already at the hospital, another dose at the age of 1–2 months, and the last dose at the age of 6–18 months of age. However, a 3-dose vaccination series can be started at any age, with maintaining the appropriate intervals between doses.

The polio vaccine, as recommended in the ACIP guidelines, should be given in four doses in children aged 2, 4, 6–18 months of age and between 4 and 6 years of age.

The Hib vaccine, depending on the vaccine type, is administered in 3 or 4 doses at 2, 4, 6 months (optionally), then between 12 and 15 months of age [7].

The World Health Organization (WHO) recommends vaccination of newborns for hepatitis B as early as possible. For vaccination against pertussis, diphtheria and tetanus (DTP), WHO recommends that three doses are administered in the first year of life. In areas where pertussis represents a particular risk for younger infants, DTP administration should start from 6 weeks of age with 2 consecutive doses given at an interval of 4–8 weeks.

Vaccination against Haemophilus influenzae type b should be given as soon as possible after 6 weeks of age. Three doses of the vaccine should be administered at the same time as DTP. Vaccination against Polio (IPV) should be performed three times at intervals of 4 weeks, for example in weeks 6, 10 and 14 weeks or at 2, 4, 6 months of age [8].

THE AVAILABILITY OF COMBINATION VACCINES IN THE EUROPEAN MARKET

Infanrix hexa is a product in the form of powder and suspension for suspension for injection in a pre-filled syringe, used for vaccination against diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and Haemophilus influenzae type b (Hib) conjugate (adsorbed). Infanrix hexa is used for immunisation

Table 1. Summary of the analysed multi-combined vaccines

Product	Antigen composition	Manufacturer
Infanrix hexa	DTaP-IPV-Hib-HepB	GlaxoSmithKline
Infanrix IPV+Hib	DTaP-IPV-Hib	GlaxoSmithKline
Pentaxim (Pentavac)	DTaP-IPV-Hib	Sanofi Pasteur
Hexacima (Hexyon)	DTaP-IPV -Hib-WZWB	Sanofi Pasteur
Pediacel	DTaP-IPV-Hib	Sanofi Pasteur

of children under 3 years. The product has been available since 2000 [9].

Infanrix IPV + Hib is a vaccine against diphtheria, tetanus, pertussis, poliomyelitis (inactivated), Haemophilus influenzae type b (conjugated, adsorbed). The vaccine is indicated for children from 2 months to 36 months of age. The vaccine has the form of powder and suspension for suspension for injection. The product was licensed in the European Union in 2000 [5].

In April 2013, the European Commission has approved another paediatric vaccine (*Hexacima*) for use in primary and booster vaccination of infants against pertussis, diphtheria, tetanus, hepatitis B, polio and invasive infections caused by Haemophilus influenzae type b. This vaccine, although it was approved only in the second quarter of this year, is already available in Germany and Ireland. This product is available under the trade name *Hexyon* in Western Europe, and under the trade name *Hexacima* in Eastern Europe. The product has been approved for sale in the markets across the European Union on 17 April 2013 [6].

The vaccine is in liquid form and it is used in children from six weeks to two years of age.

Pentaxim is a powder and suspension for suspension for injection. It is a vaccine against diphtheria, tetanus, pertussis, poliomyelitis (inactivated) and haemophilus type b (conjugated, adsorbed). The vaccine is used in children from 6 weeks of age. Pentaxim is also available under the name Pentavac. The first marketing authori-

sation was issued in 2003 [7].

Pediacel, similarly to Pentaxim, is a 5-component vaccine against diphtheria, tetanus, pertussis, poliomyelitis (inactivated) and haemophilus type b. It is available in 29 European countries [4] [8] since November 2010.

MANDATORY AND RECOMMENDED VACCINATIONS

In the vast majority of European countries, vaccination against pertussis, diphtheria, tetanus, poliomyelitis, Haemophilus influenzae type b infections and hepatitis B is not obligatory. The vaccinations are mandatory in nine countries, namely Bulgaria, Slovakia, Lithuania, Latvia, Poland, Croatia, Italy, Spain and Slovenia [5]. In the United Kingdom and Norway, hepatitis B vaccination is recommended only for specific risk groups. However, in Norway and the United Kingdom, pentavalent vaccines are available free of charge to the entire cohort of children. In France, vaccinations are recommended and reimbursed for the entire population of children between 2 and 12 months of age, when the primary vaccination cycle and a booster dose are completed. In Serbia, combination vaccines are recommended, but they are not currently included in the national immunisation programme; it is planned to introduce them in 2014. A similar situation exists in Albania, Macedonia, Cyprus and Malta, where vaccinations for children are recommended, but they have not been included in the vaccination programme. However, in the other analysed countries [6], vaccination are carried out in the entire population using combination vaccines.

AVAILABILITY OF COMBINATION VACCINES IN THE UNIVERSAL MASS VACCINATION

In 2013, both 5- and 6-component combination vaccines are broadly available in all 33 European countries analysed.

Various products are used as part of the national immunisation programmes in Europe against diphtheria (D), tetanus (T), pertussis (P), poliomyelitis (IPV), Haemophilus influenzae type b (Hib), hepatitis B (HBV). These differences relate to the type of product used for immunisation in children, i.e. whether it is a 6-in-1 vaccine (DTP+IPV+Hib+Hepatitis B), a 5-in-1 vaccine (DTP+IPV+Hib), or DTP, IPV and Hib administered separately. Bulgaria, Estonia, Slovenia, Sweden and Lithuania, two types of pentavalent vaccines are available in the national immunisation programmes, Infanrix IPV+Hib and Pentaxim. In Iceland, from 2013, only the 5-in-1 vaccine is included in the vaccination schedule (in 2008-2012,

a 6-in-1 vaccine was also included). In Portugal, Finland, Norway, Montenegro and Bosnia and Herzegovina, only the Infanrix IPV+Hib vaccine is available. In Bosnia and Herzegovina, this vaccine has been available since 2012 in two of the three cantons.

In 15 countries, a hexavalent vaccine is available in the immunisation programmes. Infanrix hexa is available in Belgium, the Czech Republic, Latvia, Italy, Austria and the Netherlands. In Romania, the vaccinations are carried out using both 5- and 6-component vaccines. In Latvia, Pentaxim is available for children who receive a separate vaccine against hepatitis B; therefore, it is included in the immunisation schedule in addition to the 6-component vaccine Infanrix hexa. In Ireland, Slovakia, Switzerland and France, Infanrix hexa is in the vaccination programme along with Infanrix IPV+Hib. In Slovakia, Infanrix hexa is fully reimbursed when the child's mother is HBsAg-positive [7]. In Denmark, a 4-component

Legend:
- Infanrix IPV+Hib
- Infanrix hexa
- Pentaxim
- Infanrix IPV+Hib i Infanrix hexa
- Infanrix IPV+Hib i Pentaxim
- Infanrix hexa i Pentaxim
- Infanrix IPV+Hib i Infanrix hexa, Hexacima
- Infanrix IPV+Hib i Infanrix hexa, Pentaxim
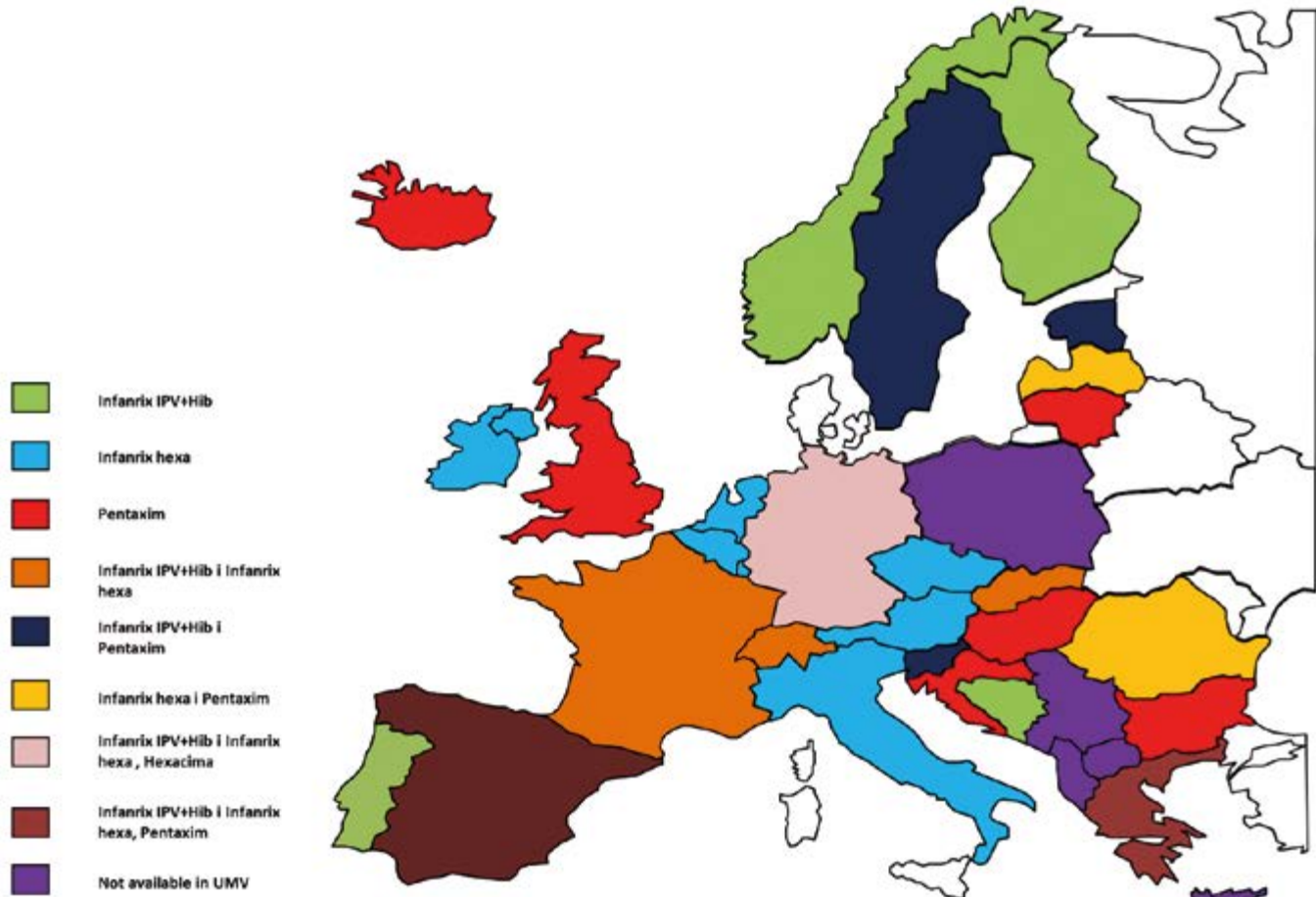- Not available in UMV

Figure 1. The availability of the analysed 5- and 6-valent vaccines in the national immunisation programmes across Europe
Source: own study; UMV, Universal Mass Vaccination

vaccine produced by a domestic supplier is available [9].

The widest ranges of available vaccines against the analysed diseases are fully reimbursed in Greece, Spain and Germany. In Greece, there are both 5-component vaccines – Infanrix IPV+Hib and Pentaxim – and a 6-component vaccine Infanrix hexa. In Spain, the available vaccines include Infanrix IPV+Hib, Infanrix hexa and the pentavalent vaccine Pentavac (Pentaxim). In addition, there are plans to introduce the hexavalent vaccine Hexyon (Hexacima) in the Spanish market. In Germany, there are also three vaccines available, Infanrix hexa, Infanrix IPV+Hib and Hexacima (Hexyon). Hexacima is a new vaccine and the existing German system involves assessment of an innovative product after one year of market use, then a decision is made whether to continue funding the vaccine. This vaccine is available in Ireland, but it has not been introduced in the vaccination schedule yet, so it is currently not available free of charge, since Infanrix hexa will be reimbursed until 2016 as a result of a tender performed.

FUNDING AND ADDITIONAL MECHANISMS TO INCREASE ACCESS TO IMMUNISATION

In addition to providing the vaccine products in the public health care system, access to vaccines could be improved by the possibility of purchase on the private market, which means that the cost of purchasing the vaccine is fully covered by the parents/guardians of the child.

In countries such as Switzerland, Norway, Lithuania, Finland, Ireland, Belgium, Germany, Spain, there is one or more of the analysed vaccines available free of charge.

Another option is to provide access to a given vaccine or to more products as part of the national immunisation programme, and additionally allow the purchase of alternative products on the private market. An example is the Czech Republic where for several years the vaccination programme has been implemented using the 6-component vaccine Infanrix hexa, while the 5-component vaccine is available on the private market and the cost of its purchase is fully cov-

ered by the parents/guardians of the child as an alternative to Infanrix hexa. In Iceland, the vaccination programme includes Pentavac and it is the only vaccine available free of charge under the national immunisation programme, and from 2013, there is a possibility to purchase Infanrix IPV+Hib on the private market (in 2008–2012 it was available free of charge).

In Cyprus, the vaccination schedule includes a tetravalent vaccine Tetraxim (DTaP-IPV). These vaccines are available for the entire population visiting public hospitals (60% of the population of children); for the remaining 40% of the population of children, the 6-component vaccine can be purchased by the patient for the full payment during visits to private paediatric clinics. A similar situation is in Croatia, Slovenia and Slovakia, where in addition to free of charge vaccinations with 5- or 6-component products as part of the national programmes, the patient may choose to purchase a different vaccine for full payment.

If a product is not included in a universal vaccination schedule, the private market provides the only opportunity to purchase combination vaccines. This solution exists in the UK, Poland, Albania, Serbia, Malta, Cyprus and Macedonia. The planned start of Infanrix IPV+Hib reimbursement in Serbia is September 2013.

In Poland, combination vaccines are only available on the private market for full payment (multiple vaccines are not funded from the state budget); they are used by roughly 55% of parents [8]. Also in Slovenia, Cyprus and Romania, Infanrix hexa can be purchased on the private market for full payment. The availability of new, innovative technologies depends, among other things, on the impact of the Health Technology Assessment agency on decision making regarding funding within the public system. The main factor influencing the rate of appearance of a product on the market is the role of health technology assessment reports in the health care system of a given country. For example, in Germany, the functioning mechanisms allow for public funding of medical technologies, in this case vaccines, from the time of their approval, and evaluation of the product is performed after a certain time. A different solution, which has been

used, among others, in France and Sweden, is to conduct a health technology assessment before determining the price and the level of reimbursement. The longest average waiting time for product reimbursement was in Belgium and Portugal, and the shortest in Austria and Denmark, which directly affects the public availability of innovative medical technologies [10].

In addition, another mechanism that allows the patient to choose the vaccine is to offer one product free of charge, and another product for partial payment; this is the case in Croatia, where Pentaxim is available free of charge, and Infanrix hexa can be purchased for a fixed price. In Belgium, co-financing is only available in exceptional cases, for older children which have not been vaccinated according to the recommendations. In this case, 25% of the vaccine price is covered by the patient.

MECHANISMS OF PURCHASING VACCINES IN THE EUROPEAN HEALTH CARE SYSTEMS

The mechanism of purchasing combination vaccines as part of the vaccination programmes is similar in the analysed countries. Purchase mainly occurs in the form of tenders, most commonly in a central tender. Only in five countries the purchase takes place in a regional tender – in Germany (1 region), Belgium (3 regions), France (15 regions), Spain (19 regions), and Italy (20 regions). In Germany, the situation is unusual, because only in one region the vaccine Infanrix IPV+Hib is available as a result of a won tender, while in the other regions the physician is free to choose from among the vaccines available on the German market.

Infanrix IPV+Hib is the most popular vaccine, which is the most widely available within the European public health care systems. In 2008 and 2009, as a result of a won tender, Infanrix IPV+Hib was available in 4 countries since 2008 or 2009 (the Netherlands, Norway, Finland, Montenegro). From 2012, this vaccine has also won a tender in Slovenia, and in Bosnia and Herzegovina. In Lithuania, in 2008–2010, both Infanrix IPV+Hib and Pentaxim were reimbursed; however, since 2011, the only vaccine selected by tender has been Pentaxim.

Infanrix hexa is also a universal vaccine, which has been available already for several years in

Table 2. Form of financing and purchasing individual vaccines in the European markets

Access		Vaccine	Country
Reimbursement list		Infanrix IPV+Hib	Slovakia, Greece, France, Switzerland
		Infanrix hexa	Belgium, Slovakia, Greece, France, Switzerland
		Pentaxim	Croatia, Greece
Tender	Central	Infanrix IPV+Hib	Estonia, Norway, Slovenia, Finland, Montenegro, Serbia**, Bosnia and Herzegovina***, Lithuania^, Iceland*, Portugal
		Infanrix hexa	Romania, the Netherlands, Czech Republic, Ireland, Austria, Latvia
		Pentaxim	Estonia, Croatia, Romania, Slovenia, Lithuania, Bulgaria, Iceland, Latvia
	Regional	Infanrix IPV+Hib	Germany (1 region), France (15 regions), Spain (19 regions)
		Infanrix hexa	Belgium (3 regions), France (15 regions), Spain (19 regions), Italy (20 regions)
		Pentaxim	-

Source: Data on file.
N/A, not available; * in 2008–2012; ** since 2014; *** Infanrix IPV+Hib available in two of the three cantons since 2012; ^ until 2011.

the following countries: Italy, Ireland, Czech Republic, Austria, the Netherlands since 2011, and Romania since 2012. As part of a regional tender, both Infanrix IPV+Hib and Infanrix hexa have been available on the French market since 2008.

In the Netherlands, until August 2011, the vaccine chosen in a tender and available in the public health care system was Pediacel, and since 2011 it has been Infanrix hexa. Pediacel was also available in the years 2008–2010 in Croatia but since 2011 only Pentaxim has been available. Also in Bulgaria, Pentaxim was available free of charge in the vaccination schedule following a central tender in the years 2010 and 2012–2013. By 2012, only two or three kinds of vaccines were available in many countries as a result of a won tender. Currently Infanrix hexa and Pentaxim are publicly funded only in Romania, and both Infanrix IPV+Hib and Pentaxim are funded in Estonia and Slovenia. In Portugal, the vaccines are purchased by tender, and the government sets the price ceiling. In Cyprus, only the 4-in-1 vaccine has been available as a result of a central tender. However, in 6 countries the vaccines are included on the reimbursement lists, and therefore the target population has access to multi-combined vaccinations free of charge.

The mechanisms of purchasing the analysed vaccines based on the available data for the European countries are presented in the table below.

PLACES OF PATIENT ACCESS TO VACCINES

An important issue in the availability of vaccines is its place of purchase. The vaccines that are included in the immunisation programmes are delivered to the vaccination sites/medical practices; there are also no additional administrative costs associated with their administration.

In Belgium, Infanrix hexa may be available at pharmacies, but only in special cases not covered by the vaccination program. The vaccines can be purchased at the point of vaccination in Belgium, Poland and Italy. In Portugal, Finland, the Netherlands, Slovenia and Cyprus, children can receive a vaccine only at paediatric clinics (for healthy children), and in Lithuania, only in the primary health care institutions. In Romania, as part of the vaccination programme, combination vaccines are available in pharmacies and in the family doctors' offices. In Poland, combination vaccines are available both at the points of vaccination and in pharmacies. In Germany, the patient receives a vaccine that has been included in the UMV directly from his/her doctor, and if a given product is not reimbursed by the health fund, then the patient can purchase the product for full payment in a pharmacy. In Switzerland, Infanrix hexa and Infanrix IPV+Hib, which are included in a UMV, are available for patients in paediatric practices; however, in a few regions, it is possible to purchase the vaccine in pharmacy with subsequent vaccination of the child by a paediatrician.

PAEDIATRIC VACCINATION SCHEDULES IN EUROPE

The table below shows the regimen of administration of multiple vaccines in different countries. The analysis was performed for multi-component (5- or 6-component) vaccines, depending on the available data.

Table 3. Dosage regimens of the analysed combination vaccines in different European countries

Country	1st year of age										2nd year of age					subsequent years
	1st day	1m	2m	3m	4m	5m	6m	7m	11m	12m	13–14m	15m	16m	18m	24m	
Austria				■		■				■						
Belgium				■	■	■						■				
B&H				■	■	■										
Bulgaria			■									■				
Czech Republic			■	■	■									■		
Cyprus			**		**		**					15–18m				
Montenegro																
Croatia						■				■ ■						
Denmark				■			■									
Estonia				■		■									■	
France			■		■								16–18m			
Finland						■										
Spain			■		■		■					■				
the Netherlands		**	**	**												4 and 12 yrs
			*	*												
Iceland			■							■						14 yrs
Ireland			■			■										
Lithuania			■		■		■							■		
Germany			■	■	■				11–14m							
Norway				■	■					■						5 yrs
Portugal			■			■										
Romania			■		■	■				■						
Slovakia				■	■				■							
Slovenia				■										■		
Switzerland			■		■		■					15–24m				
Hungary			■	■										■		
United Kingdom			■	■												
Italy				■		■			11–13m							

■ DTaPHibHepIPV
■ DTaPHibIPV

Sources: Data on file and http://apps.who.int/immunization_monitoring/globalsummary

m – month of vaccine administration: * 3 doses (Catch-up – risk group). ** Private market

^ Children born after 1 August 2011, and children born earlier and have at least one parent from the country in which the incidence is >2%, if the mother is HBsAg-positive and the Down syndrome cohort

OVER THE LAST 12 YEARS (FROM 2000 TO 2012), IN THE VAST MAJORITY OF COUNTRIES THERE IS A TENDENCY TO MAINTAIN HIGH VACCINATION RATE, OR AN INCREASE IN THE LEVEL OF VACCINATED CHILDREN. THE DATA INDICATE THAT THERE HAS BEEN NO DECREASE IN THE CHILDCHOOD VACCINA-TION RATE AGAINST THE ANALYSED DISEASES.

When analysing data from the schedules of vaccination with combination products, some differences can be seen in both dosing regimens and the time of administration. In the vaccination program in Austria and Serbia, the 6-component vaccine (DTaP-Hib-Hep-IPV) is given in a 2+1 vaccination schedule (at 3, 5 and 11–12 months of age). However, in Belgium it is administered in a 3+1 vaccination schedule (2, 3, 4 and 15 months of age). The 3+1 vaccination schedule has also been used in the Czech Republic, Germany and the Netherlands; the only difference is related to the booster dose administration time, namely in the Czech Republic, a booster dose is administered at 18 months of age, in Germany at 11–14 months of age, and in the Netherlands at 11 months of age (similarly to the 5-component vaccine available on the Dutch market for children born before 1 August 2011). The 3+1 vaccination schedule (2, 3, 4 months of age) is also approved for the 5-component vaccine (DTap-Hib-IPV) in Bulgaria and Hungary; the difference also relates to the last dose – in Bulgaria it is administered at 16 (not earlier than one year after administration of the 3rd dose), and in Hungary at 18 months of age. In Estonia and Slovenia, the 5-component vaccines are administered from the 3rd month of age, then in months 4 and 6, and the booster dose is given at 24 and 18 months of age, respectively (3+1 vaccination schedule). In Finland, Iceland, Norway and Croatia, the 5-component vaccine is administered in a 2+1 schedule at 3, 5 and 12 months of age, and in Portugal, Montenegro and the United Kingdom, at 2, 4 and 6 months of age. A similar dosing regimen is used in Ireland and Italy for the 6-component vaccine, which is administered at 2, 4 and 6 or at 3, 5–6 and 11–13 months of age, respectively. In Switzerland and Lithuania, immunisation with the 5-component vaccine is performed in a 3+1 vaccination schedule at 2, 4 and 6 months of age, and there is a difference in the booster dose which is given at 15–24 or 18 months of age, respectively. In Switzerland, the same scheme has been used for the 6-component vaccine. In the Netherlands and Spain, immunisation with both 5- and 6-components vaccines is given in a 3+1 vaccination schedule (at 2, 3, 4, 11 months of age and at 2, 4, 6 and 15–18 months of age, respectively), whereas in France

it is administered according to a 2+1 vaccination schedule for both vaccines (2, 4, 16–18 months of age). In Romania, the 6-component vaccine is given at 2 and 6 months of age, and the 5-component vaccine is administered at 4 and 12 months of age.

ANALYSIS OF VACCINATION COVERAGE

Based on the available European data for 2012 (last updated July 2013[11]) it can be concluded that the level of vaccination rates against tetanus, diphtheria, pertussis, polio and Haemophilus influenzae type b invasive infections in most countries is at a high level, close to 95–99%. For hepatitis B vaccinations, data was available from 24 countries [9] and the vaccination rates in most countries was high (96–99%). The lowest vaccination rate was reported for Austria (83%) and France (74%). A vaccination rate close to 100% (approximately 98–99%) against most diseases analysed in this study was seen in: Albania, Belgium, Cyprus, Hungary, Malta, Slovakia and Poland. The detailed data on the vaccination rate in each country in 2012 are presented in the table below.

Over the last 12 years (from 2000 to 2012), in the vast majority of countries there is a tendency to maintain high vaccination rate, or an increase in the level of vaccinated children. The data indicate that there has been no decrease in the childhood vaccination rate against the analysed diseases.

DISCUSSION

Combination vaccines which represent pharmacological innovations have become increasingly commonly used over the years, and many countries have decided to reimburse them within the public health care system. The introduction in recent years of combination vaccines on the European market has provided a possibility of simultaneous immunisation against several diseases in a single injection.

Analysis of the data showed that the current immunisation programmes in Europe are not uniform. The differences mainly concern the time of

Table 4. Vaccination coverage rates against selected diseases in different European countries in 2012

Country	Vaccine type				
	DTP1	DTP3	HiB3	IPV	Hep b3
Albania	99	99	99	99	99
Austria	N/A	83*	83*	99	83
Belgium	99	99	98	87	98
Bosnia and Herzegovina	95	95	87	95	92
Bulgaria	96	95	95	N/A	95
Croatia	N/A	96	96*	99	98
Cyprus	99	99	96	99	96
Czech Republic	N/A	99*	99	94	99
Estonia	96	94	94	99	94
Finland	N/A	99	99	99	N/A
France	N/A	99	98	95	74
Germany	N/A	93*	94	99	86
Greece	99	99	95	99	98
Hungary	99	99	99	89	N/A
Iceland	97	89	89	95	89
Ireland	N/A	95	95	97	95
Italy	N/A	92	96	92	97
Latvia	95	97	91	93	91
Lithuania	97	93	93	N/A	93
Malta	99	99	99	97	93
The Netherlands	N/A	97	97	95	N/A
Norway	99	95	95	95	N/A
Poland	98.7**	99	99	98	99
Portugal	N/A	98	98	92	98
Romania	N/A	97*	92	93	6
Serbia	N/A	91	90	99	97
Slovakia	N/A	99	99	96	99
Slovenia	N/A	96	96	97	N/A
Spain	N/A	97	97	98	96
Sweden	N/A	98	98	96	N/A
Switzerland	N/A	95	95	74	N/A
United Kingdom	N/A	97	97	N/A	N/A

Source: http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragedtp3.html [12]
*2010 r. http://www.quandl.com/health/dtp3-all-countries [13]
** Immunisation in Poland in 2012 [14]
DTP1 – first dose, DTP3 – third dose, HiB3 – third dose, Hep BD – dose given at birth, N/A – not available

administering the booster dose or the dosing regimen, which may result from different epidemiological conditions and vaccination funding opportunities in each country. Pentavalent vaccines are more common than hexavalent vaccines because in many countries the hepatitis B vaccine is still administered separately. In the vast majority of countries, there is a central system of purchasing vaccines as part of a central tender. This is the case of 28 of the analysed countries. Only in five countries (Germany, Italy, Belgium, France, Spain), the tenders are performed at the regional level. Based on these data it can be concluded that in 10 countries the tenders secured the supply of vaccines for several years (2–4 years). Data on the vaccination rate indicate that vaccines against diphtheria (D), tetanus (T), pertussis (Pa), hepatitis B (HBV), poliomyelitis (IPV) and Haemophilus influenzae type b (Hib) have been widely available and used. Analysis of the data showed that the percentage of vaccinated children is close to 100%, regardless of the product used and how it has been financed.

CONCLUSIONS

Combination vaccines are generally used for the prevention of infectious diseases. Their application, in addition reduces the number of injections required during the first two years of life children.

In the European national vaccine calendars the standard is recommending vaccination against: diphtheria (D), tetanus (T), pertussis (P), polio (IPV), Haemophilus influenzae type b (Hib), hepatitis B (HBV), so several years the vaccination rate remains very high. Along with the technological development, two-, three- or four-component vaccines are replaced by multi-combined vaccines (5-or 6-component), but the degree of their use in the national immunisation programmes and the level of their financing from public funds in different countries vary considerably.

In most countries, vaccination is recommended and reimbursed for the all population of children. The national immunization calendars for individual countries include age when child getting vaccine shot. If vaccinations are not available in

national immunization programs, the only place where it is possible to obtain vaccines is the private market. In this case the cost of the vaccine is fully covered by the parents / guardians of the child.

It is reasonable conduct a further analysis of the European market in the private sector in terms of access is innovative vaccines. ◼
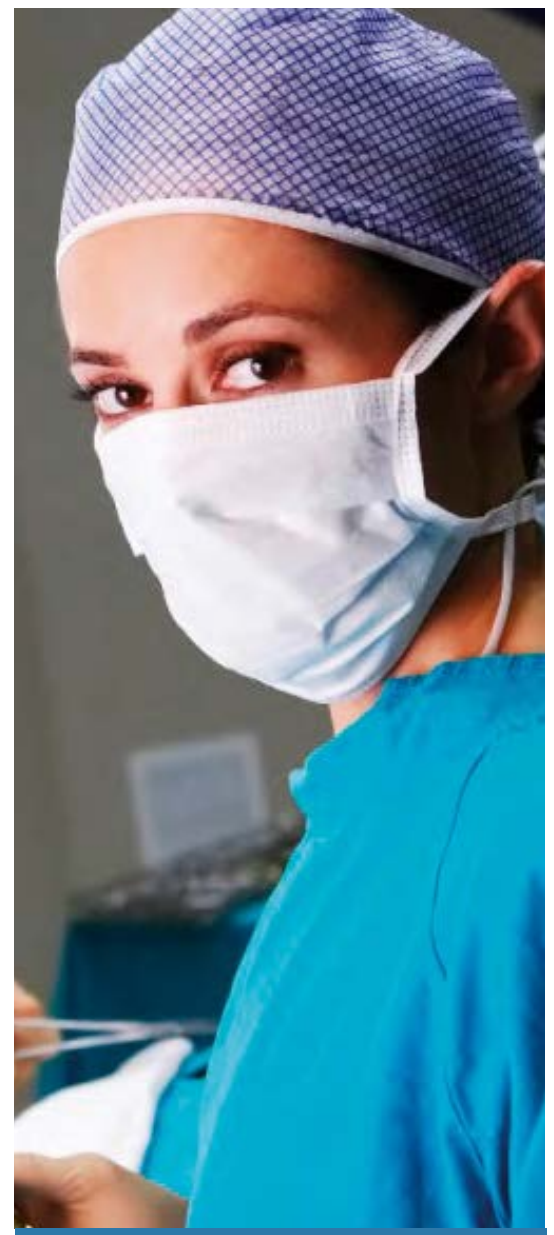
FOOTONOTES:

1. Albania, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Montenegro, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Greece, Spain, the Netherlands, Ireland, Iceland, Lithuania, Latvia, Macedonia, Malta, Germany, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Switzerland, Hungary, United Kingdom, Italy
2. Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Lithuania, Latvia, Malta, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom. Data from Germany and Liechtenstein are not shown in the cited analysis
3. Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Iceland, Lithuania, Latvia, Italy, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom.
4. Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, the Netherlands and the United Kingdom.
5. The Author`s research data
6. Czech Republic, Austria, Ireland, Switzerland, Greece, Romania, the Netherlands, Belgium, Cyprus, Finland, Estonia, Hungary, Iceland, Montenegro, Bosnia and Herzegovina, Portugal.
7. The viral antigen detected in the serum of people with hepatitis B.
8. Calculations based on the orders of the Public Procurement Department at the Ministry of Health.
9. Albania, Bosnia and Herzegovina, Bulgaria, Iceland, Malta, Portugal, Romania

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Cost-effectiveness analysis of Human Papillomavirus (HPV) vaccination using Cervarix® as an extension to the cervical cancer prevention programme in Poland

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ABSTRACT

Background: The aim of the study was to estimate the cost-effectiveness of addition of human papillomavirus (HPV) vaccination to the Polish cervical cancer prevention programme.

Methods: A cost-utility analysis was conducted. A lifetime Markov model, adapted to Polish settings, was used to compare the costs and health outcomes of the two strategies, i.e. the existing cervical cancer prevention programme with or without universal HPV vaccination in girls at the age of 14.

Results: Assuming that the whole cohort was vaccinated (100% vaccination coverage), the estimated lifetime risk of developing cervical cancer would be reduced from 0.95% to 0.23%; therefore, 1311 cases of cervical cancer and 681 deaths due to cervical cancer would be prevented in a cohort of 182,000 girls aged 14 years. If the assumed vaccination coverage was 24%, the cost of gaining an additional quality-adjusted life year (QALY) due to HPV vaccination as an extension of the cervical cancer prevention programme would be PLN 52,737.91/QALY and PLN 76,288.47/QALY from the public payer's perspective and the common perspective of the public payer and the patient, respectively. This cost effectiveness is maintained for different parameter assumptions in the sensitivity analysis. Even with high assumed discount rates for costs and health outcomes (5% for both), the ICUR value was still lower than the cost-effectiveness threshold (PLN 105,801 per QALY).

Conclusion: Addition of HPV vaccination to the cervical cancer prevention programme in Poland is a highly cost-effective intervention.

INTRODUCTION

Primary cervical cancer constitutes a vast majority of cases of uterine cancer and develops over many years from precancerous lesions known as cervical intraepithelial neoplasia (CIN) [1]. Depending on its histopathological features, CIN is currently classified into three cathegories, i.e. CIN1, CIN2, or CIN3. In Poland, cervical cancer is one of the most common cancers in women, and the absolute number of new cases and deaths due to this neoplasm in 2010 in Poland was 3078 and 1735, respectively; this was equal to the standardised incidence and mortality rates of 10.3 and 5.1/100,000 women, respectively [2]. The epidemiology of CIN in Poland is not accurately known. According to the National Cancer Registry, there were 775 cases of pre-invasive cervical cancer (currently classified along with CIN3) in 2010; however, this number is significantly underestimated because the reporting or registering of precancerous lesions is not

PRIMARY CERVICAL CANCER CONSTITUTES A VAST MAJORITY OF CASES OF UTERINE CANCER AND DEVELOPS OVER MANY YEARS FROM PRECANCEROUS LESIONS KNOWN AS CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

mandatory in Poland. Carcinoma in situ/CIN3 is much more common than invasive cancer [3]. Pap smears enable early detection and treatment of precancerous cervical lesions; thus, they constitute the basis of screening programmes aimed at reduction of the cervical cancer incidence and mortality rates. However, introduction of an active screening programme in Poland in the years 2006/2007 did not result in increased dynamics of reduction of the cervical cancer incidence and mortality rates, mainly due to low coverage and unknown quality of the programme.

A necessary (although not sufficient) aetiological factor of cervical cancer is persistent infection with human papillomavirus (HPV) [1]. HPV is classified into high-risk types (hrHPV), i.e. those with a high carcinogenic potential (14 types: HPV-16/18/31/33/35/39/45/51/52/56/58/59/66/68) and low-risk types (lrHPV), e.g.HPV-6 or 11. Cervical cancer develops most commonly as a result of infection with HPV-16 or 18 which are responsible for more than 70% of all cases of cancer at that location, and, in addition, for a majority of high-grade intraepithelial precancerous lesions of the uterine cervix, vulva, vagina, anus, and penis [4,5]. At present, no anti-HPV medications are available on the market and therefore no causal treatment aimed at eradication of HPV is possible.Currently only treatment of histological abnormalities caused by HPV is possible and is most commonly based on its removal or destruction [6].

There are two HPV vaccines registered, i.e. Cervarix® (GSK) and Silgard® (MSD), and HPV vaccination programmes for women have been introduced in 19 countries in Europe. In most of these countries vaccination is completely financed from public resources [7]. According to the Polish Vaccination Programme (PVP) for the year 2013, HPV vaccination is recommended but not financed by the Ministry of Health from its budget [8]. In Poland, HPV vaccines are available on the market to patients but not reimbursed; they are also available locally in health programs introduced by regional government entities and other local authorities.

The aim of this analysis was to evaluate cost-effectiveness of Cervarix® in Poland if financed from public resources and used in prevention of cervical cancer and precancerous lesions associated with specific carcinogenic types of human papillomavirus. In this paper the results of a cost-utility analysis comparing the costs and outcomes of current practice in prevention of cervical cancer in Poland (i.e. a Pap smear performed every 3 years in women aged 25-59 years; the "Screening" strategy) with those of the same practice plus HPV vaccination using Cervarix® (the "Cervarix + Screening" strategy) are presented.

MATERIALS AND METHODS

The costs and outcomes associated with addition of HPV vaccination to the cervical cancer prevention programme in Poland were estimated based on a Markov cohort model developed by Demarteau et al., widely discussed in the literature, in which costs and outcomes of an intervention are assessed in a lifetime horizon – Global Cervarix Model version 12.0 (the model makes it possible to compare both a strategy including HPV vaccination vs. no vaccination and vaccination with Cervarix® vs. vaccination with Silgard®; therefore, data concerning genital warts were included in order to make potential comparison of costs and health outcomes of both registered vaccines possible) [9,10,11]. This model has been adapted to Polish settings by means of inclusion of Polish epidemiological and cost data related to cervical cancer and CIN.

The analysis was performed from the public payer's perspective and a common perspective of the public payer and the patient, assuming 30% patient's co-payment for the HPV vaccine and partial coverage of the costs of treatment of genital warts by the patient (in Poland these costs are not completely covered by the public payer). In the base-case scenario, discount rates of 5% for the costs and 3.5% for health outcomes were assumed. The incremental cost-utility ratio (ICUR) was estimatedand cost-effectiveness of HPV vaccination was evaluated; the threshold value for one additional quality-adjusted life year gained was assumed at PLN 105,801, according to the guidelines of the Agency for Health Technology Assessment in Poland [12].

The effects of changes in the parameters assumed in the model on the results of the analysis were assessed using one-way sensitivity analysis and probabilistic analysis. The following parameters were taken into account: vaccination efficacy, the utilities of specific health states, the incidence and prevalence rates for specific HPV types in the population, costs of treatment of

PRIMARY CERVICAL CANCER CONSTITUTES A VAST MAJORITY OF CASES OF UTERINE CANCER AND DEVELOPS OVER MANY YEARS FROM PRECANCEROUS LESIONS KNOWN AS CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

Table 1. Screening efficacy and utility values for specific health states included in the model

PARAMETER	VALUE	DATA SOURCE
SCREENING EFFICACY		
CIN1 DETECTION RATE	58%	26
CIN2/CIN3 DETECTION RATE	61%	26
PROPORTION OF POSITIVE PAP SM EARS	5.5%	32
UTILITIES (DISUTILITIES)		
NO HPV INFECTION	1	29, 31
HPV INFECTION	1	29, 31
GENITAL WARTS	(0.0180)	35
CIN1 DETECTED	(0.0128)	29, 31
CIN2/CIN3 DETECTED	(0.0094)	29, 31
CERVICAL CANCER TREATED	(0.2730)	29, 31
CERVICAL CANCER CURED	(0.0620)	29, 31
DEATH	0	-

Table 2. Efficacy of HPV vaccination and distribution of specific HPV types in Polish population

PARAMETER	DISTRIBUTION OF HPV TYPES — MEAN (RANGE)	EFFICACY OF CERVARIX® — MEAN (RANGE)
CIN1		
- HPV 16/18	23.9% (22.9%; 24.9%) [24]	98% [21, 27, 28, 30, 33, 34]
- CROSS-PROTECTION	45.6% (39.1%; 51.4%) [24]	48% (29%; 62%) [21, 3]4
PROPORTION OF POSITIVE PAP SM EARS	6.8% (5.6%; 8.0%) [24]	0%
OVERALL EFFECTIVENESS CIN1		65.2%
GENITAL WARTS (GW)		
- HPV 6/11	76.2% [25]	0%
- CROSS-PROTECTION		0%
CIN2/CIN3		
- HPV 16/18	53.0% (51.9%; 54.1%) [24]	98% [21, 27, 28, 30, 33, 34]
- CROSS-PROTECTION	43.3% (42.2%; 44.1%) [24]	68% [21, 23]
OVERALL EFFECTIVENESS CIN2/CIN3		81.4%
CERVICAL CANCER		
- HPV 16/18	72.4% (67.5%; 77.1%) [24]	98% [21, 27, 28, 30, 33, 34]
- CROSS-PROTECTION	13.4% (5.4%; 26.5%) [24]	68% (48%; 82%) [21, 23]
OVERALL EFFECTIVENESS CERVICAL CANCER		80.1%

CIN, genital warts and cervical cancer, and the participation rate in screening.

Target population

In the model it was assumed that HPV vaccination would be administered to girls at the age of 14 years. Vaccination using a vaccine against type 16 and 18 human papillomavirus (Cervarix®) is indicated in individuals aged 9 years or more [13]. Depending on the country, national vaccination programmes include HPV vaccination in females aged 9-18 years. The Polish Gynaecological Society [14] and the Polish Paediatric Society [15] recommend basic HPV vaccination in girls aged 11-12 years and supplementary vaccination (catch-up programmes) in girls aged 13-18 years, while the Polish Society of HPV Infections Prophylaxis recommends basic HPV vaccination in girls aged 12-15 years and supplementary vaccination in young women aged 16-25/26 years [16]. HPV infection usually develops as a result of the first sexual contacts [17]. Based on the results of a representative study conducted in Poland [18], the estimated sexual initiation rate in Polish girls below 15 years of age is very low. Target vaccination age of 14 years has been selected in order to maximize vaccination coverage of the cohort as a result of co-administration of Cervarix® with the booster vaccination against diphtheria and tetanus which, according to the PVP, is obligatory at this age [8].

Initial data

The health state utility values implemented in the economic model and data concerning the efficacy of cytological screening are presented in Table 1. Data concerning the efficacy of Cervarix® taken into account in the economic model were obtained from the PATRICIA study (in which the efficacy and safety of Cervarix® administered according to the 0, 1, 6 months schedule were compared with those of placebo [19,20,21,22,23]) or assumed based on the opinion of the experts involved in development of the model [9,10,11] (Table 2).

The target population size was estimated based on data published by the Central Statistical Office of Poland (CSO) and in the model the cohort size was assumed at 182,000 girls.

In the base-case scenario, taking into account data obtained from the Ministry of Health's report on realisation of the National Cancer Control Programme for the year 2011 and the CSO data concerning the proportion of women who declare they had a pap smear performed in the previous 3 years, it was assumed that 49.29% of women took part in screening (either organised or opportunistic).

In the analysis it was assumed that 24% of the target population would be actually vaccinated. Such coverage was observed in 2008 in France, where 65% of the cost of HPV vaccination is reimbursed from public resources [7]. In addition, in order to evaluate the maximum health outcomes associated with introduction of HPV vaccination, a coverage level of 100% was assumed in a separate scenario [11].

Data used in the model included Polish epidemiological data concerning overall death rate (CSO data) and the number of new cases and deaths due to cervical cancer [2] as well as those concerning the prevalence of specific HPV types in the population and the HPV infection incidence rates, obtained from national registries and the World Health Organization database [24] (Table 2).

Direct medical costs incurred by the patient (i.e. patient's co-payment for the HPV vaccine and costs of pharmacotherapy of genital warts) and the public payer (i.e. co-financing of HPV vaccination and the costs of diagnostics and treatment of CIN and cervical cancer as well as those of surgical treatment of genital warts) were taken into account in the analysis. The average costs of diagnostics and treatment assumed in the model and the price of Cervarix® are presented in Table 3.

Table 3. Costs of diagnostics and treatment of specific health states

| COST DATA	COST [PLN]
REGULAR SCREENING – WOMEN WITH NEGATIVE PAP SMEAR (INCLUDING FALSE NEGATIVE RESULTS)	53.87
MANAGEMENT OF CIN1 ASSOCIATED WITH HRHPV INFECTION FOR ONE YEAR AFTER ITS DETECTION	964.53
FURTHER MANAGEMENT AFTER CIN1 HAS BEEN CURED	53.87
MANAGEMENT OF CIN2 OR CIN3 FOR ONE YEAR AFTER ITS DETECTION	2195.00
FURTHER MANAGEMENT AFTER CIN2 OR CIN3 HAS BEEN CURED	107.74
ANNUAL COST OF TREATMENT OF CERVICAL CANCER	5613.38
TREATMENT OF GENITAL WARTS	281.82
CERVARIX® - VACCINE COST PER INJECTION	393.76
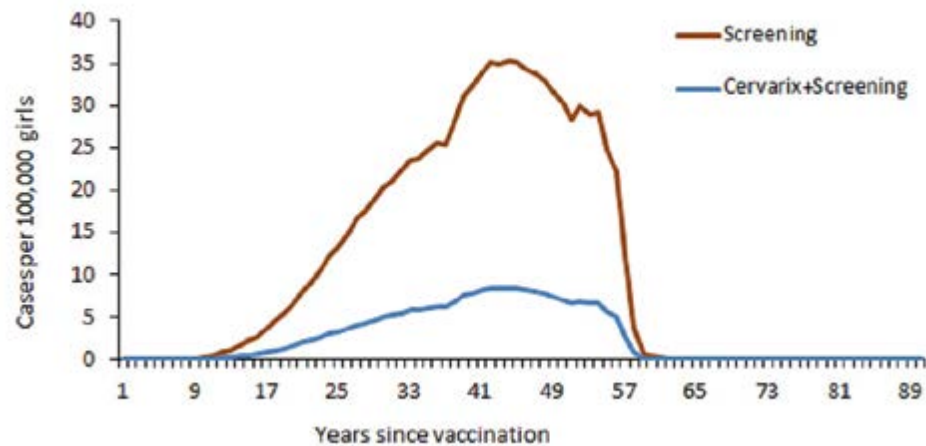
Figure 1. Incidence of cervical cancer (undiscounted results of modelling)

RESULTS

The results obtained in the model indicate that addition of HPV vaccination using Cervarix® to prevention of cervical cancer in Poland is cost-effective. In a lifetime horizon, vaccination in girls aged 14 years was associated with additional health outcomes as expressed both in life years (LY) and quality-adjusted life years (QALY). Assuming a coverage level of 24%, the individual incremental value was 0.0036 QALY, which equals 657 additional QALY in the whole cohort of 182,000 girls.

Table 4. Results of the economic analysis

CATEGORY	CERVARIX® + SCREENING	SCREENING	INCREMENTAL OUTCOMES
HEALTH OUTCOMES: QUALITY-ADJUSTED LIFE YEARS (QALYS)	26.2836	26.2836	0.0036
TOTAL COSTS [PLN] (PUBLIC PAYER)&	409.02	218.56	190.46
TOTAL COSTS [PLN] (PUBLIC PAYER AND PATIENT)&	497.05	221.54	275.51
INCLUDING:			
- HPV VACCINATION	283.51	0.00	283.51
- TREATMENT OF CIN1	24.55	26.48	-1.93
- TREATMENT OF CIN2/CIN3	7.42	8.85	-1.43
- TREATMENT OF CERVICAL CANCER	26.63	31.65	-5.02
- TREATMENT OF GENITAL WARTS	9.79	9.79	0.00
- SCREENING	145.15	144.77	0.38
INCREMENTAL COST-UTILITY RATIO (ICUR)#			
TOTAL COSTS [PLN] (PUBLIC PAYER)&	PLN 52,737.91		
- PUBLIC PAYER AND PATIENT	PLN 76,288.47		

& - *Health outcomes and costs per patient in the modelled cohort (discounted values).*
# - *The ratio of the difference in costs to the difference of health outcomes of both interventions.*

In comparison with cytological screening alone, addition of HPV vaccination (Cervarix®) was associated with increased efficacy with respect to prevention of CIN1 and CIN2/CIN3 as well as new cases and deaths due to cervical cancer. When a coverage level of 100% was assumed, HPV vaccination prevented 1311 cases of cervical cancer and 681 deaths due to cervical cancer (Figure 1) as well as 33,313 cases of CIN1 and 6791 cases of CIN2/CIN3 in the cohort's lifetime. As expected, the "Cervarix + Screening" strategy did not prevent development of genital warts (Cervarix® is not indicated in prevention of this condition).

Regardless of the perspective adopted, the strategy including cytological screening and HPV vaccination in comparison with the strategy based on cytological screening alone was a cost-effective intervention (Table 4).

The results of one-way sensitivity analysis and probabilistic analysis confirmed high cost-effectiveness of HPV vaccination. In the assumed ranges of variation of the parameters included in sensitivity analysis, the results obtained in the model indicated cost-effectiveness (i.e. the ICUR value below the cost-effectiveness threshold) of the "Cervarix + Screening" strategy in comparison with the "Screening" strategy in all the analysed scenarios (data not shown).

CONCLUSIONS

The analysis demonstrated that a strategy assuming addition of HPV vaccination using Cervarix® in girls aged 14 years to current cervical cancer prevention practice in Poland (i.e. Pap smears in women aged 25-59 years in a reimbursed screening programme) is a highly cost-effective intervention in comparison with current practice. Cervarix® prevents a higher number of precancerous lesions and cervical cancer cases as well as deaths due to cervical cancer than screening alone.

The results of this analysis indicated that, in comparison with current practice, a strategy including vaccination with Cervarix® in a cohort of girls aged 14 years and assuming a coverage level of 24% would make it possible to reduce both the incidence of cervical cancer and mortality due to cervical cancer by 16%. If the coverage level was 100%, the "Cervarix + Screening" strategy would make it possible to reduce both the incidence and mortality rate by 76%.

The analysis demonstrated that the cost of additional quality-adjusted life year gained (i.e. the ICUR value) for addition of HPV vaccination to the current cervical cancer prevention programme versus current practice alone was much lower than the recommended cost-effectiveness threshold in Poland (i.e. PLN 105,801 at present), regardless of the adopted perspective of the analysis. Financing of Cervarix® from public resources would make it possible to reduce the incidence of cervical intraepithelial neoplasia as well as the incidence and mortality due to cervical cancer, which in turn would reduce the costs associated with treatment of those conditions, in Poland at present amounting to nearly PLN 70 million annually.

DISCUSSION

Numerous economic analyses conducted in other countries indicate that HPV vaccination performed in parallel with cytological screening constitute an efficacious and cost-effective strategy [37,38,39,40,41,42].

The benefits would be highest if all teenage girls were vaccinated; however, experience gained in the countries in which vaccination is partially reimbursed by the public payer indicate that it is not possible, at least in the first few years after introduction of reimbursement, to obtain such a high vaccination coverage. According to the opinion of Polish experts, in Poland the expected coverage rate in girls aged 14 years may be 10-15% in the first year of reimbursement of HPV vaccination. In subsequent years the coverage level may increase to 25-30% [43].

Evaluation of economic aspects of HPV vaccination is relatively difficult. This is due to the specificity of HPV infection and the fact that its consequences (especially cancerous lesions) develop even decades after the infection. Epidemiological data concerning HPV infection indicate

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that most sexually active women and men were, are, or will be infected with this virus. Introduction of universal vaccination against HPV, despite significant expenses in the first stage of a woman's life, may result in savings due to a lower risk of CIN and cervical cancer in later stages. Taking into account that in most cases women are diagnosed with cervical cancer at the age of 50-60 years, HPV vaccination may also result in lower productivity loss.

Primary prevention of cervical cancer with vaccination may contribute to nearly complete elimination of the problem of mortality due to cervical cancer in Poland and therefore limit the number of orphaned families. Intangible costs associated with the disease cannot be estimated; however, epidemiological data, i.e. more than 3000 new cases and nearly 2000 deaths each year, demonstrate the scale of the problem affecting thousands of families and "wiping out" a population equivalent to a small town every few years. Therefore, reimbursement of HPV vaccination may be an important step towards a change of this situation. ■

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Schizophrenia and negative symptoms – burden of disease in seven Central and Eastern European (CEE) countries.
Literature review and retrospective data collection – project design and rationale

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ABSTRACT

Objective: Schizophrenia is a serious public health problem: it affects approximately 1% of world's population and is a leading cause of disability. The main objective was to develop a report concerning burden of schizophrenia with special attention to negative symptoms in seven Central and Eastern European countries.

Methods: The project consisted of two phases: literature review and retrospective data collection. The literature review involved a search for published literature in international databases and country-specific data from local sources in relation to: epidemiology, clinical guidelines, standards of care, cost of illness, resource utilisation, health related quality of life and caregiver burden. The second phase involved retrospective data collection on the basis of patients' medical cards and gathering the medical experts' opinions. In each country 3–6 medical centers participated in the project. Psychiatrists completed questionnaires with data from randomly selected medical cards. Statistical analysis was used to test differences between included centers and countries with regards to the treatment of schizophrenia.

Results: The results of literature review served as the framework for retrospective data collec-tion. For the second phase of the project, the sample size included about 1,000 patients' cards from participating countries showing the daily clinical practice of schizophrenia treatment. Results from the project were presented and discussed with medical experts and key opinion leaders during local workshops.

Conclusion: The project addresses relevant issues related to the burden of schizophrenia and complements data presented in the literature with additional data gathered in clinical practice, especially in the area of schizophrenia negative symptoms.

BACKGROUND

Schizophrenia is one of the most common psychiatric disorders, estimated to affect from 0.4% to 1.4% [1,2] of the population and has a mean annual incidence of 11-16 per 100,000 [1-3]. Schizophrenia affects men and women equally; however, there is an earlier onset in males [4]. Due to its early onset and chronic course, schizophrenia is a relatively frequent and burdensome disease. Moreover, schizophrenia affects both patients and, indirectly, their caregivers [5-7]. Schizophrenia is broadly characterized by three domains of psychopathology, including negative symptoms (eg. social withdrawal, lack of motivation and emotional reactivity), positive symp-

toms (hallucinations, delusions) and cognitive deficits (working memory, attention, executive function) [8]. Some data indicate that negative symptoms are the important cause of poor patient functional outcomes and impairments in quality of life [9,10]. Available antipsychotics have limited impact on negative symptoms and their treatment is considered a key unmet medical need in the schizophrenia [11]. The main objective of the project was to prepare a comprehensive report on the burden of schizophrenia, with particular focus on negative symptoms of the disease in seven chosen Central and Eastern European countries (CEE): Croatia, Estonia, Hungary, Poland, Serbia, Slovakia and Slovenia. Other objectives were to verify the gathered data during local workshops and to discuss the results with the medical experts and key opinion leaders in each country involved to understand better the current practice and needs in the schizophrenia area.

METHODOLOGY

Study design

The project Schizophrenia and Negative Symptoms – Burden of the Disease in Seven Cen-

tral and Eastern European (CEE) Countries was designed as a retrospective, multicenter and non-interventional project. It was divided into two parts:

1. Literature review, which considered data from international databases and from local data sources
2. Retrospective data collection performed in each country of interest based on unified questionnaires

The results of the retrospective data collection, with data from the literature review as a background, were presented and discussed during the workshops – first, at seven country-specific workshops, then, additionally, one final cross-country workshop is planned as a final summary of the project. Results were also shared at international conferences and are planned to be published in regional and international journals.

Literature review: international and local

The aim of the literature review was to gather relevant and current information regarding burden of schizophrenia and, in particular, negative symptoms of schizophrenia. As a first step the following international data sources were searched using an English-language search strategy:

- **PubMed (MEDLINE via PubMed)**
- **Cochrane Library (all libraries)**
- **Centre for Review and Dissemination (CRD): Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database**
- **National Guidelines Clearinghouse**
- **National Institute for Health and Clinical Excellence (NICE)**
- **European Medicines Agency (EMA)**

Publications found as a result of the search underwent a two-step selection process. First, based on the titles and abstracts of all studies retrieved from the search, the relevant records were selected. In the second step, full text versions of the papers included in the initial screen-

ing phase were examined for inclusion within the review. To focus on the most current publications the literature search was limited to papers published after 1995, but no language restrictions were applied. The detailed inclusion and exclusion criteria are presented in Table 1.

The second part of the literature review comprised a search of local databases in order to identify relevant data published in local languages. The following local data sources were searched (if available):

- Websites of HTA agencies,
- Patient registries,
- National medical journals,
- Databases of National Health Service,
- National/Central Statistical Office,
- National Psychiatric Association,
- Local psychiatric websites,
- Other relevant data sources.

The information gathered in each country by a local expert were translated to English, then recorded in a predefined data extraction sheet and finally incorporated in the report. A search was performed to include publications dedicated to the following areas:

Definitions of schizophrenia – classifications of the disease; definitions of positive, negative and cognitive symptoms; definitions of different types of schizophrenia,

Epidemiology – incidence and prevalence; mortality; risk factors; age at disease onset; demographic characteristics of schizophrenia patients – gender distribution, marital and social status,

Disease management of schizophrenia focusing on the negative symptoms – clinical guidelines; recommendations; standard of care/treatment patterns: pharmacotherapy, psychotherapy; compliance/adherence to treatment,

Economic and humanistic burden of the disease – cost data based on information about: drugs used in schizophrenia treatment, hospitalizations, outpatient ambulatory procedures,

Table 1. Inclusion/exclusion criteria for literature review

	INCLUSION CRITERIA	EXCLUSION CRITERIA
PUBLICATION TYPE	Guidelines and recommendations on schizophrenia treatment, review and systematic review	Other than: review, systematic review review and systematic review
	For epidemiological data: relevant review and systematic review	
	Quality of life – primary studies	Other than primary studies
	Cost and burden of disease, stigmatization and discrimination – primary and secondary studies, review and systematic review	Other than: review, systematic review, guidelines, practical guidelines, burden of disease, meta-analysis, economic analysis, cost studies
YEAR OF PUBLICATION	1995 - present	Studies published before 1995
COUNTRIES CONSIDERED	Poland, Slovenia, Estonia, Slovakia, Hungary, Serbia, Croatia. In case of lack of relevant publications for these countries and in order to complete background, the data from other European countries were included	
CONDITION	Schizophrenia (F.20 according to ICD-10 classification)	Schizotypal and delusional disorders (F.21-F.29 according to ICD-10 classification)

outpatient ambulatory visits, GP visits, diagnostic and monitoring tests and procedures, costs of lost productivity, rehabilitation, social worker visits, etc.; resource utilization data (drug doses, length of inpatient stays, number of hospitalizations per patient per year, number of outpatient visits per year, number of monitoring tests per year, patterns of AE treatment, choice of antipsychotic drugs in the first and second line of treatment and in refractory patients, compliance and adherence data, etc.); HRQoL (health related quality of life) data; caregiver's burden.

List of reimbursed drugs with official price tariff and the level of reimbursement (to estimate average price from NHF and patient perspectives) for: neuroleptics, antidepressants, mood stabilizers and anxiolytics (from databases of NHS).

Based on the relevant papers and data identified as a result of the literature search, the report on burden of schizophrenia was prepared. The country-specific data from the chosen CEE countries were in scope of this report and, in case of lack of relevant records for the CEE region, worldwide data were also included.

STUDY AREA AND PARTICIPANTS

Seven CEE countries were chosen to participate in the project: Croatia, Estonia, Hungary, Poland, Serbia, Slovakia and Slovenia (Figure 1).

Figure 1. Distribution of countries involved in the project

In each country 3 – 6 medical centers were involved in the project: psychiatric hospitals with ambulatory and general hospitals with mental wards. The choice of sites reflected the management of schizophrenia in particular countries, and the number of reviewed medical records allowed for a representative size of patient populations in each of the countries for further discussion of the findings.

RETROSPECTIVE DATA COLLECTION

Retrospective data collection was performed by filling in two types of questionnaires:

1. Based on data from patients' medical records
2. Insight by local medical experts specializing in psychiatric practice from each country of interest.

The collected data reflected the daily practice of medical diagnostic and therapeutic procedures used in patients with schizophrenia, with emphasis on negative symptoms in the local conditions.

Between 5 and 9 experts from each country were involved in the retrospective data collection. Involved psychiatrists had at least 8 – 10 years of experience in the treatment of schizophrenia and treated at least 10 patients with schizophrenia per month. An additional assumption was that doctors had practices in both hospitals and outpatient clinics, or at least they had access to the patients' outpatient and inpatient records.

Each expert involved in the project completed between 10 and 30 questionnaires based on patient cards. Where possible, the reviewed data covered the whole disease history; in other cases the last 5 years of patient treatment data were gathered. Patient data were anonymously collected in the questionnaires.

The choice of patient cards was performed randomly by each of the experts according to the same principles:

1. Patients treated for schizophrenia during the last 5 years
2. Where possible, the proportion of patient medical cards coming from hospitals and outpatient clinics reflected the proportion of patients treated in hospital (inpatients) and outpatient settings in each particular country
3. It was assumed that the number of newly diagnosed patient cards (from each specialist) should not exceed 20% of selected medical cards

Length of schizophrenia and severity of disease were not defined in order to obtain a representative sample of patients.

The questionnaire based on patients' medical records gathered data regarding patient profile, type of schizophrenia, duration and severity of illness, characteristics of the disease – type of presenting symptoms during the course of disease, co-morbidities and relapses. The questionnaire also included data on applied treatment, including hospitalizations, pharmacotherapy, psychotherapy and other forms of treatment. Separate parts focused on the treatment of negative symptoms and the social status of patients with schizophrenia.

The second type of questionnaire used in the project was one specially designed to collect the experts' opinions. In some centers a few experts from one site were allowed to complete together a single questionnaire regarding the specialist in psychiatry practice insight.

This questionnaire was completed to reflect experts' opinions based on their personal experience with patients with schizophrenia and knowledge from medical practice. The questionnaire focused on data regarding psychiatrists' experience in the treatment of schizophrenia, characteristics of the schizophrenia population in each country of interest, social aspects of the disease in the general population of schizophrenia patients and in the population of patients who suffer from negative symptoms of schizophrenia. Data were also collected concerning treatment patterns, resource use and adverse event management.

The exemplary questions are presented in Table 2.

Table 2. Sample questions from questionnaires

PATIENT MEDICAL CARD	EXPERT INSIGHT
1.1. Age 1.2. Sex 1.3. BMI	1.1. Country 1.2. Center/clinic 1.3. Experience in schizophrenia treatment [years] 1.5. How many patients with schizophrenia have been treated in your unit during the last year?
2.2. Year/age* of first diagnosis of schizophrenia 2.3. Year/age* of starting treatment of schizophrenia 2.7 Type of schizophrenia (according to ICD-10 classification) 2.8 Presence of any primary negative symptoms during the course of schizophrenia 2.9. Type of primary negative symptoms 2.14. Year/age* of onset of primary negative symptoms 2.16. Presence of any positive symptoms during the course on illness 2.19 Number of psychotic relapses	2.1. What is the percentage of individuals with diagnosed schizophrenia among all patients with schizophrenia in your country (using ICD-10)? 2.2. What is the proportion of non-compliant patients with diagnosed schizophrenia? 2.3. What is the proportion of patients with different types of schizophrenia using ICD-10 in your ward/clinic (patients treated by you)? [%]? 2.4 What is the percentage of treated patients with schizophrenia who suffer from any primary negative symptoms? 2.11. What is the percentage of treated patients with diagnosed schizophrenia who have/had suicidal thoughts or attempts? 2.11.1. What is the percentage of treated patients (with schizophrenia) who are experiencing primary negative symptoms and who have/had suicidal thoughts or attempts? 2.12. What is the percentage of treated patients with diagnosed schizophrenia who had a relapse of the disease during the last 5 years? 2.12.1. What is the percentage of patients suffering from primary negative symptoms who had a relapse of the disease during the last 5 years?
4.1. Civil status 4.2. Employment status 4.3. Education 4.4. Residence situation 4.5. Patient incapacitated 4.6. Patient had to stop working/learning because of disease	4.1. How many employed patients have to stop their work/education because of the disease [%]? In pts with schizophrenia/schizophrenia patient with primary negative symptoms 5.1.1. What is the standard treatment pattern as the first course? (please describe)\ 5.1.2. What is the proportion of pts who receive only psychological/psychosocial support (without pharmacotherapy) as the first course of treatment? 5.1.4. Which of antipsychotic medications are used as the first course of treatment and in what doses? 5.1.5. What are the most common reasons for treatment discontinuation? 5.4.1. What is the type of hospital where patients stay during hospitalization? 5.9.3. Occurrence of AEs and typical treatment of AEs

After collecting all questionnaires, the accuracy of the data was verified, and all findings were discussed and agreed between the experts. All explanations of the information provided were recorded to be included into the final report.

In the final step all data from the questionnaires were processed, analyzed, discussed and summarized in a final report.

least one variable and the Fisher exact test indicated dependency between the variables, then a post hoc analysis was applied (post hoc Fisher exact test with Bonferroni correction). The dependency between the data was visualized with Forest plots of proportion. Continuous data were analyzed using ANOVA or the Mann–Whitney–Wilcoxon test. The choice of test depended on the assumptions that were met by the data. Boxplots were used to display differences between the subgroups.
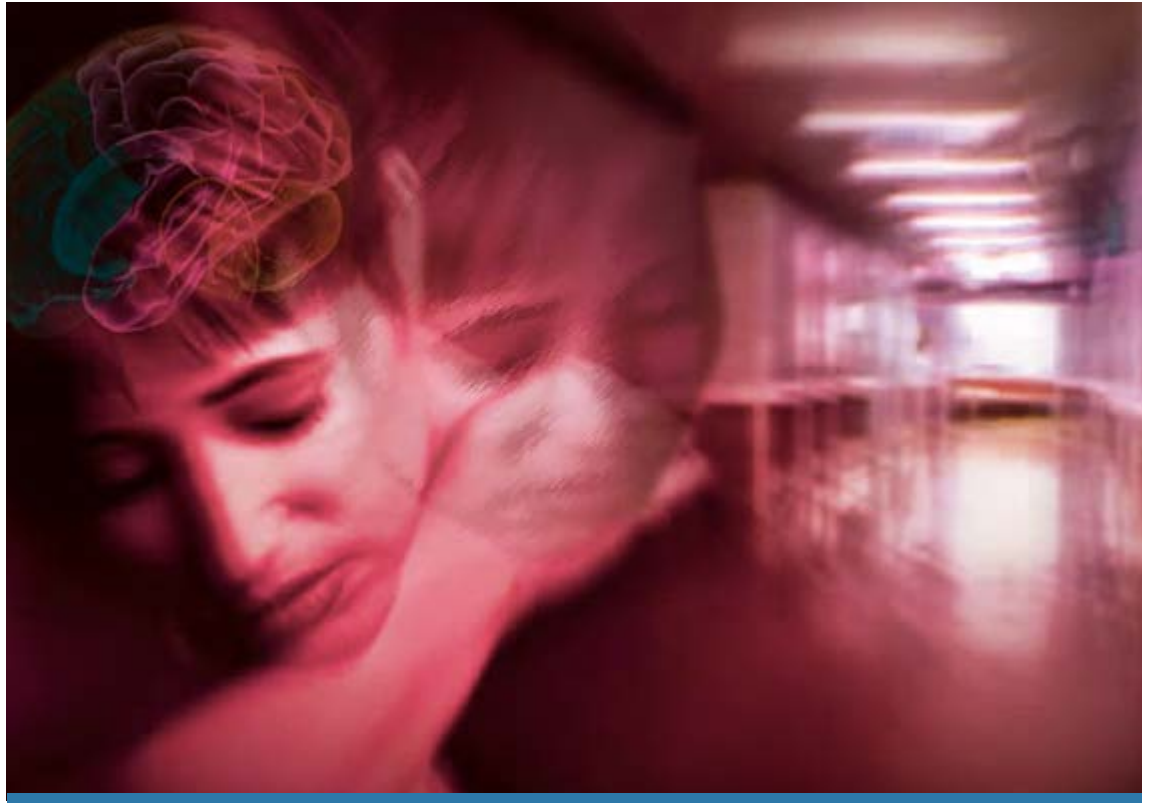
THE AIM OF THE ANALYSIS WAS TO DETECT ALL SUBSTANTIAL DIFFERENCES BETWEEN THE RESULTS OF QUESTIONNAIRES GATHERED FROM DIFFERENT CENTERS/ COUNTRIES AND TO DETECT ASSOCIATIONS BETWEEN PARTICULAR QUESTIONS.

STATISTICAL ANALYSIS

The aim of the analysis was to detect all substantial differences between the results of questionnaires gathered from different centers/countries and to detect associations between particular questions. This was conducted independently for each question in the questionnaire. The methodology was chosen based on the type of data elicited by a particular question (categorical and/or continuous data). A contingency table was used to summarize categorical data. An analysis of contingency was performed with the Fisher exact test to verify if there were non-random associations between the two categorical variables. If there were more than two categories for at

WORKSHOPS

The workshops were divided into two parts. The first part of the workshops consisted of separate meetings in each country of interest to present local results of the retrospective data collection. The second part of the workshops will convene representatives of all countries participating in the project. The main objective for the workshops scheduled in each country was to present and discuss with all the involved experts the collected data from all parts of the project – literature review, expert opinions and retrospective data collection. Other aims of the workshop meetings were to clarify ambiguous wording, to validate the collected data and to present the collective

application. The objective of the final cross-country workshop is to compare collected data between involved countries: mainly to identify the trends and similarities, but also to indicate the differences and outliers.

RESULTS: SUMMARIES FOR EACH COUNTRY AND CROSS-COUNTRIES

Retrospective data collection was based in total on more than 1,000 patient medical cards and about 30 questionnaires completed on the basis of experts' opinions. The numbers of questionnaires and experts involved in the project are presented in Table 3.

The deliverables of the project were:

- Literature review report,
- Report summarizing the results for each country of interest separately and cross-countries findings,
- Presentations for the workshops.

As a final step of the project posters regarding the findings were presented at international meetings and conferences, and publications regarding cross-country comparisons of data obtained, as well as country-specific results, are planned to be publicly available.

Table 3. Summary of involved sites, experts and questionnaires (final number of questionnaires can differ slightly as the project is still ongoing)

COUNTRY	NUMBER OF INVOLVED CENTERS	NUMBER OF INVOLVED EXPERTS	NUMBER OF QUESTIONNAIRES FROM PATIENT CARDS	NUMBER OF QUESTIONNAIRES FROM EXPERTS' OPINIONS
CROATIA	5	5	150	5
ESTONIA	3	9	150	3
HUNGARY	4	7	150	7
POLAND	6	7	165	6
SERBIA	6	7	150	7
SLOVAKIA	4	5	81	4
SLOVENIA	3	9	190	1
TOTAL	31	49	1036	33

CONCLUSION

The project with the employed methodology will allow a comprehensive platform from which an assessment of the burden of schizophrenia to patients/caregivers/healthcare systems can be further analyzed. ■

TIMETABLE, PARTICIPATING UNITS AND FUNDING

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Cost-effectiveness of injectable atypical long-acting antipsychotics for chronic schizophrenia in Poland

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ABSTRACT

Objective: In order to determine the cost-effectiveness of paliperidone palmitate (PP-LAI), a long-acting injectable formulation, indicated for once-monthly injections as antipsychotic therapy, it was compared with risperidone, a long-acting, injectable (RLAI) and biweekly agent, administered for treatment of chronic schizophrenia in Poland, as perceived from the perspective of the National Health Fund (NHF).

Methods: We adapted a 1-year decision tree model to the Polish healthcare system with literature-derived and clinical expert inputs. The compared drugs included PP-LAI, a new treatment option of antipsychotic therapy, and RLAI, the established treatment for Polish patients. Clinical rates were derived from published trials. Model outputs included expected cost per patient, as well as the rates of hospitalization, emergency room visits, days free of symptoms and quality-adjusted life-years (QALYs). One-way sensitivity analyses were applied to major inputs. All the inputs were also simultaneously varied in probabilistic sensitivity analyses.

Results: Despite its higher acquisition cost, PP-LAI demonstrated a lower expected cost per treated patient. PP-LAI was associated with 0.824 QALYS, 323 days with stable disease and 44.6% hospitalization. RIS-LAI had 0.817 QALY, 317 stable days and 51.3% hospitalization. PP-LAI dominated RIS-LAI in the base case and in 55.0% of 10,000 simulations, and was cost-effective in 76.6%. However, the cost-effectiveness was sensitive, being lost with modest increases for PP-LAI or decreases for compared drugs with respect to their prices, relapse and adherence rates. Because it is injected monthly as opposed to biweekly, PP-LAI saves caregiver time as it is administered monthly, as opposed to the biweekly regimen.

Conclusions: From the viewpoint of the National Health Fund of Poland, when compared with RLAI, PP-LAI is a cost-effective drug with potential to reduce healthcare expenses.
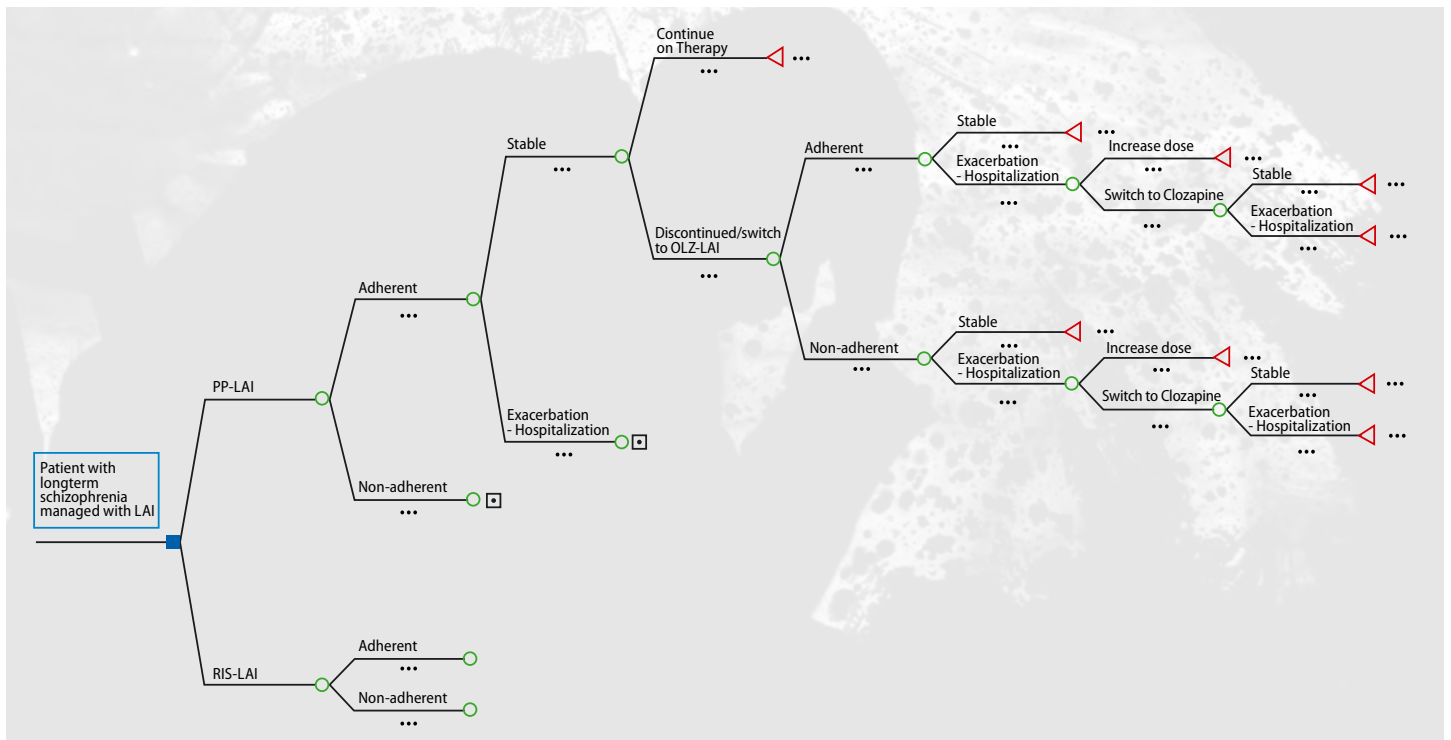
Figure 1. Decision tree used for the analysis

INTRODUCTION

With a population of 38.4 million [1], Poland has got a healthcare system based on national health insurance, managed by the National Health Fund (NHF). NHF, with a total annual budget of €15 billion in 2012, allocates funds for hospital and outpatient care, as well as for prescribed, reimbursed drugs [2].

Schizophrenia is a major burden for healthcare systems, affecting about 1% of the world population [3]. The problem with schizophrenia is very serious and aggravating, due to intensive use of resources, including hospital beds and medications, where in-patient therapy represents a large cost centre [4,5].

Hospitalization costs are related to patients' adherence to their antipsychotic medications [6]. Current innovative solutions, aimed at improving adherence rates, include the long-acting, injectable (LAI) depot formulations of drugs [7]. Although depots have been available for many years, atypical antipsychotic depots have been developed and marketed in the last decade only [8].

Even if these new products continue their upward trend on the market, their pharmacoeconomic profiles are a largely unknown issue in many countries, including Poland. A literature search was attempted to identify studies on the costs and economic aspects of schizophrenia therapies, which are available in Poland. Medline and Embase localised merely five relevant publications, all of them drafted as abstracts for poster presentations at scientific conferences [9-13]. No full text peer-reviewed articles were identified. Consequently, a task for defined and undertaken to determine the cost-effectiveness of atypical LAIs in Poland, the evaluation to be approached from the NHF's analytic viewpoint.

MATERIALS AND METHODS

A model, previously developed in Greece [14], was adapted to the reality of the Polish healthcare system, see Figure 1. The introduced adaptations were based on published reports and inputs from local professionals.

Patients with chronic schizophrenia had experienced prior relapses. All of them required treatment with long-acting injectable (LAI) antipsychot-

ics. They entered the model with their disease in remission. The drugs of interest included the long-acting injectable (LAI) forms of paliperidone palmitate (PP-LAI) and risperidone LAI (RLAI).

Clinical inputs were derived from clinical trials upon which success rates were based, or from daily clinical practice (i.e., medical records). Drug regimens and doses, used for maintenance therapy and to manage relapses, were based on published sources and adapted from the previous model (see Table 1).

The clinical rates, used to populate the decision tree, are presented in Table 2. The analysis was arranged from the point of view of the NHF

and considered direct costs of care only. The direct costs included medications, hospitalization and medical care (i.e., services provided by physicians and other healthcare professionals). Drug prices were obtained from the current price list, published by the Ministry of Health [15]. The service prices were based on the NHF procedure pricing system and on opinions of professionals. The costs were provided in EURO for the 2012 exchange rate,, adjusted from other years by the Consumer Price Index for Poland [16]. The cost inputs are exhibited in Table 3.

The primary outcome was quality adjusted life years (QALYs). Their calculation was based

Table 1. Regimens used to treat patients with schizophrenia, with appropriate references

DRUG	REASON FOR ADMINISTRATION	REGIMEN	SOURCE
PP-LAI	Maintenance of stable schizophrenia	69.3 mg monthly	Average of Fleischhacker [31] Gopal [32]
	Treatment of relapse	150 mg week 1, 100 mg week 2; then 84.9 mg every 4 weeks maintenance	EMA Xeplion® product summary [33] Maintenance dose = average of Gopal [34] Hough [35] Nasrallah [36] Pandina [37] Pandina [38]
RIS-LAI	Maintenance of stable schizophrenia	40.3 mg every 2 weeks	Average of Fleischhacker [39] Kissling [40] Lasser [41] Lee [42] Olivares [43]
	Treatment of relapse	50 mg every 2 weeks	Average acute dose set to the maximum of 50 mg, pro-rated from PP-LAI ratio of acute:maintenance doses and validated by Chue [44] Eerdekens [45] , Kane [46]

EMA, European Medicines Agency; LAI, long-acting injection;; PP, paliperidone palmitate; RIS, risperidone microspheres.

Table 2. Clinical rates used as inputs for the model

CLINICAL STATE	DRUG	ADHERENT	NON-ADHERENT
ADHERENCE	PP-LAI	0.872	0.118
	RIS-LAI	0.823	0.177
STABLE DISEASE	PP-LAI	0.803	0.148
	RIS-LAI	0.763	0.14
RELAPSED	PP-LAI	0.197	0.852
	RIS-LAI	0.237	0.86
*RATES ADOPTED FROM PREVIOUS MODEL			

Table 3. Consumed resources and their costs

RESOURCE	ITEM	COST (EURO)
HOSPITAL	ACUTE PSYCHIATRIC WARD	42.06
	EMERGENCY ROOM (2 HOURS)	26.72
	LONG TERM WARD	28.04
ADHERENCE	PSYCHIATRIC OUTPATIENT VISIT	13.17
	FOLLOW-UP VISITS	6.58
	PRIMARY CARE PHYSICIAN (HOUR)	4.66
ALLIED HEALTHCARE	SYCHIATRIC NURSE (HOUR)	4.66
DRUGS	PP-LAI*	€9.30/DAY
	RIS-LAI	€8.46/DAY
*ESTIMATED COSTS AS NOT YET REIMBURSED		

on previously obtained utility scores, reported in the literature [17-20]. Other patient outcomes included days free of symptoms and the rates of relapse. The expected cost per treated patient was calculated for each drug. The incremental cost-effectiveness ratio (ICER) for gained QALYs was interpreted as economic outcome. Ratios below €25,000 were considered cost-effective, as per PolAHTA guidelines [21].

In order to examine the model stability and obtainable results, a series of sensitivity analyses was run. Each of the major inputs (e.g., adherence rates, hospitalization rates, costs, etc.) was tested with one-way (break-even) analyses to determine if obtained results would change within reasonable limits. Also, a probabilistic (Monte Carlo) synthesis was undertaken with 10,000

RLAI comparing iterations. The rates and costs at each decision node varied across a plausible range, using standard distributions for each variable. The proportions of iterations were also calculated, which favoured PP-LAI and comparison drugs. Two sets of outcomes were examined. In the first one, the threshold values were explored for dominance; in the second one, the threshold for cost-effectiveness was analysed, using the limits, as established by PolAHTA.

RESULTS

Even with higher acquisition cost, PP-LAI would have a lower expected cost per treated patient, when the benefits are included in the estimation model (Table 4). PP-LAI was associated with 0.824 QALYS, 323 days with stable disease and 44.6% hospitalization. RIS-LAI had 0.817 QALY, 317 stable days and 51.3% hospitalization. PP-LAI dominated RIS-LAI in the base case and in 55.0% of 10,000 simulations, and was cost-effective in 76.6%. However, the cost-effectiveness was sensitive and lost with even modest increases for PP-LAI or with decreases for compared drugs with respect to drug prices, relapse and adherence rates. Because it is injected monthly as opposed to biweekly, It also saves caregiver's time, being injected monthly, as opposed to biweekly regimens.

DISCUSSION

Despite its higher acquisition cost, PP-LAI demonstrated the lowest expected cost per treated patient. Because its therapeutic effect lasts a full month, having a reasonable side effect profile [22], its adherence rates are fairly high. Consequently, it exhibits higher efficacy, since adherence has been identified as the major driver of costs and patient status [23,24].

These results suggest that PP-LAI should be the atypical LAI of choice in Poland. Since more patients remain in stable condition, a broader adoption of the therapy should result in fewer hospital admissions, reducing patient loads on hospitals.

No indirect costs were taken into account in this analysis. The impact of the therapy on the number of sick leave episodes was assumed to be minimal, considering the very low employment level of schizophrenic patients; however, it is also possible that this medication could allow some of the patients to resume work or, at least, function more efficiently at home [25,26]. Other disregarded indirect costs included those, associated with the legal and justice system. It is well known that a proportion of persons with schizophrenia become violent and are frequently incarcerated, often many times [27,28]. Finally, no costs of adverse events were incorporated. At least two government agencies concluded that side effects contributed very little to the overall treatment costs [29,30]. Therefore, the results represent a conservative estimate with some underestimation of the total cost. Nonetheless, all of these aforementioned biases would be against PP-LAI.

LIMITATIONS

All research reveals certain limitations, either due to selected approach or the conduct of research tasks or for any other reason. A decision tree model was employed to simulate treatment and its outcomes. The results are therefore limited by the validity of inputs and the assumptions made in the modelling process. Decision trees estimate the average cost for the average patient under average conditions. The results apply therefore only to patients who meet inclusion

Table 4. Clinical and pharmacoeconomic outcomes

CLINICAL STATE	EXPECTED COST/ PATIENT (EURO)	REMISSION DAYS	HOSPITALIZATION RATE	QALYS/ PATIENT	COST (EURO)/ QALY	ECONOMIC OUTCOME
PP-LAI	PP-LAI	323.4	PP-LAI	44.60%	0.824	DOMINANT
RIS-LAI	3648	317.3	51.30%	0.817	4467	DOMINATED

criteria. They may or may not apply to related diseases, such as schizoaffective, schizophreniform, or bipolar disorder. The model was also limited to patients with chronic schizophrenia without comorbid conditions. Any extrapolations to other populations should thus be done with caution.

Inputs, specific for Poland, were used in this analysis, being, however, limited by the unavailability of certain data. In cases where some information was not available, we used data from similar environments in other countries or from multi-country trials, which may or may not have included patients from Poland. Local experts were also enquired to counsel concepts, validate assumptions and assure that inputs were appropriate and applicable.

In calculations, no co-payments were considered, assuming that they would be similar across drugs and would therefore not affect the outcomes to any great extent. The impact of that assumption is, however, not known.

CONCLUSIONS

In this model, PP-LAI dominated the other atypical LAIs. Therefore, it is perceived as an atypical LAI of choice for patients with chronic schizophrenia. From the viewpoint of the National Health Fund of Poland, PP-LAI is a cost-effective drug with real potential to reduce healthcare expenses. ◼

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Clinical and economic analysis of non-medical technologies in Russia

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ABSTRACT

Health technology assessment includes several aspects: (1) technology position in health care system (characteristic of disease burden and expected socio-economic impact of technology), (2) the main characteristics of studied technologies, (3) clinical efficacy (experimental and in typical clinical practice), (4) safety, (5) clinical and economic evaluation, (6) the ethical aspects of technology applications, (7) psychological aspects, (8) legal aspects, (9) organizational and logistic issues, (10) social issues, including equitable distribution of resources and fair access to technology. Any assessment of medical technology expects answers to be provided to all the above questions.

Non-drug medical technologies can be divided on the basis of different classification approaches. From the position of the functional approach – there are diagnostic, therapeutic (invasive, non invasive), rehabilitation, prevention, and technologies for care and maintenance functions.

Regarding the use of different components, there are technologies which include drugs or blood components, also foodstuffs for special nutritional uses or medical devices. An example of medical devices may be laboratory gear used for in vitro studies. The paper presents evaluation results of technologies, which employ medical devices.

Finally, there are institutional medical technologies.

In this article, the authors present studies about therapeutic, prophylactic and organizational technologies. Prevention of contact dermatitis and ulcers in immobilized patients with urinary incontinence. Clinical and economic research unit for physiotherapy and an assessment of the organization of medical technologies that was conducted, due to reforms in the Russian health care system.

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During any assessment of medical technology answers are expected to be provided to all the above-mentioned questions.

THE FEATURE OF NON-
DRUG TECHNOLOGIES IN
TERMS OF CLINICAL AND
ECONOMIC ANALYSIS IS
LESS SCRUTINY OF BOTH
EFFICIENCY AND SECURITY
AND THE COSTS ARE MUCH
LESS STUDIED.

Non-drug medical technologies can be divided on the basis of different classification approaches. From the position of the functional approach – there are diagnostic, therapeutic (invasive, non invasive), rehabilitation and prevention technologies, as well as technologies for the care and maintenance functions. From the position of using different components, there are those which include medicinal products and blood components, foodstuffs for special nutritional uses and medical devices, which include, for example, laboratory gear for in vitro studies. Laboratory blood tests or magnetic resonance tomography, diagnostic surgery or biopsy are examples of diagnostic technologies. Medical technologies – such as surgery – involve the use of various devices with therapeutic effects (for example - physical therapy), the use of different non medical devices, such as catheters or cardiac pacemakers.

Preventive vaccination in a clinical and economic analysis can be considered similar to assessing drug technologies. At the same time, clinical examination or application of anti-smoking activity (for example, a legislative ban on smoking in public places) requires a different approach to assess the cost-effectiveness of technologies.

Similar problems arise in the clinical and economic evaluation of rehabilitation approaches. This may be a simple procedure, such as a logopedic manual for patients who have had a stroke, or more complex, for example, activities to adapt a disabled person to his / her familiar environment. Here, complex, psychological techniques are used and the development of technical equipment, ranging from simple light switches or TV to robotic devices (device for moving a patient lying on the toilet or use the exoskeleton to walk).

Finally, organizational technologies are usually massive. For example, the treatment of rare diseases, which is at the expense of the state budget, which is conventionally called the "7 Diseases program." There is also a drug component and the logistics of drug delivery to regions and patients and the results of the monitoring system and the maintenance patient registers. Such

a program should be evaluated holistically, not isolating it from the various components.

It is clear that an evaluation of the effectiveness of non-pharmacological medical technologies requires appropriate criteria. These criteria may be similar to the indicators for assessing medical technologies, especially when it comes to the treatment and prevention technologies, or may differ materially. Thus, in order to study the effectiveness of prevention of bedsores by the use of diapers, an adequate indicator can be not only the incidence of pressure sores but the evaluation of quality of life or QALY index.

The feature of non-drug technologies in terms of clinical and economic analysis is less scrutiny of both efficiency and security and the costs are much less studied. Convincing studies are now concentrated on technology, behind which there are instruments, and these technologies are recorded in health technology assessment bodies of different countries (NICE, IQWIG, etc.) for inclusion in the program of cost refund. At the same time, the old, traditionally used technologies (e.g., clinical blood tests or ECG monitoring) are not assessed from the position of clinical and cost-effectiveness. It is that due to the lack of need for such an analysis in regulators and payers – it is simpler to pay for traditionally used non-drug technologies than to enter into a conflict with the manufacturers of this equipment, accustomed to its use by doctors and patients, who are in need of these technologies. For example, a convincing evidence of the effectiveness of the procedures, associated with magnetization of tissues, the impact of various weak currents on tissues - what is called physiotherapy in Russia

- talking about it causes a negative reaction from doctors, patients, and administrators.

For Russia, this problem is particularly acute, due to the fact that, for the last 7-8 years, the Russian health care projects have involved a procurement of medical equipment worth billions of euro. Only the health care IT project - the Unified National Health Information System – consumed nearly a billion of dollars in 2012 from the state budget.. That money has funded a project of doctor appointments via the internet. Accordingly, even if a sick person turns up personally at the clinic, he / she has to make an appointment with the doctor in the terminal. It is clear that such "service" is not conducive to an increased access to health care and no one tried to evaluate the cost-effectiveness of the project, even to assess the effectiveness of investments, using objective indicators.

Another example. April 2013. The conversation of the Minister of Health, Ms. Veronika Skvortsovaya, with Mr Vladimir Putin, the Russian President, regarding perinatal centers. It has been planned to spend some 50-60 billion rubles (1 460 million euros) on the program, including building of new 100-bed medical centers at 5 regions, 130-bed medical centers at other five regions, 150-bed medical centers at 9 regions and 200-bed medical centers at 6 regions. According to the Minister of Health's concept, women with uncomplicated pregnancy will give birth at standard maternity hospitals; those with minor complications and chronic diseases - at large hospitals, while the new centers will be designed only for very difficult deliveries. The smallest center will cost 2 billion rubles (49 million euro), and the largest one - 3 billion rubles (73 million euro).

However, nothing has been said about how the pregnant women are going to be selected and distributed (the logistic aspect),. The criteria for assessment of risks and their validity seem to be beyond the understanding of the official organs..

Our assessment of this situation is following: all over the country, small maternity units in towns and villages are closed. The result: women cannot drive hundred miles off-road or fly (aviation is not available everywhere) to luxury apartments so they give birth in unsuitable conditions. The medical centers, equipped with high tech diagnostic and therapeutic apparatus but located off the general hospitals, will not be able to provide highly qualified assistance that requires participation of different specialists: bringing required staffs of experts and medical gear will be very difficult in isolated centers. Therefore, the path-

way to develop perinatal centers leads to a dead end, while its costs, being extremely high, make the project little cost-effective..

Another challenge was the design and construction of expensive high-tech medical centers. Planned at the beginning of 2006 as a priority project, 15 federal centers should have been completed by 2009 but none of them was and, only in 2013, the construction of 13 centers was completed, the other two will be demolished (the Federal Center of Traumatology, Orthopedics and Arthroplasty in Vladivostok and the Federal Center of Traumatology, Orthopedics and Prosthetics in Krasnodar). The construction costs of the Krasnodar center - at the moment the construction was stopped – amounted to 3.923 billion rubles. Its demolition and construction of a new building on the site will need other

2 billion rubles, and the cost of equipment to be transferred to regional hospitals, has been estimated at 200 million rubles.

In Russia, there is no public system of health technology assessment. Since the late 1990s, by orders of the Ministry of Health, attempts have been made to draft clinical cost estimates with lists of available therapies, reaching an appropriate standard of evaluation. However, those approaches have not been implemented into the practice of decision-making officials and administrators, and, moreover, they do not apply to non-drug medical technologies. In 2010, a standard for evaluation of medical technology was created, approved and developed by our team, but it has not been used by administrative organs.

However, the course taken by the Russian government on the commercialization of medicine, is leading to the mainstreaming of surrogate economic evaluations of medical technologies from the standpoint of searching for additional incomes. The surrogate assessments concentrate on how to obtain more money from patients, how to increase capital turnover, leaving aside the aspect of economic benefit, the incurred costs and their economic effectiveness.

In Russia, medical devices for self-treatment and home care are massively distributed. The devices are in 100% purchased by patients from their personal budgets. It would seem that the manufacturers of such devices should be the target group of researchers of economic efficiency but the reality is not like that: there are no barriers to unscrupulous marketers who impose on customers, not familiar with the system of the evidence of effectiveness, devices and related technologies that have never passed performance tests but have been registered with fake documents or have not been registered at all. The lack of transparent directories of registered technologies and devices, lack of instructions of use and no guidelines or standards for the use of proposed technologies, create conditions for fraud, in which there is no room for clinical or economic evaluations.

Thus, the economic assessment of non-drug

medical technologies is a top issue for Russia. The Russian branch of ISPOR − Russian Society for Pharmacoeconomics Research (RSPOR) − has conducted several studies of non-pharmaceutical diagnostic and therapeutic technologies. For example - two studies involved modeling and two - clinical trials, where one was a randomized, double-blind study. Below, these two studies have been summarized.

PREVENTION OF CONTACT DERMATITIS AND ULCERS IN IMMOBILIZED PATIENTS WITH URINARY INCONTINENCE [2]

Among available preventive measures, we need to identify methods to prevent the use of non-pharmaceutical products, such as diapers or nursing facilities to prevent pressure sores in immobile patients.

There is no data on the incidence of contact dermatitis and pressure ulcers in Russia [3]. On the contrary, the world medical literature offers many reports of studies on the epidemiology of contact dermatitis and ulcers in patients with urinary incontinence. The incidence of contact dermatitis and ulcers varies widely [4].

The studies have mainly been focused on the development of new therapies of already formed ulcers; too little attention is paid to their prevention. Adequate prevention of pressure sores can avert their development in more than 80% of patients at risk [5]. The Industry standard: "Treatment Protocol. Bedsores", developed by our group and approved by Regulation of the Ministry of Health of Russia from 17.04.2002 № 123 [3], recommends absorbing agents and skin care products for prevention of pressure ulcers but the low level of use of these devices is probably due to their high cost.

The purpose of the undertaken clinical and economic analysis was to analyze the cost-effectiveness of the use of diapers of particular manufacturers for prevention of contact dermatitis and pressure sores in patients with fixed incontinence. The work was to estimate typical practice of the management of these patients who developed contact dermatitis or pressure sores on the

IN RUSSIA, MEDICAL DEVICES FOR SELF-TREATMENT AND HOME CARE ARE MASSIVELY DISTRIBUTED. THE DEVICES ARE IN 100% PURCHASED BY PATIENTS FROM THEIR PERSONAL BUDGETS.

basis of a survey of 7 experts with experience in treating these patients at different institutions in Russia. We have calculated the direct medical costs of prevention and treatment of contact dermatitis and pressure sores. Then we have developed an economic Markov model and conducted clinical and economic analysis of the use of diapers in prevention of dermatitis and ulcers.

Evaluation of the cost of medical services was performed, as described by RSPOR, in accordance with the Moscow regional health care fund's tariffs (2010) [1]. Calculations of nursing service costs were based on the nomenclature, works and services in health care, approved by the Ministry of Health in Russia on 12.07.2004. Calculations of the cost of absorbent materials and skin care products were based on their retail prices, acquired from the Internet (www.aptekamos.ru) in November 2011, for the sensitivity analysis, wholesale prices from 2 sources (www.tovary-plus.ru, www .air.ru / optom.html) were applied. The cost of medicines was calculated from their average prices, obtained from the www.pharm-index.ru database for the same period.

The calculated costs took into account hotel services (hospital stay), care, medicines, absorbents and care laboratory and instrumental methods of examination, as well as expert counseling;

Markov model (Figure), was based on the following assumptions:

- **one step in the cycle was assumed to be 4 weeks;**
- during the first 4 weeks, prevention of dermatitis and ulcers was conducted in 100% of the patients;
- adsorbing state is death, the incidence of which was extrapolated from the study by Fleurence RL [6], and accounted for 8% of patients in each cycle;
- for patients, who died at the end of the cycle, prevention of dermatitis and ulcers was conducted through all that time (4 weeks) because it was assumed that they had died on the last day of the cycle;
- the percentage of patients who developed stage 1 / stage 2 pressure sores, when standard preventive schemes were followed - extrapolated from studies by Palese A. [7], Gray M. [8], amounted to 22%;
- the percentage of patients who developed stage 3 / stage 4 pressure ulcers, when standard preventive schemes were followed - from studies of Palese A. [7], Gray M. [8], amounted to 7%;
  - the percentage of patients with stage 1 / stage 2 pressure sores, in whom no appropriate prophylactic standards were applied, was determined for 28%; that percent was extrapolated from a study by Fleurence RL (6).
  - the percent of patients, who developed stage 3 / stage 4 pressure sores, with initially absent stage 1 / stage 2 pressure sores, when standard prevention schemes were applied at the onset of stage 3 / stage 4 pressure sores, amounted to 8% - extrapolated from the study by Fleurence RL [6].
- the percentage of patients who developed bedsores of the same stage, when standard preventive schemes were applied, amounted to 12% and was extrapolated from the study by Fleurence RL [6];
- the percentage of patients who developed bedsores without the use of standard prevention procedures is twice higher, according Brandeis GH [9]

DISTRIBUTION OF PATIENTS BY MARKOV STATES: ABSORBENT CONDITION - DEATH

Model 1. Prevention and treatment of contact dermatitis and ulcers in patients with fixed incontinence, using absorbents and care products for over 20 weeks, each Markov cycle of 4 weeks, and a total of 5 cycles (see Table 1).

Model 2. Prevention and treatment of contact dermatitis and ulcers in patients with fixed incontinence without absorbers and care products for over 20 weeks, the duration of each Markov cycle: 4 weeks for a total of 5 cycles (see Table 2).

There is an assumption that the treatment of contact dermatitis or bedsores without absorbents and skin care products increases the

Table 1. Coefficients, used to calculate costs in model 1, 5 cycles (20 weeks)

PATIENT'S CONDITION	AT THE BEGINNING OF CYCLE	AT THE END OF THE 1ST CYCLE	AT THE END OF THE 2ND CYCLE	AT THE END OF THE 3RD CYCLE	AT THE END OF THE 4TH CYCLE
NO OF COMPLICATIONS	100	63	46.41	38.36	33.67
STAGE 1 / STAGE 2 PRESSURE SORES	0	22	30.34	31.67	30.55
STAGE 3 / STAGE 4 PRESSURE SORES	0	7	7.89	7.84	7.42
DEATH	0	8	15.36	22.13	28.36
ALL	100	100	100	100	100

Table 2. Coefficients, used to calculate costs in model 2, 5 cycles (20 weeks)

PATIENT'S CONDITION	AT THE BEGINNING OF CYCLE	AT THE END OF THE 1ST CYCLE	AT THE END OF THE 2ND CYCLE	AT THE END OF THE 3RD CYCLE	AT THE END OF THE 4TH CYCLE
NO OF COMPLICATIONS	100	34	25	21.74	19.75
STAGE 1 / STAGE 2 PRESSURE SORES	0	44	41.96	38.99	36.00
STAGE 3 / STAGE 4 PRESSURE SORES	0	14	18.68	18.05	16.73
DEATH	0	8	15.36	22.21	27.52
ALL	100	100	100	100	100

number of nursing procedures: preparation and change of bed clothes and the care of the perineum are held every 2 hours, while moving the patient in bed. Total costs for care without the use of absorbents and care products accounted for 10,165 rubles. As it can be seen in Table 3, the use of abso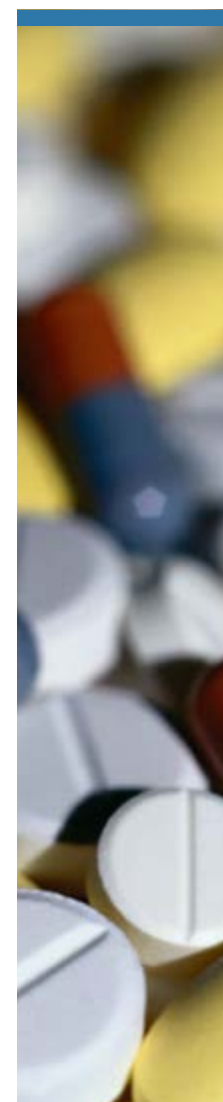rbents and care products for prevention is cheaper than their lack. The treatment of contact dermatitis and ulcers in stationary incontinent patient, using absorbents and care products, is cheaper than without their application (see Table 4 and 5).

Table 3. Total costs of prevention of dermatitis and ulcers in 1 patient (7 days)

GROUPS OF SERVICES	TOTAL COSTS WITH THE USE OF ABSORBENTS AND CARE PRODUCTS, EURO	TOTAL COSTS WITHOUT THE USE OF ABSORBENTS AND CARE PRODUCTS, EURO
HOTEL SERVICES IN HOSPITAL	106.65	106.65
NURSING SERVICES	104.45	248.35
ABSORBENTS	38.06	–
MEANS OF CARE	2.13	–
TOTAL	269.85	355

Table 4. Total costs for one patient with urinary incontinence, using absorbents and care products, with dermatitis or pressure ulcers (7 days)

GROUPS OF SERVICES	TOTAL COSTS FOR THE TREATMENT OF DERMATITIS OR PRESSURE ULCERS OF 1-2ND DEGREE, EURO	TOTAL COSTS FOR THE TREATMENT OF PRESSURE ULCERS OF 3-4TH DEGREE, EURO
HOSPITAL STAY	106.65	106.65
LABORATORY TESTS	6.30	12.31
THE USE OF INSTRUMENTS	2.57	4.40
CONSULTATION WITH SPECIALISTS	6.08	8.43
SERVICES FOR PREVENTION AND TREATMENT	18.47	60.40
DRUGS	1.83	41.51
NURSING SERVICES	104.45	109.06
ABSORBENTS	38.06	38.06
MEANS OF CARE	2.13	2.13
TOTAL	305.1	401.54

EVALUATION OF THE COST
OF MEDICAL SERVICES
WAS PERFORMED, AS
DESCRIBED BY RSPOR,
IN ACCORDANCE WITH
THE MOSCOW REGIONAL
HEALTH CARE FUND'S
TARIFFS (2010)

Table 5. Total costs for one patient with urinary incontinence without the use of absorbents and care products who developed dermatitis or pressure sores (7 days)

GROUPS OF SERVICES	TOTAL COSTS FOR THE TREATMENT OF DERMATITIS OR PRESSURE ULCERS OF 1-2ND DEGREE, EURO	TOTAL COSTS FOR THE TREATMENT OF PRESSURE ULCERS OF 3-4TH DEGREE, EURO
HOSPITAL STAY	106.65	106.65
LABORATORY TESTS	6.30	12.31
THE USE OF INSTRUMENTS	2.57	4.40
CONSULTATION WITH SPECIALISTS	6.08	8.43
SERVICES FOR PREVENTION AND TREATMENT	18.47	60.40
DRUGS	1.83	41.51
NURSING SERVICES	248.35	248.35
TOTAL	390.25	482.04

Table 6. Costs of prevention and treatment of contact dermatitis and pressure ulcers in 1 patient with urinary incontinence for 20 weeks, rub

CYCLES OF RESEARCH	MODEL № 1		MODEL № 2
	RETAIL PRICES	RETAIL PRICES	
CYCLE 1 (4 WEEKS)	1079.40	1030.83	1419.96
CYCLE 2 (4 WEEKS)	1147.30	1098.73	1553.16
CYCLE 3 (4 WEEKS)	1077.40	1032.71	1474.69
CYCLE 4 (4 WEEKS)	999.56	958.47	1362.67
CYCLE 4 (4 WEEKS)	922.70	884.88	1254.43
TOTAL	5226.36	5005.62	7064.94

The treatment of contact dermatitis and ulcers in stationary incontinent patient, using absorbents and care products, is cheaper than without their application (see Table 4 and 5).

Overall costs of prevention and treatment of contact dermatitis and pressure sores in bed-ridden patient with urinary incontinence were obtained for 20 weeks by model 1 and model 2 simulations.

Sensitivity analysis was performed on model 1 and retail prices of absorbents and care were changed to wholesale prices. The results are shown in Table 6.

The sensitivity analysis showed that cost reduction in absorbent and care materials by 12.14 euro leads to total cost reduction by 220.74 euro.

Therefore, the prevention and treatment of contact dermatitis and pressure sores in patients with fixed incontinence is cheaper, when using absorbents and care products than without their use: the total cost, calculated on the Markov model for prevention and treatment of contact dermatitis and ulcers of 1-4 - degree in a still patient with urinary incontinence for 20 weeks with the use of absorbents and care products in retail prices amounted for 5,226.36 euros, while without their application - 7,064.94 euro. Consequently, the use of absorbents and care products for the prevention and treatment of contact dermatitis and ulcers in patients with fixed incontinence should be a dominant approach.

CLINICAL AND ECONOMIC RESEARCH FOR PHYSIOTHERAPY

ALMAG-01 – a magnetotherapy device for local effects on human body of pulsed magnetic field. The theoretical basis for the use of the instrument is the concept of change and the impact of changing the pulsating magnetic field, inducing electric currents in human body. The impact on the living system is activating the sub-molecular, molecular and supramolecular structures, with changes at the cellular, organ and systemic levels.

In several observational studies with a low degree of evidence, the efficacy and safe use of the ALMAG-01 device were demonstrated in patients with osteoarthritis. The patients reported good tolerability and, when assessing the overall clinical effectiveness of the technology to reduce the clinical symptoms and get better the general condition of patients, an improvement was seen in 79% of patients and a slight improvement - in 21% of patients. Deterioration of patient condition was not observed in any case. The device is widely advertised in the media and sold to the population for the treatment of joint diseases.

The purpose was to conduct clinical and economic analysis of the ALMAG-01 device in patients with osteoarthritis. To do that, criteria were defined to evaluate the effectiveness of magnetic therapy, a clinical study of the efficacy and safety of the ALMAG-01 device in patients with osteoarthritis was conducted, the direct medical costs of physiotherapy with the ALMAG-01 device were calculated comparisons were made, and clinical and economic analysis of the ALMAG-01 device was carried out.

Study Design: prospective, controlled, randomized, double-blind study. All the enrolled patients were divided into 2 groups: the main group used the ALMAG-01 device - in the control group, a placebo unit, similar in appearance and design was applied. The only difference was the absence of contact between the generator and effector of electromagnetic radiation.

The object of study - patients with gonarthrosis undergoing treatment in hospital. The period of observation of the patient - 21 days. Each patient filled physician clinical maps, which included data on costs of resources, tolerability and efficacy of treatments.

Two types of randomization were assumed: cluster (between centers) and randomization of patients directly at the clinical center. Cluster randomization was performed by employees of RSPOR, who prepared 6 sets of devices (4 sets, including ALMAG-01 and placebo, 1 set including 2 ALMAG-01 and 1 set including two placebo-devices). All devices in the sets were labeled with numbers "1" and "2" (random numbering by machines). The numbering was known only for the RSPOR employees. At the research center after, following patient recruitment, the doctor opened and envelope with the number of the machine on which the patient had been treated.

The study included men and women, aged 18 years and older, with gonarthrosis or coxarthrosis, except for severe (stage IV in X-ray), with informed consent of patient to participate in the study.

The following criteria were applied to assess the effectiveness of treatment: reducing the intensity of pain (visual analog scale), the intensity of functional disorders (6 scales from the International Classification of functional disorders (WHO, 2001) - mobility of several joints, total joint mobility, stability of several joints, the overall stability of the joints, walking short distances, walking long distances), the quality of life for EQ-5D. The angle of flexion and extension of affected joint and its circle were evaluated.

Data from 170 patient profiles were analyzed (75, used ALMAG-01, 44.1%, 95 used the placebo 55.9%). The groups were comparable at baseline in terms of knee joint and foot status and movement, except there were significantly more patients with no knee mobility disturbances in the main group, in comparison with the control group (8% vs. 1%, respectively, p <0.05). In the study group, the flexion angle was greater than in the placebo-treated group (about 71.88 and about 64.9, respectively), and the circumference of the affected joint was less (47.15 cm and 50.05 cm, respectively) than in the control group.

In the study group, there were significantly less patients with moderate or severe deterioration of the quality of life in terms of self-service (18.7% and 55.8%, respectively), and activities of daily living (61.3% and 80%, respectively). Despite the significant differences between groups in the proportion of patients who did not experience pain or discomfort, as well as having severe anxiety and depression, those differences did not affect the composite indicator - the proportion of patients with moderate or severe handicaps, which is the basis for the analysis. Quality of life scores on the visual analog scale were 0.51 (+ / -0.11, median - 0.50, 1st quartile - 0.45, third quartile - 0.60) in the intervention group and 0 , 59 (+ / -0.13, median - 0.58, 1st quartile - 0.50, third quartile - 0.70) in the control group.

The average duration of treatment in the study group was 13.2 + / - 5.2 days, median - 13 (1 quartile - 10, quartile 3 - 17) in the control group - 10.4 + / - 6.9 days, the median - 10 (quartile 1 - 3, quartile 3 - 17).

The test group showed a greater, but not statistically significant decrease in the volume of affected joint, as compared with the control group (3.9 cm and 2.9 cm, respectively), the affected joint flexion angle decreased in the intervention group by about 0.31, while in the control group, it increased by about 2.4. The angle of extension of affected joint increased in both groups, but the increase in the study group was larger, compared with the control group (-7.41 and -3.15, respectively).

Neither group differed in terms of the quality of life dynamics but the study group had less patients with moderate or severe disorders in

terms of pain or discomfort (38.7% and 62.1%, respectively). However, at the onset of the study, the parameters differed. The quality of life score on the visual analog scale was 0.62 (+ / -0.12, median - 0.63, 1st quartile - 0.5, third quartile - 0.7) in the intervention group and 0 , 69 (+ / -0.14, median - 0.70, 1st quartile - 0.60, third quartile - 0.75) in the control group. Change in the quality of life, measured on the visual analog scale in the study group was 0.11 points and 0,1 in the control group. Thus, significant differences were noted in the quality of life dynamics, as assessed by the EQ-5D visual-analog scale questionnaire..

No statistically significant differences were noted in the dynamic and functional parameters within the studied groups but the positive dynamics of joint mobility was indicated in pulmonary diseases and their absence was significantly more pronounced in the study group, compared with the control group (21.3% and 9.5%, respectively).

In the control group, a significant reduction in the proportion of patients with severe or moderate disturbances in terms of walking distance to 1 km (from 69.4% to 46.3%) and an increase in the proportion of patients with mild impairment of that ability (with 10.5% to 31.6%) were statistically observed. A comparison of both groups revealed that, in the „short distance walking" context, there were significant differences, depending either on the presence or the absence of pulmonary medical conditions (14.6 vs. 4.2%).

Thus, the ALMAG-01 DEVICE has a more significant influence on the quality of life component, associated with the presence of pain and discomfort, compared with the placebo device, what was not confirmed by the indicators of the EQ-5D questionnaire, where a greater effect was demonstrated when using the placebo. ALMAG-01 did not demonstrate any significant effect on the functional parameters (angle of flexion and extension, the amount of joint performance impairment). Opposite changes at different scales do not allow to speak of clinical benefits from the use of electromagnetic interference with the use of the ALMAG-01 device vs. placebo.

The total cost of keeping a patient in the study group was 186,86 euro, in the control group - 234.65 euro. Taking into account the hypothesis on electromagnetic field efficacy in the context of ALMAG-01 applications, one may perceive is as a cost-effective strategy, improving the quality of life by reducing severe and moderate pain sensations and aiding the comfort of patients.

In the study group, 327.80 euro were spent for reduction of moderate to severe quality of life violations, associated with pain and discomfort in 1 patient, which was almost twice lower than in the control group - 634.16 euro to achieve the same effect in 1 patient.■

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Analysis of direct costs of drug-induced skin reactions treatment considering DRG classification in the perspective of medical service provider and public payer

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ABSTRACT

Background: The aim of this study is an assessment of direct costs of patients' hospitalization caused by drug-induced skin reactions in Dermatology Department of Military Institute of Medicine during the period 2002-2012 from the public payer's perspective and service provider, based on the DRG classification.

Data and methods: The study was carried out in a retrospective way on a group of 164 adult patients hospitalized in Department of Dermatology between 2002 and 2012. The analysis was based on data from patients' medical records. Due to the changes in health care system settlement during the long period taken into account for resources used identification, the one-year time horizon was settled to standardize cost calculations. The costs were evaluated in the perspective of public payer and service provider based on the DRG classification.

Results: It was evaluated, that patient hospitalization due to drug-induced skin reactions within specific DRGs (J38 and J39), in the perspective of the public payer costs on average 971 euro per patient (J38) and 481 euros (J39) depending on the DRG group. When analyzing the complex diagnostics and pharmacologic therapy of the same group of patients in the perspective of the hospital costs the results is 636 euro in the J38 and 558 euro in J39 group per patient.

Conclusions: Within the DRG, in case of J38 group the National Health Fund bear higher treatment costs than health care service provider. Higher costs are usually connected with higher amount of diagnostic examinations in case of severe dermatologic diseases, qualified to the J39 group

INTRODUCTION

Adverse effects of drugs are still a major challenge for physicians, pharmacists and the patients. Particular attention should be given to OTC drugs (over the counter), which can also cause adverse reactions. In last several years the sale of drugs in Poland is increasing. Our country is the sixth biggest drug market in Europe as stated by Office for Registration of Medicinal Products, Medical Devices and Biocides in 2010 [1].

The drugs can cause severe adverse reactions which may become life-threatening or lead to death, hospitalization, permanent disability, malformations or other reactions, which can be assessed as severe by the physician [2].

They occur in different age ranges, however their prevalence is higher in adults than in chil-

dren. They affect 7% of population – 30% of them are drug-induced skin reactions [3].

The clinical picture of drug-induced skin reactions is diverse, often imitates other dermatoses. For the last few years in Poland, as worldwide, the economic analyses evaluating costs of the adverse treatment reactions are performed. The results of these studies are often of significance, supporting decisions, which implement new and/or modify actual therapeutic standards.

Following the Polish Law, an assessment of the economic component is obligatory in drug reimbursement approving procedure, in order to optimize the allocation of funds by the public payer. Economic analyses as part of the Health Technology Assessment (HTA) dossier are evaluated by experts of the Agency for Health Technology Assessment and the process is completed by a recommendation on a new technology issued by the Chairman of the Agency for the Minister of Health. The adverse reactions are part of every HTA analysis, not only for safety conclusions but also as one of the costs component included in the pharmacoeconomic evaluations.

BACKGROUND

The aim of this study is an assessment of direct costs of patients hospitalization caused by drug-induced skin reactions in Department of Dermatology Military Institute of Medicine between 2002 and 2012 from the perspective of public payer and service provider, based on the homogenous DRG (Diagnosis Related Group classification).

DATA AND THE METHODS

It was a retrospective study. The analysis was performed on data collected from patients' medical records and medical order cards. All those documents provided information on used resources, such as diagnostic tests, specialist consultations, administered medicinal products (used for treatment) and hospitalisation period. Based on the identified resources, used for the adverse reactions treatment, the costs of the therapy were estimated. The costs of laborato-

ry diagnostic tests, specialist consultations and hospitalisation were evaluated based on internal hospital pricelist determined by Medical Services Sales Department of Military Institute of Medicine in the 2012. Cost of pharmacotherapy was evaluated based on drug's wholesale prices in 2012.

From the public payer's perspective, the costs of specialist consultation visits (dermatologist), laboratory diagnostic tests and hospitalisations were taken into account on the basis of prices for medical services, determined by the National Health Fund via contracts with healthcare units, following the Act on medical services, financed from public funds in 2012. In case of a contract with the National Health Fund, the costs of laboratory tests, other diagnostic tests and are included in the costs of the, so-called, specialist visit. The value of service costs, incurred by the National Health Fund, was based on the International Statistical Classification of Diseases and Related Health Problems – ICD 10 and the Diagnosis Related Groups (DRG).

The analyzed group of patients was classified according to different criteria, such as: age, diagnosis, drugs which caused drug-induced dermatoses and ICD 10 criteria.

In order to obtain accurate analysis an analytic tool in Microsoft Excel was created. Usage of this tool allowed to calculate costs of used drugs, performed laboratory tests, overall and average costs of hospitalization and on the basis of prescriptions drugs the costs generated by the need to continue the treatment in outpatient setting. The analysis considered only the cases of drug-induced skin adverse reactions, which presented explicit form and drug dosage.

RESULTS

Between the years 2002 – 2012 there was 10267 patients hospitalized in Department of Dermatology Military Institute of Medicine, including 164 patients (57 male and 107 female patients) with drug-induced skin adverse reactions, which is 1.59% of overall hospitalizations. The average age of patients was 53.7 years.

The most frequently observed adverse reactions were maculopapular rash 52%, erythema multiforme 25% and Stevens-Johnson syndrome 4%. The others are: skin eczema, chronic nettle-rash, toxic epidermal necrolysis (TEN), erythema fixum and phototoxic dermatitis.(Figure 1.)

The drugs which caused drug-induced skin reactions most frequently were antibiotics (45.12%) and NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) (25.6%). Amoxicillin was the most frequently described antibiotic. Among the NSAIDs the most frequently described drug causing skin adverse reactions was ibuprofen. 3 groups of diagnoses were analyzed: severe dermatologic diseases J38, large dermatologic diseases J39 and mild dermatologic diseases J49. The J38 group included 83 patients, J39 – 80 patients and J49 – one patient.

The average age of patients in the J38 group was 59.12 years and among the patients qualified to the J39 group – 50.64 years. Skin drug-induced adverse reactions in patients with severe dermatologic diseases occurred on average after 5.16 days since the drug was administered, and in the group of large dermatologic diseases they occurred after an average of 20.37 days.

The hospitalization period of the patients for the specific groups was respectively: J38 – 4.60 days, J39 – 4.14 days. Following DRG classification, the National Health Fund assigned the following scores, 82 for J38, 33 for J39 and 27 for J39. A score 1equaled to 12,5 euro (year 2012). On this ground the overall cost of direct treatment according to DRG classification from the perspective of public payer was evaluated.

The costs of specialist consultation visits (dermatologist), laboratory diagnostic tests and hospitalization were taken into consideration on the basis of prices for medical services, determined by the National Health Fund via contracts with healthcare units, following the Act on medical services, financed from public funds in 2012. In case of a contract with the National Health Fund, the costs of laboratory tests, other diagnostic tests and pharmacologic therapy are included in the costs of the visits classified as a specialist visit.

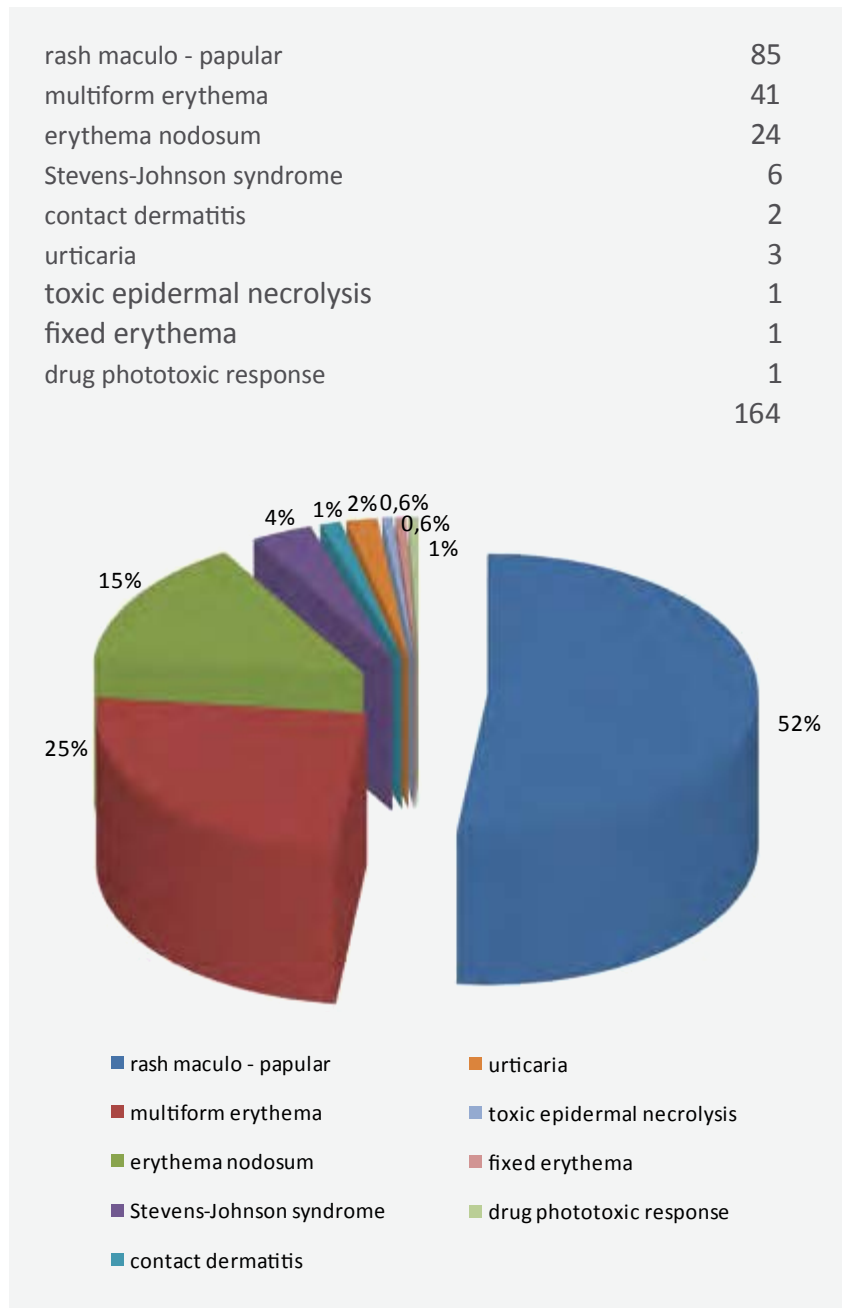|	
rash maculo - papular	85
multiform erythema	41
erythema nodosum	24
Stevens-Johnson syndrome	6
contact dermatitis	2
urticaria	3
toxic epidermal necrolysis	1
fixed erythema	1
drug phototoxic response	1
	164

Figure 1. Adverse skin drug reactions

For the group of patients with severe dermatologic diseases (83 patients) the overall direct cost was evaluated and amounted to total sum of 82 444 euro. In the group of large dermatologic diseases there was 80 patients and overall direct cost amounted to 34 097 euro. In the group of mild dermatologic diseases only one case of one patient was analyzed and the cost of direct treatment was 334 euros. The average costs

Analysis of direct costs of drug-**induced**
skin reactions treatment considering
DRG classification in the perspective of
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ICD10	ICD-10 score	M	F	mean age	mean days of hospitalization	drug-induced skin reactions [mean days]	total direct costs - public payer [EUR]	total direct costs - public payer [EUR], mean cost per 1 patient
J38	82	26	57	59,12	4,60	5,16	346268,00	972,00
J39	33	31	49	50,64	4,14	20,37	143208,00	481,00
J49	27	0	1	25,00	2,00	10,00	1404,00	334,00

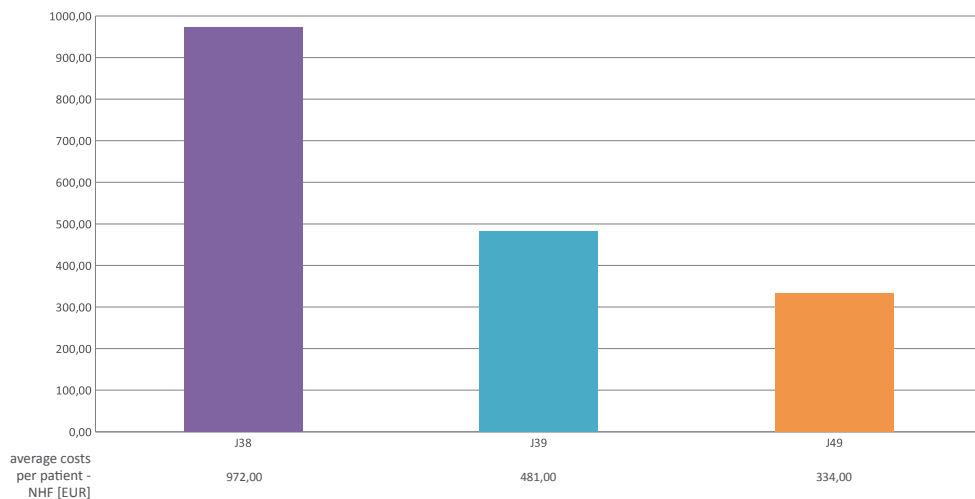|	J38	J39	J49
average costs per patient - NHF [EUR]	972,00	481,00	334,00

Figure 2. Average costs per patient - NHF

ICD-10 score	total direct costs - service provider	total direct costs- mean cost per 1 patient
J38	231478,50	637,00
J39	231860,52	558,00
J49	1592,00	379,00

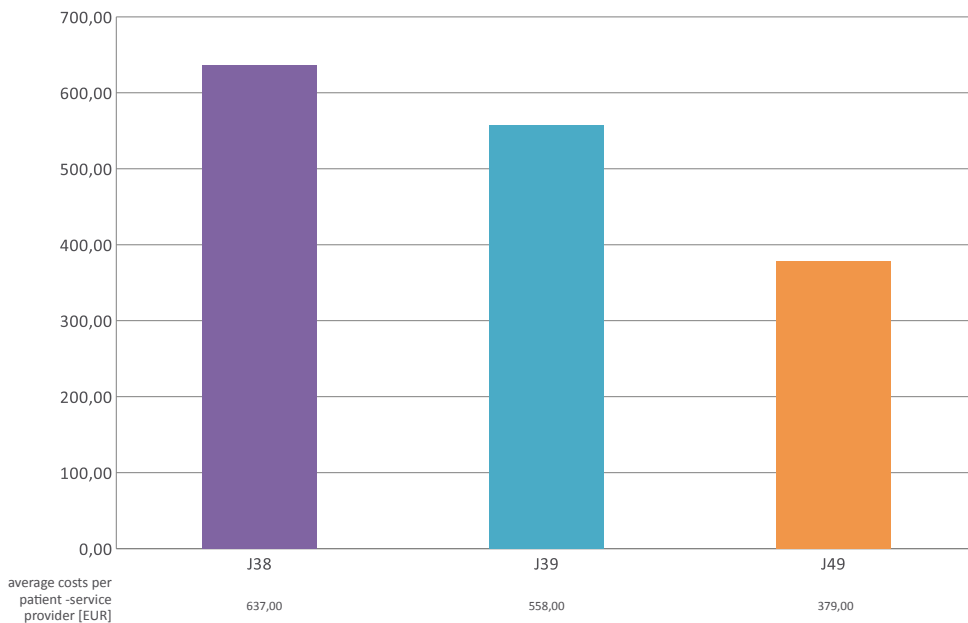|	J38	J39	J49
average costs per patient -service provider [EUR]	637,00	558,00	379,00

Figure 3. Average costs per patient - service provider

were higher for the patients with J38 diagnosis and amounted to 972 euros, and for the patients with J39 diagnosis– 481 euros. Fig.2. The costs in specific groups depends only on the scores assigned by NHF, without considering the period of hospitalization.

In the perspective of medical service provider in calculation of direct costs the most critical was the hospitalization period and the cost per day of hospitalization, which was 121 euro/day in WIM Department of Dermatology. This amount included physician and medical personnel salary, media, hospital beds and full board costs.

In the group of severe dermatologic diseases (J38) the cost of direct treatment was 55 114 euro. In the group of large dermatologic diseases (J39) it was 55205 euro. In the group of mild dermatologic diseases only one case was analyzed and the cost of direct treatment was 379 euros. The average costs in particular groups are similar and amount to 637 euro in the J38 group and 558

euros for the J39 group. (Figure 3.)

Evaluated costs of the pharmacological treatment in those groups are similar. In the J38 group costs of used drugs was 1778 euro and in the J39 group – 1732 euro. The average costs of the treatment for one patient was 17 euro in J39 and 15 euros in the J39 group. Fig.4. In the analyzed groups the amount of hospitalized patients was almost the same, so assessed costs are the proof, that the costs of pharmacological treatment are comparable in those two different groups.

The costs of diagnostic procedures performed during hospitalization was evaluated on the basis of hospital's internal pricelist and the one-year time horizon (year 2012) was applied in the analysis. In J38 group of patients the cost of medical procedures performed by hospital was 16 euro per one patient.

On the other hand in the J39 group the cost of diagnostic procedures was much higher – 457
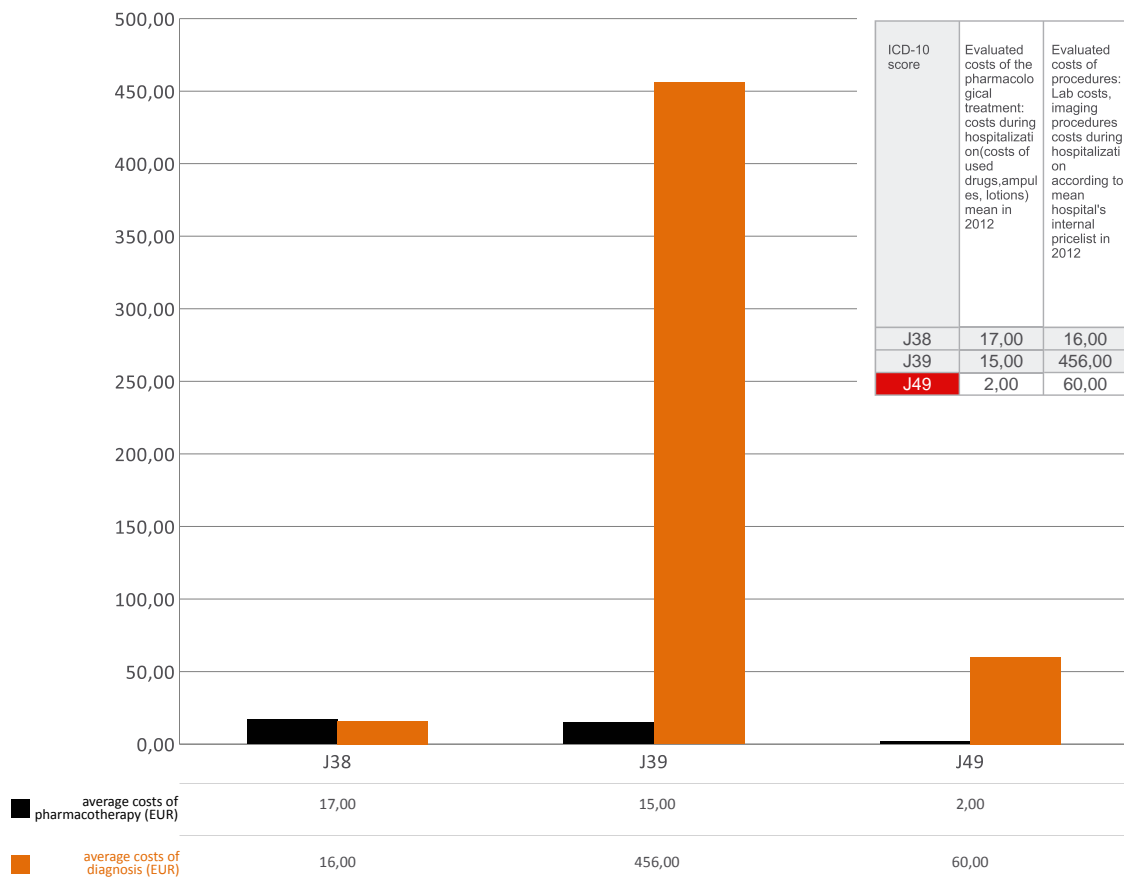

ICD-10 score	Evaluated costs of the pharmacological treatment: costs during hospitalization(costs of used drugs,ampules, lotions) mean in 2012	Evaluated costs of procedures: Lab costs, imaging procedures costs during hospitalization according to mean hospital's internal pricelist in 2012
J38	17,00	16,00
J39	15,00	456,00
J49	2,00	60,00

		J38	J39	J49
■	average costs of pharmacotherapy (EUR)	17,00	15,00	2,00
■	average costs of diagnosis (EUR)	16,00	456,00	60,00

Figure 4. Average costs of pharmacotherapy and diagnosis per patient

euro per patient. Fig.4. The differences in particular groups results from qualifying patients with severe skin adverse reactions to the J39 group. Diseases like erythema multiforme, erythema multiforme major or erythema nodosum are conditions, which require more diagnostic tests and imaging examinations.

DISCUSSION

Facing the challenge of the economic impact in diagnostics and patient treatment, not only for healthcare managers, but also for physicians, who are obligated to perform effective therapy on a basis of available funds, we ran the analysis of direct medical costs for the public payer and health care service provider in the group of 164 patients hospitalized in Department of Dermatology because of drug-induced skin adverse reactions in the years 2002 – 2012.

It was evaluated, that the costs of related to DRG classification, in the perspective of public payer is on average 971 euro per patient in J38 group and 481 euro in J39 group. On the other hand, complex diagnostics and pharmacologic therapy in the same group from the perspective of costs generated by hospital is averagely 636 euro for J38 and 558 euro for J39 per one patient.

As a part of J38 diagnoses, the NHF bears higher costs that medical service provider. In the J39 group the hospital bears higher costs than public payer. Higher costs are mostly connected with bigger amount of required and repeated diagnostic tests in case of severe dermatologic diseases, qualified to the J39 group.

In the published literature a lot of meta-analyses, analyses of direct and indirect cost of drug adverse reactions treatment or cost efficacy analyses are available. Nevertheless, there is still no analyses concerning costs in relation to DRG classification. The Ophthalmic Surgeons Association in Poland released the report concerning costs of surgical cataract removal using phacoemulsification method with implantation of intraocular lens in 2013. The direct and indirect costs listed above were evaluated taking into consideration changes in NHF settlements

at the turn of recent years. According to the data published by NHF the average cost of JGP B13 procedure in 2012 – removal of uncomplicated cataract using phacoemulsification method with simultaneous lens implantation - is 722 euro. Obligatory valuation applies (till June 30, 2013) in case of hospitalization scoring 61 points – 858 euro, in case of "one day hospitalization" – 55 points – 732 euros. The costs refunded by NHF are respectively in case of hospitalization – 697 euro and in case of „one day hospitalization" – 629 euros. Since July 01, 2013 new settlement rules concerning JGP B13 procedures were introduced, they standardize points applied to the procedure. On the basis of the new evaluation the costs refunded by NHF were lowered by 69 euro. According to Ophthalmic Surgeons Association in Poland those changes can lead to dangerous savings in medical personal and used medical materials costs, which can influence the patient's quality of life [4].

Nowadays, when new medicinal products are introduced to the market the subject of drug-induced changes is still present. Many patients, especially with severe drug-induced dermatoses will require hospitalization.

The patients should be educated about possible drug adverse reactions. The cooperation of physician and pharmacist is extremely important to report every adverse drug-related reaction to the Department of Monitoring Adverse Drug Reactions, The Office For Registration The Medicinal Products, Medical Devices and Biocidal Products.

Those actions can facilitate quicker detection of dangers coming from drug administration and allow determining their value compared to different drugs from the same therapeutic group[5]. Thanks to this fact the risk that adverse drug-induced reactions occur will be more predictable and the part of those cases will not require hospitalization.

Siok Swan Tan while discussing the DRG and cost accounting systems is comparing the situation in different countries. Some European countries, also Poland, despite having imported

DRG weight from other countries is using cost accounting data in order to adjust the DRGs to local situation. However Poland bases most of their DRG assumptions on UK HRG calculations and calculates locally DRG only for specific procedures. According to Siok Swan Tan the revisions of existing cost-accounting systems should be undertaken in order to improve the effectiveness and fairness of DRG-based hospital payment systems. An accurate cost-accounting system is needed in order the DRG functions well, however, both, DRG and cost accounting should be developed independently of each other to validate the systems' performance individually [6].

CONCLUSIONS

Drug-induced skin reactions therapy is a significant cost both for payer and health care service provider taking into consideration DRG classification. On the basis of analyzed group of patients it may seem, that procedures connected with adverse reactions therapy are correctly evaluated, however limitations of the analysis should be considered, especially the number of analyzed reactions and amount of patients. The attention should also be paid to possible renewed drug-induced dermatoses classification within DRG having regard to assigned points by the NHF and clinical form of drug-induced skin reactions. This kind of analyses can make the cooperation between NHF and hospital more efficient. ■

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How to optimize public spending on antihypertensive treatment in Poland - an example of rationalization analysis

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ABSTRACT

Background: Approximately 13% of global deaths are assigned to high blood pressure. ACE-Is and ARBs belong to most frequently prescribed classess of antihypertensive treatment. Recent meta-analyses have confirmed lack of evidence for predominance of ARBs over ACE-Is. Nevertheless, in Poland ARBs remain premium priced and better reimbursed compared to ACE-Is.

Objective: To assess economic impact of combining existing separate limit groups of the RAAS inhibitors into one group. Presented analysis is an example of rationalization analysis – a new type of analysis introduced by the reimbursement law 2011.

Methods: Reimbursement spending in one year horizon was assessed in two scenarios, assuming separate and common limit groups for ACE-Is and ARBs. List of products analysed and their unit prices are based on MoH listing of reimbursed drugs for 1 July 2013. Yearly volume of reimbursed packs was based on the most recent available data ie. NHF reports May 2012 to April 2013.

Results: Yearly savings from the public payer perspective is estimated at 155 mln PLN, a significant fraction (2.3%) of the actual spending on drug reimbursement. Average cost of reimbursement of a monthly therapy using ACE-Is and ARBs is estimated at 2.22 and 3.85 PLN respectively, as compared to 2.35 and 10.85 PLN prior to the change.

Conclusion: Combining ACE-Is and ARBs into a common limit group could ensure significant savings for the payer without compromising public health. Existing clinical evidence suggests that current practice of financial preference of ARBs over ACE-Is may lead to suboptimal allocation of the public resources.

INTRODUCTION

From the beginning of the year 2012, most of the provisions of the Act on Reimbursement of Medicines, Foodstuffs for Special Nutritional Purposes and Medical Devices (Reimbursement Act) came into effect in Poland [1]. Having considered its multidimensional influence on almost all participants of the Polish healthcare system, it constitutes one of the most significant reforms introduced in Poland over the past few years. Given its fundamental objectives, i.e. ra-

tionalization of the National Health Fund (NHF) expenditures on reimbursement and facilitation of access to drugs, including innovative drugs in particular, the Act appears to be parallel to the activities undertaken in other European countries [2-4].

The Reimbursement Act introduced the restriction on the NHF expenditures on drugs to 17% of the total resources directed to the financing of guaranteed services in the NHF financial plan. As a consequence, the financial policy became stricter. In particular, access to the drugs is regulated to a large extent by the mechanism of therapeutic reference pricing. Drugs which have the same international nonproprietary name (INN) or different INN but have a similar therapeutic effects and similar mechanism of action, could be classified into common limit group, based on the criteria of same reimbursed indications and similar efficacy. Thus, the Act grants the possibility to develop extensive limit groups, including above all the therapeutic indications specified in the Summary of Product Characteristics and related clinical efficacy and not only the active substance.

If justified, modifications within already existing limit groups are also acceptable. The organ entitled to implement such modifications is the Minister of Health (MoH). The fundamental-advisory role in this respect are played by the President and the Transparency Council of the Agency for Health Technology Assessment in Poland (AHTAPol). Based on the comparison of the health effects or additional health effects obtained, it may recommend introducing changes in the limit groups.

New regulation has also modified the manner of establishing base for the limit. The reference point in a given limit group does not constitute the price of the cheapest drug, as it was done earlier, but the medicine which is representative for the particular limit group (as quantitative market share amounting to 15% in this limit group). The list of reimbursed drugs (with the level of reimbursement, limit groups, patient's contribution and the base of financing limitation) is currently published in the form of the MoH announcement every two months.

The Reimbursement Act [1] introduced a new type of analysis - rationalization analysis, required in case the budget impact analysis (BIA) for a health technology submitted for reimbursement indicates an increase in the payer's reimbursement cost. The rationalization analysis should provide solutions, the inclusion of which in the reimbursement will result in a release of public funds at an amount which corresponds to at least the increase in the costs arising from the BIA.

RAAS INHIBITORS IN HYPERTENSION TREATMENT - ARE THEY EQUIVALENT?

In Poland, among the most frequently prescribed drugs are the ones for the treatment of cardiovascular related diseases, including antihypertensive drugs. Cardiovascular diseases (CVD) are the leading cause of mortality in Europe and worldwide with 48% of all deaths attributable. According to the statistics, an estimated 80 million people in Europe have greater than one in four, 10-year risk of a vascular event [5,6]. High BP is the main risk factor leading in 49% to ischemic heart disease and in 62% to stroke. Moreover, approximately 13% of global deaths are assigned to this manifestation [5,7,8]. Given the fact that an estimated 44% of Europeans over 35 years suffer from hypertension, the primary objective of current European hypertension guidelines, ie. blood pressure (BP) reduction aiming at cardiovascular mortality and morbidity decrease appears to be fully justified [9,10].

Proven effectiveness of nonpharmacologic interventions in lowering BP has its reflection in Polish and worldwide recommendations [9,11,12]. Irrespective of that, application of medication in many individuals is inevitable. The existing and widely used antihypertensive drugs incorporate renin angiotensin aldosterone system (RAAS) inhibitors, calcium channel blockers, beta-blockers and the diuretics [13,14]. They are licensed for initiation or maintenance of hypertension treatment and applied in monotherapy or in combination with other medicines [9]. Having regard to comorbidities and particularities of patients as well as specific properties, advantages and limitations assigned to the particular class of drugs, treat-

ment should be individualized to achieve maximum therapeutic effect [9].

Having considered the role of the RAAS in regulation of homeostasis, arterial pressure, tissue perfusion and extracellular volume [15], drugs related to its blockade: angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) have pivotal role in the treatment of hypertension in routine medicinal practice [2,5]. They are considered to be clinically equivalents, although it is equivocal proclamation as they both block RAAS by different ways of operation. While ACE-Is prevent the enzyme ACE from converting angiotensin I into II, ARBs prevent the binding of angiotensin II to AT1 receptor [15,16]. Additional ACE-Is features of clinical implication are inhibiting degradation of the bradykinin resulting in vasodilatation and its potential beneficial role in cardiac protection, but also some adverse events not attributable to ARBs: dry cough (occurring in 5- 20 % of the patients) and angioedema (observed in 0.1% to 0.2% patients) [15,16].

A number of randomized controlled trials studying the ACE-Is and ARBs separately proved their high efficacy in reduction of mortality, myocardial infarction, stroke, heart failure and readmissions in patients suffering from heart failure [17], with stated left ventricular dysfunction [18-20], at high-risk and with vascular disease history [21-23] and at high-risk diabetes [24]. The direct and indirect comparisons of the two classes of drugs under the meta-analysis may settle their clinical equivalence.

Having regard to blood pressure reduction, meta-analysis of 2008 demonstrated that ACE-Is and ARBs are of clinical equivalence. This head to head comparison conducted on a group of adult patients with essential hypertension suggested that discussed therapies provide similar antihypertensive effect [25]. No significant differences in the frequency of selected end points, ie. death, cardiovascular events, major adverse events and quality of life were presented. No particular groups of patients of higher effectiveness, better tolerance or less frequency of adverse events occurrence were identified. However, it was stated that the use of ACE inhibitors is linked with

more frequent occurrence of cough. Presumably following that, ARBs were associated with higher rates of persistence with initial therapy than ACE-Is [25].

Effectiveness of ACE–Is and ARBs as drugs used additionally in a standard therapy in stable ischemic heart disease with preserved ventricular function was compared in systematic reviews of 2009 and 2011 [26,27]. According to those publications, evidence on reduced mortality, myocardial infarctions and stroke were assigned to ACE-Is only. No additional effects were attributed to neither using ARBs nor by combining an ACE inhibitor and an ARBs [26,27].

The predominance of ACE-Is over ARBs was identified in the treatment of patients with diabetes in systematic review of 2008 [28]. Review included randomized controlled trials (RCT) of antihypertensive drugs among hypertensive or normotensive patients suffering from diabetes without nephropathy and RCT of ACE-Is or ARB in patients with diagnosed diabetic nephropathy. It was revealed that ACE-Is are the only drugs having positive renal effect in patients with diabetes without nephropathy as well as were associated with proven survival benefit in patients with diabetes and nephropathy [28].

Landmark conclusions were provided by meta-analysis conducted in 2012, the first attempt to assess the RAAS inhibitors influence on mortality in hypertension as basic indication. Comparison of RAAS inhibitors with another antihypertensive treatment or placebo in the group of 158,998 hypertensive patients allowed to conclude that RAAS inhibitors resulted in the decrease of all-cause mortality [29]. It should be emphasized however that gained health effects were constrained to the ACE-Is and were not observed for ARBs; stratified subgroup analysis showed significant 10% relative reduction in all-cause mortality associated with the usage of ACE-Is compared with no mortality reduction observed for ARBs [29].

The results of the meta-analysis of 2013, comparing ARBs and ACE-Is versus placebo in 108,212 patients without heart failure was consistent

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with the previous results. Unlike ARBs, ACE-Is significantly reduced not only all-cause deaths but also new onset of heart failure and diabetes mellitus [30]. Meta-analysis showed no advantage of ARBs over ACE-Is in reducing the risk of the composite outcome of CV death, MI and stroke. Taking the above results into account, one of the main conclusion is ARBs approval as a therapeutic substitute to reduce CV mortality and morbidity in patients for whom ACE-Is cannot be applied, eg. for patients experiencing ACE-inhibitor induced cough [30].

REIMBURSEMENT OF RAAS INHIBITORS IN POLAND

Data reported by National Health Fund [44-46] confirm that RAAS inhibitors constitute an important class of products reimbursed in Poland, both in terms of the volume of yearly consumption (50.5 mln packs) and the level of public expenditure on reimbursement (430.5 mln PLN). Yearly number of reimbursed patient-months of therapy [1] is nearly 96 mln.

Under currently existing system, the RAAS blockers are available in Poland as separate limit groups with different methods of reimbursement. ACE-Is belonging to 44.0 [2] limit group are available for patients for lump sum up to the defined limit above which patient additional payment is required. ARBs belonging to 45.0 limit group are reimbursed at 30% copayment up to a defined refund limit. At the moment of analysis (July 2013), the 44.0 group consists of 138 products (EAN codes) containing either monotherapy or a fixed-dose combination of ACE-Is with a diuretic or a calcium-channel blocker. The 45.0 group consists of 194 products containing either monotherapy or fixed-dose combination with hydrochlorothiazide.

It should be emphasized that the fixed-dose combinations of ACE-Is are reimbursed only up to a limit calculated based on the amount of the ACE-I contained in the pack, and therefore generate additional savings for the payer resulting from reduced number of reimbursed packs of the diuretic or calcium-channel blocker. This is not the case for reimbursed fixed-dose combinations of ARBs (hydrochlorothiazide is not reimbursed from public funds).

Consequences of separate limit groups are different upper limit funding used in relation to the discussed groups of drugs. Average limit of financing a monthly therapy [30 DDDs] from public funds is 2.8 times higher for ARBs vs ACE-Is (Fig 1). This results in significantly different level of public payer expenditure for both classes. Average cost of reimbursement from public funds of a monthly therapy [30 DDDs] is 4.6 times higher for ARBs vs ACE-Is (Fig 2). This translates into macro-scale – on a yearly basis (May 2012 to April 2013), the number of patient-months of therapy reimbursed from public funds amounted to 75.3 mln and 20.6 mln, respectively for ACE-Is and ARBs (95.6 mln patient-months of therapy with both classes). Public spending reported by National Health Fund was 190.8 mln PLN and 239.6 mln respectively for ACE-Is and ARBs, and over 430 mln PLN for products in both groups. This means that 56% of public expenditure for RAAS inhibitors was spent for reimbursement of ARBs despite only 22% share in the treatment of patients (Table 1).

Taking into consideration lack of clinical evidence confirming predominance of ARBs over
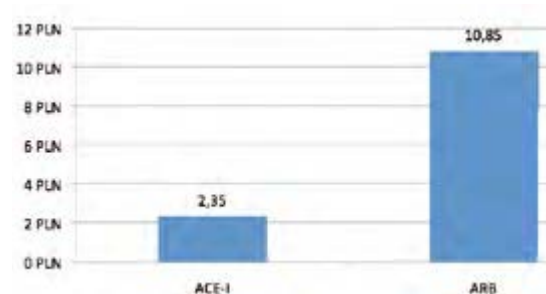

Figure 1. Average limit of financing from public funds for a monthly therapy [30 DDDs] with an ACE-1 and an ARB
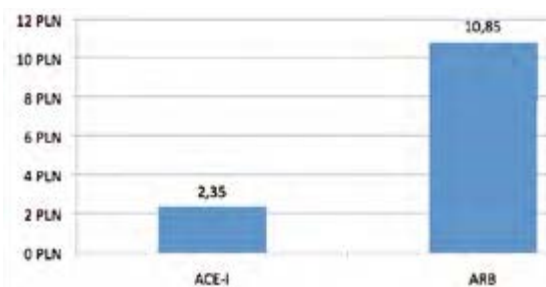

Figure 2. Average cost of reimbursement from public funds of a monthly therapy [30 DDDs] with an ACE-1 and an ARB

ACE-Is and proven additional effects resulting from ACE-Is only, premium pricing of the ARBs is unjustified. One of the proposed solution to eliminate financial favoritism of ARBs could be combining the two limit groups, ACE-Is and ARBs into one limit group. As a consequence, one common reimbursement limit would be defined.

the analyzed time horizon, ie. the reimbursement schemes applicable to analysed products existing at the time of analysis would not be subject to modifications (lump sum payment for ACE-Is and reimbursement of 70% for ARBs will not change). The selling prices of analysed products were assumed constant in both scenarios and are based on the official reimbursement listing valid at the moment of analysis, ie. 1 July 2013 [31].

Table 1. Number of packages of ACE-Is and ARBs reimbursed in Poland May 2012 to April 2013, along with the reimbursement spending reported by National Health Fund

LIMITS GROUP IDENTIFIER	NAME OF THE LIMIT GROUP	NUMBER OF PACKAGES REIMBURSED [000]	NUMBER OF PATIENT-MONTHS OF THERAPY [000]	-	REPORTED REIMBURSEMENT SPENDING [000 PLN]	
44.0	ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACE-IS)	35,602	75,305	(78%)	190,779	(44%)
45.0	ANGIOTENSIN RECEPTOR BLOCKERS (ARBS)	14,896	20,642	(22%)	239,631	(56%)
TOTAL		50,498	95,948	(100%)	430,410	(100%)

Sources: authors' calculations

The objective of the analysis is to assess the direct financial consequences following implementation of the solution consisting in combining two existing limit groups representing the RAAS inhibitors, ie. ACE-Is and ARBs, belonging to the groups 44.0 and 45.0 respectively, into one limit group while retaining the current reimbursement schemes, ie. lump sum payment in relation to ACE-Is and reimbursement of 70% with reference to ARBs (proposed scenario). The resulting spending are to be confronted with expenditures under currently applicable conditions ie. coexistence of two separate limit groups (existing scenario).

METHODS

The analysis was performed from the public payer perspective. The time horizon was one year. The only costs included in the analysis are those related to the NHF spending on reimbursement of drug prices, as the proposed solution does not affect any other related fields of the healthcare system.

For the purpose of the study, assumptions indicating a static market model were adopted in

To estimate economic impact resulting from combining two limit groups into one common group, a new drug constituting a base for limitation for both drug categories will be determined. The limiting drug is designated consistent with the art. 15 para 4 of the Reimbursement Act [1]. According to the Act, the base for limitation in a given limit group constitutes the highest among the lowest wholesale price for DDD of medicine which covers at least 15% of monthly quantitative turnover achieved in this limit group, in a month which is 3 months prior to the publication of the MoH announcement. For the purpose of the analysis, drug serving as a base for limitation in the new limit group will be stated having regard to the value of drug reimbursement under the EAN codes as in March 2013. The value of reimbursement of March 2013 will be calculated as the difference between the value of drugs reimbursement of January-March 2013 and January-February 2013 [32,33]. The official price of the product serving as a basis for limitation in the new limit group will be adopted on a basis of the announcement of the Ministry of Health of 24 June 2013 on the list of reimbursed medicines, foodstuffs for special nutritional purposes and medical devices as of 1 July 2013 [31].

Taking into account the new drug serving as a base for limitation, annual reimbursement expenditures will be assessed. The annual consumption of drugs will was assumed based on the most recent data published in announcements of the Department of Medicines Policy of NHF. Number of boxes reimbursed over the period May 2012 to April 2013 is calculated based on cumulative reports for January-April 2013 [34], January-December 2012 [35] and January-April 2012[36]. All analysed products pricing and unit reimbursement costs were determined using official sales prices defined in the reimbursement listing valid since 1 July 2013 [31], taking into account appropriate wholesale margin and retail margin considering the new limit base, as defined in the Reimbursement Act [1] in art 7 para 4.

IN THE CASE OF COMBINING ACE-IS AND ARBS IN ONE LIMIT GROUP, THE MEDICINE WHICH WOULD MEET 15% QUANTITIVE TURNOVER CALCULATED ACCORDING TO DEFINED DAILY DOSE (DDD) FOR TWO GROUPS OF DRUGS WOULD BE VIVACE 10 MG, 30 TABS.

All unit costs and total spending figures are expressed in the local currency (PLN); at the time of drafting the article (July 2013) the average official exchange rate of National Bank of Poland was 1 EUR=4.2756 PLN [37].

RESULTS

In order to standardize different pack sizes and available doses of the analysed products, the number of packs reported by NHF was recalculated into numbers of "standard packs" containing 30 DDDs of the reimbursed molecule. This might be interpreted as the number of patient-months of therapy with the given product. The number of standard packages reimbursed on an annual basis was assessed to be 75.3 mln and 20.6 mln, respectively for ACE-Is and ARBs (Table 2). While maintaining the present method of reimbursement (ie. reimbursement in two separate groups), the yearly reimbursement level is estimated at 177.3 mln PLN and 223.9 mln respectively for ACE-Is and ARBs, which in total amounts to 401.2 mln PLN. Therefore the average payer cost of one ACE-I package is 2.35 PLN and 10.85 for and ARBs package - 4.6 times difference in unit costs (Fig 2).

In the case of combining ACE-Is and ARBs in one limit group, the medicine which would meet 15% quantitive turnover calculated according to defined daily dose (DDD) for two groups of drugs would be Vivace 10 mg, 30 tabs. The official selling price of the medicine being a new basis for limit is PLN 16.09, with wholesale price PLN 17.06 and estimated retail price PLN 21.97. If ACE-Is and ARBs were combined in one limit group, the yearly reimbursement would amount to 167.0 mln PLN for ACE-Is and 79.4 mln PLN for ARBs, with the total reimbursement sum being 246.3 mln PLN. The unit reimbursement cost of ACE-Is and ARBs package is estimated at PLN 2.22 and 3.85, respectively.

The potential savings for the public payer in Poland resulting from the combining of ACE-Is and ARBs (group limits 44.0 and 45.0) in one group limit was assessed to be 155 mln PLN per year.

Table 2. Comparison of the two scenarios (existing-separate limit groups for ACE-Is and ARBs against proposed solution - combining the two limit groups into common group) in terms of estimated NHF spending in annual perspective

LIMITS GROUP IDENTIFIER	NAME OF THE LIMIT GROUP	NUMBER OF STANDARD PACKAGES SOLD WITHIN ONE YEAR [000]	EXISTING SCENARIO		PROPOSED SCENARIO	
			REIMBURSEMENT SPENDING IN ONE YEAR [000 PLN]	AVERAGE UNIT COST [PLN]	REIMBURSEMENT SPENDING IN ONE YEAR [000 PLN]	AVERAGE UNIT COST [PLN]
44.0	ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACE-IS)	75,305	177,276	2.35	166,950	2.22
45.0	ANGIOTENSIN RECEPTOR BLOCKERS (ARBS)	20,642	223,909	10.85	79,372	3.85
TOTAL		95,948	401,185		246,322	

Sources: authors' calculations

LIMITATIONS

The limitations identified in the present analysis are with regard to the adopted static market model in annual perspective. It concerns the aspects associated with proportional consumption of drugs, drug prices and the drugs indicated to be the basis for limitation in the studied limit groups.

The adopted assumption results from the lack of appropriate tool enabling to perform more precise simulation of modifications observed in the future. The announcement of the MoH is updated every two months. It is connected with high changeability of the market, frequent modifications of drugs prices and the limit base in therapeutic groups (eg. if the share of the inexpensive drugs rise on the market, the limit is decreasing) which cannot be precisely modelled.

DISSCUSSION

Given the limited funds assigned to guaranteed services in the NHF financial plan, rational decisions not only cost-effective but also clinically-efficient should be the only ones acceptable. This paper has stressed several essentials of great necessity of change in Poland.

The existing algorithm of RAAS-drugs grouping results in significant premium pricing of ARBs over ACE-Is. Public payer actual spending per one standard package is 4.6 times higher for ARBs than ACE-Is. Taking into account the similar effectiveness of ARBs and ACE-Is in BP reduction, proven additional clinical effects - reduction in mortality resulting from application of ACE-Is [29] and additional health benefits attributable to the usage of ACE-Is in selected groups of patients [26-30], higher acquisition costs of the ARBs is unreasonable. Proposed solution in the form of combining ACE-Is and ARBs into one limit group, could serve for elimination of the ARBs premium pricing, and thus rationalize public reimbursement spending.

Among the advantages of the proposed solution are immediate release of funds, independent from influencing the supply and demand-side, including eg. intervening in clinical decisions regarding the administration of medicines for patients by the physicians. Estimated savings for the public payer as a consequence of passing postulated administrative decision were assessed to be 155 mln PLN annually. This might be a conservative estimate taking into account the recently observed trends in the RAAS inhibitors prescription patterns (decrease of ACE-Is and increase of ARBs), especially after implementation of the Reimbursement Law which changed ARBs reimbursement level from 50% to 70%.

Proposed solution appears to be consistent with the mechanism of classifying drugs into limit groups defined under Reimbursement Act. Despite different INN, ACE-Is and ARBs might be considered to be clinical substitutes; having regard to similar pharmacodynamics and the therapeutic indications. As an example in the NICE reccomendation they have the same position in therapeutic schemes [12,38]. Moreover, due to the analogous pharmacodynamics, dual blockade of the RAAS by combining these two groups of drugs in the patients suffering from hypertension is not recommended [12,38]. Irrespective of existing favorable effects, use of dual treatment is unsuccessful in mortality reduction. Additionally, more frequently accruing hyperkalaemia, hypotension, and renal failure in comparison to monotherapy questions rationale of the dual therapy [40].

The findings of the latest meta-analyses which revealed the predominance of ACE-Is are reflected in the latest, updated worldwide recommendations. These indicate that ACE-Is are preferred to ARBs as therapeutic option. According to the recommendations of the Heart Foundation of 2012 [40], in patients suffering from coronary heart diseases (CHD) and those at high risk of recurrent events, prescribing ARBs should be constrained for patients intolerant to ACE-Is. It is also recommended that ACE-Is should be the first-line antihypertensives in patients with pre-existing CVD, diabetes, diabetes with proteinuria and hypertension [41]. The recommendations of the Heart Foundation of 2011 suggest prescribing ACE-Is for people with all grades of systolic heart failure, asymptomatic systolic LV dysfunction and as prevention in high risk peo-

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ple with a history of MI or other cardiovascular disease. ARBs are considered to be an alternative for people unable to tolerate ACE-Is [41]. In reference to the patient with stroke, recommendations of 2010 stated that application of ACE inhibitor singly or in combination with a diuretic is the most effective way of BP lowering [42].

According to the reimbursement decisions issued for the analysed products, they are subject to reimbursement from public funds only in case of prescription in approved therapeutic indications, ie. based on Section 4.1 of the Summary of Product Characteristics (SmPC). All approved therapeutic indication for ARBs are applicable for ACE-Is too. Among therapeutic indications not approved for ARBs but approved for ACE-Is we can find: myocardial infarction, secondary prevention after myocardial infarction, left ven-

tricular dysfunction after myocardial infarction, coronary artery disease, ischemic heart disease (with left ventricular dysfunction), renovascular hypertension and chronic kidney disease (Table 3).

In relation to European recommendations, tendency to favour ACE-Is in clinical decisions also can be noted in special patient populations:

- According to the NICE recommendations of 2010 it is advised to use ACE-Is as drugs of first choice with beta blockers in heart failure due to left ventricular systolic dysfunction. Recommendations suggest using ARBs as an alternative to ACE-Is for patients presenting side effects after application of ACE-Is [38].

-Under guidelines of the European Society of Cardiology (ESC) and European Society of Hyper-

*Table 3. Comparison of indications for
ACE-I and ARB reimbursed in Poland
[43]*

APPROVED THERAPEUTIC INDICATION FOR AT LEAST ONE CE	ACE-I:	ARB:
HYPERTENSION	YES	YES
HEART FAILURE	YES	YES
DIABETES T2	YES	YES
DIABETIC NEPHROPATHY	YES	YES
STROKE PREVENTION	YES	YES
CV EVENT PREVENTION IN PATIENTS WITH ESTABLISH ATHEROSCLEROSIS (ISCHEMIC HEART DISEASE, STROKE, PERIPHERAL ARTERY DISEASE)	YES	YES
CHRONIC KIDNEY DISEASE	YES	NO
CORONARY ARTERY DISEASE	YES	NO
ISCHEAMIC HEART DISEASE (WITH LEFT VENTRICULAR DISFUNCTION)	YES	NO
LEFT VENTRICURLAR DISFUNCTION AFTER MYOCARDIAL INFARCTION	YES	NO
MYOCARDIAL INFARCTION	YES	NO
SECONDARY PREVENTION AFTER MYOCARDIAL INFARCTION	YES	NO
RENOVASCULAR HYPERTENSION	YES	NO

tension of 2007, ACE-Is are preferred over ARBs in the treatment of hypertension and asymptomatic arteriosclerosis [9];

- Recommendations of the Polish Association of Hypertension of 2011 suggest usage of ARBs as an alternative when ACE-Is cannot be applied in the treatment of hypertension with the coexisting ischemic heart disease or heart failure [11];

- Recommendations of ESC as of 2006 stated that ARBs may be applied as an alternative in the stable ischemic heart disease when ACE-Is cannot be applied with additional indications to inhibition of RAAS system [43].

Many countries decided already to improve RAAS drugs prescribing efficiency to obtain positive results in savings. They could serve as good example for Polish authorities, as latest legislation changes make up a background for positive modifications.

Austria was one of the first countries which decided to limit the prescribing of more expensive ARBs to patients intolerant to ACE-Is. The decision was made in consequence of lack of relevant data demonstrating increased effectiveness of ARBs versus ACE-Is justifying request of manufacturers for premium pricing. As a result, utilization of ARBs in Austria in 2007 accounted for approximately 27% of all RAAS inhibitors and was significantly lower than in Sweden (43%) at the same time [2,4].

In Sweden, reassessment of the value of almost 2,000 drugs incorporated in the national reimbursement scheme in 2008 resulted in restrictions put on 26 substances including all ARBs and one ACE-Is [4,14]. The absence of documented health benefits to rationalize higher ARBs price if ACE-Is were well tolerated determined the decision to reimburse ARBs only for patients intolerant to ACE-Is or as a complement to ACE inhibitors and reimburse Monopril for patients with seriously decreased kidney function. Consequently, the number of patients treated with ARBs declined by 24% and increased for ACE-Is by 14%. Upward trend in expenditures for ARBs was stopped and accounted for 4% in 2008 compared

to the year 2006 and 2007 when 13% and 9% increase was noted, respectively [4,14].

In Canada, economic analysis, comparing direct cost in two scenarios with and without policy restrictions on the use of ARBs demonstrated potential budgetary savings following restricted access to ARBs to be 77 mln dollars per year [44].

In Croatia, a variety of measures aiming at moderating ARBs prescribing were implement-

ed. Restrictions on prescribing of ARBs in second-line therapy; to patients intolerant to ACE-Is and non-specific solutions, addressed to all drugs ie. academic detailing, monitoring of issued prescription, financial penalties belonged to the major, potentially most influential modifications. In consequence, reimbursed expenditures per defined daily dose (Exp/DDD) of ACE-Is and ARBs from 2001 to 2007 in Croatia decreased from Euro 0.34 to Euro 0.22, EXP/DDD of all ARBs, administered in single and combination therapies decreased from Euro 0.69 to Euro 0.21,EXP/DDD of all ACE-Is declined from 0.33 to 0.21 3.

The issue which needs further investigation in Poland is the proportion of ARBs consumption in comparison to ACE-Is. Referring to the NHF data, ARBs utilization is currently assessed to be about 22% in Poland (Table 1). From the perspective of clinical studies coughing, the predominant factor in charge of switching therapies, occurred in approximately 10% of patients to whom ACE-Is were prescribed. However, about 5 % of them discontinued usage of these drugs [45, 46]. Reduced mortality due to the usage of ACE-Is implies that they should be used as the medicines of first choice in the treatment of hypertension. The additional health benefit assessed in the absolute values to be 3.8 per 1,000 patient-year would simply result in saving of many human lives at a low costs.

The proposed policy might appear to have a financially negative impact on patients' spending. However, setting a common limit for both classes of RAAS inhibitors will eliminate the currently existing financial incentive promoting treatment with no added clinical benefit demonstrated. Thus it is expected that the structure of utilization will be adjusted accordingly (ie. increased use of ACE-Is), which could generate additional health gain for the patients. In order to secure current copayment levels for the relatively small group of patients intolerant to ACE-I treatment, one could consider to maintain a separate limit on ARBs in case of documented intolerance to ACE-Is, and a common limit otherwise. This approach would only slightly reduce the estimated savings presented in our analysis.

CONCLUSIONS

There is a strong need to improve RAAS inhibitors prescribing efficiency in Poland. Combining ACE-Is and ARBs into one common limit group could trigger an estimated 155 mln PLN annually, while maintaining at least the currently existing clinical effectiveness. The estimated savings constitute a significant part of the total public spending on drugs in Poland – 2.3% [47]. The proposed solution is consistent with the applicable regulations, Reimbursement Act in particular, and does not interfere with individual clinical decisions of the health professionals. However, in the face of quoted clinical data, further restrictions towards excessive ARBs prescription should be considered. The modifications implemented in drugs policy in the EU and non-EU countries could serve as a benchmark to rationalize usage and pricing of RAAS inhibitors. ■

[1] 30 DDDs of the reimbursed molecule

[2] 44.0 and 45.0 are references to the system of numbering the limit groups, used in the official Announcements of the Minister of Health

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Mapping the cancer-specific EORTC QLQ-BR23 onto the preference-based EuroQol-5D instrument

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ABSTRACT

Background: For cost-effectiveness analysis quality of life weights estimated by preference based utility measures are needed. In many studies however, quality of life is estimated by instruments that cannot provide utility measures. The aim of the study was to derive a function which can map the EORTC QLQ-BR23 questionnaire onto the EuroQol-5D (EQ-5D) questionnaire in breast cancer patients.

Methods: A cross sectional study was performed in Hungary in 615 breast cancer patients with different states of the disease. Quality of life was measured by both EORTC QLQ-BR23 and EuroQol-5D. Ordinary stepwise backward least-squares regression was used to develop a mapping function. Adjusted R2, Akaike's Information Criterion (AIC) and root mean square error (RMSE) were used to assess model performance. The robustness of the models was tested by 10-fold cross-validation and bootstrapping.

Results: The "best fitting" model contained 26 BR23 item levels as predictors selected in a stepwise backward procedure. However, this model showed considerable variability in the selection of predictors. A model, which performed only marginally worse than the "best fitting model" (adjusted R2 0.44, RMSE: 0.216, AIC:-85.8) and contained the BR23 items was much more stable, therefore we considered it as the best mapping function.

Conclusions: The expected value of EQ-5D can be reasonably well predicted based on the results of EORTC QLQ-BR23 in patients with breast cancer. Its applicability, however, for prediction on the individual level is limited.

BACKGROUND

Patient reported outcomes considered important by the researchers, physicians and patients, as well. Therefore, in many research projects not only outcome events, health states are assessed, but the quality of life of patients, too. Quality of life is an important measure in health economic analyses, too. When cost-effectiveness of interventions is compared, the incremental cost corresponding to incremental health gain is estimated. In these analyses health gain is measured by quality adjusted life years (QALYs). To obtain a valid estimate of QALY, one needs a preference

> THE PRIMARY RESULT OF THE SCALE IS THE DOMAIN SPECIFIC MEAN RAW SCORES. THESE RAW SCORES ARE THEN LINEARLY TRANSFORMED TO THE FINAL SCORES OF 0-100 SCALES.

based utility measure of quality of life. In many instances ample of data is available on the quality of life of patients with different health states, but usually measured by disease specific instruments which are not capable to provide utility measures. In these cases mapping should be considered as the second-best solution. The advantage of mapping is that it enables outcomes data collected in a study to be used in economic evaluation, even if the main source trial or study did not include a preference based measure [1]. The aim of this study was to develop a function which can map the EORTC QLQ-BR23 questionnaire onto the EuroQol-5D (EQ-5D) questionnaire [2,3].

METHODS

Participants, setting

The study was performed in 12 centers specialized in the care of cancer patients in Hungary. The data collection was completed in 11.2009-06.2010. Women were selected according to the treatment modalities. Quotas according to these modalities were given to the centers, and they enrolled the patients consecutively. The primary objective of the study was to estimate the quality of life of patients in different stages of breast cancer. This report presents the results related to the secondary objective, which was mapping EORTC QLQ-BR23 onto EQ-5D. The study was approved by the institutional ethical boards and by the National Ethical Board for Medical Research.

Instruments

All patients were asked to fill-in the EORTC QLQ-BR23 and the EQ-5D questionnaires. The questionnaires were self-administered, but help was provided by the study personals upon request. EQ-5D consists of the EQ-5D descriptive system and the EQ visual analogue scale [2]. We used the former for the analysis. QLQ-BR23 is the breast cancer supplement module of the EORTC QLQ-C30 questionnaire [3].

The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The respondent indicates which statement in each of the 5 dimensions describes her/his state the most appropriately. A total of 243 possible health states can be defined this way. Utility values were attached to these states in our analysis by the time trade-off (TTO) valuation technique from a UK study [4].

The QLQ-BR23 functional and symptom scores are constructed following EORTC scoring rules. The questionnaire contains 20 four-level questions in five multi-item domains: systemic therapy side effects, arm symptoms, breast symptoms, body image and sexual functioning; and in addition, three single items to assess sexual enjoyment, upset by hair loss and future perspective. The primary result of the scale is the domain specific mean raw scores. These raw scores are then linearly transformed to the final scores of 0-100 scales. Larger values correspond to better quality of life for functional domains (body image, future perspective, sexual functioning, sexual enjoyment), and worse quality of life for symptomatic domains (systemic therapy side effects, arm symptoms, breast symptoms, upset by hair loss) [5].

The questionnaire includes a few filter questions. If the answer to the filter question BR4 ("Have you lost any hair?") was 'Not at all', then the upset by hair loss score (BRHL) which is a single-item measure calculated from BR5 ("Were you upset by the loss of your hair?"), was set to 0, its minimum. This recoding was in accordance with the EORTC Scoring Manual.

We used the same technique for the sexual enjoyment score (BRSEE): the score was set to 0 if the filter item BR15 ("To what extent were you sexually active?") was "Not at all". The latter recoding is not mentioned in the EORTC Scoring Manual but the technique we used was a straightforward extension of the technique applied for the other screening question. In this way we got valid, interpretable hair loss and sexual enjoyment scores even if the patient had not lost her hair and was not sexually active.

An overall BR23 score (OBR23) was calculated as the sum of the 8 scores. In the calculation of OBR23 the symptom scores were calculated in a reversed way to have the same direction as the functional scores (greater value corresponds to better quality of life). The EORTC Scoring Manual does not recommend using such a global score to measure quality of life, however, from pure statistical considerations, it could be worth using the overall score as predictor in the first simplest regression model serving as a point of reference for more complex models.

Analysis

OLS regression models

The essence of our approach was to explore the relationship between the two instruments by ordinary least-squares (OLS) regression analyses.

We built four regression models using EORTC QLQ-BR23 questions aggregated to different extent as predictors. In each model the dependent variable was the EQ-5D index (the utility value). The individual EQ-5D dimensions were not attempted to be predicted separately, as previous studies showed it to be a less efficient or equally efficient procedure in terms of prediction [6,7].

The predictors of the models were refined step by step, always using a lower level of data aggregation. In the first model the predictor was the calculated QLQ-BR23 overall score. In the next model the predictors were the eight QLQ-BR23 scores. Next the predictors were the 23 QLQ-BR23 items (questions), separately. These models require the assumption that the predictors are measured by an interval scale, i.e. the same difference in a predictor has the same effect on the utility value regardless of the actual value of the predictor. For example in the model with the QLQ-BR23 scores as predictors if a score changes from 20 to 30 it has the same effect on the utility values as changing from 50 to 60 since the difference in the scores is 10. In the next more complex model the four levels of the items were entered as categorical predictors, not assuming this linear trend for the items of a question. Thus, in this case the number of the independent variables was three times the number of questions (because each item has four levels, one of which was the reference category).

If the full models fitted reasonably well, then we looked for more parsimonious models by running stepwise backward regression. We started with the full model and set the removal criterion to p= 0.1 and the re-entry criterion to p=0.05. This means that if a predictor was not significant at the level of 0.1 then it was removed from the model but could re-enter if its significance reached 0.05 after removing other predictors.

OLS regression assumptions were examined by the following methods:

1. VIF index was used to test collinearity. Some of the problematic (VIF>10) predictors were removed.
2. Nonlinearity in any of the predictors was checked with the help of augmented partial residual plots.
3. Normality assumption for regression residuals was checked with plotting the quantiles of the regression residuals against the quantiles of standard normal distribution (Q-Q plot).
4. The assumption of the homoscedasticity of the residuals was visually checked with plotting predicted values against standardized residuals since known statistical tests for homoscedasticity are very sensitive to violation of the normality assumption hence they cannot be used if normality assumption fails.

Assessment of goodness-of-fit

Goodness-of-fit and predictive power were measured with the root mean square error (RMSE), the adjusted R2 indices and Akaike's Information Criterion (AIC). AIC is an information-theoretical model selection criteria with the advantage of applicability to non-nested models. Lower AIC values indicate a better model. The range of the predicted EQ-5D values is also reported since OLS models struggle to produce EQ-5D indices that are negative or equal to 1.

Internal validity

Judging the internal validity of the results is of primary importance when predictive models are built. Since no external dataset is available, within-sample validation was carried out with the help of replication techniques. Two tests were conducted. Firstly, stability of the model coefficients is of interest since the relatively large number of predictors may lead to an overparametrised model. Stability, tendency-to-overfitting was tested using k-fold cross-validation.

Table 1. Characteristics of the study population

CHARACTERISTICS	N (%)
AGE (YEARS) 50 51-60 61-70 >70	144 (23.4) 188 (30.5) 177 (28.7) 107 (17.4)
T1 STAGE* T2 STAGE T3 STAGE T4 STAGE	152 (30.4) 196 (39.2) 50 (10.0) 102 (20.4)
LYMPH NODE METASTASIS	373 (61.6)
DISTANT METASTASIS	231 (38.1)
ADJUVANT CHEMOTHERAPY	76 (12.3)
ADJUVANT RADIOTHERAPY	85 (13.8)
ADJUVANT HORMONE THERAPY	93 (15.1)
ADJUVANT TARGETED THERAPY	83 (13.5)
PALLIATIVE CHEMOTHERAPY	87 (14.1)
PALLIATIVE RADIOTHERAPY	80 (13.0)
PALLIATIVE HORMONE THERAPY	93 (15.1)
PALLIATIVE TARGETED THERAPY	74 (12.0)

* only 500 patients had tumour (T) classification at the time of questioning

Secondly, stepwise backward selections were validated with refitting the stepwise-backward model in 200 independent bootstrap samples of the same size as the original model had, using simple random sampling with replacement. The validity, robustness of the selection is described in terms of what percent of the replications retrieve each of the predictors selected in the original model.

The whole analysis was conducted by the software package STATA 10.0 [8].

RESULTS

615 women with breast cancer participated in the study. Table 1 shows the major characteristics of the study population. Patients were roughly equally distributed in the treatment modalities defined study groups as planned. Seventy percent of the tumors were in stage T2 or in T1, approximately 60% had lymph node metastasis and 40% had distant metastasis.

Skip errors and missing data

55 patients should have skipped BR16 but answered it; their answers were recoded to missing. Similarly, 50 patients should have skipped BR5 but answered it; their answers were also recoded to missing.

The number of patients with missing data for one or more questions varied between 0.5% and 8% by score.

Table 2 presents the summary results of the calculated QLQ-BR23 scores and EQ-5D index. As figure 1 shows, the distribution of the EQ-5D index was heavily skewed with 22% of the indices equal to 1, 89% of the indices above 0.5 and 5% below 0.

Fulfilment of the model assumptions

Normal quantile plots seemed to indicate that normality assumption did not hold for any of the OLS models. Residual distributions had high kurtosis and were left-skewed basically due to the left-skewness of the EQ-5D distribution. Technically, violation of normality affects the confidence intervals of the parameter estimates and hence the validity of the hypothesis tests, but does not affect the parameter estimates themselves. The confidence intervals of the parameters, however, should be interpreted with

Table 2. Summary statistics of QLQ-BR23 scores and EQ-5D index

|	N	MEAN	SD	MEDIAN
BRBI (BODY IMAGE)	615	73.62	25.05	83.33
BRFU (FUTURE PERSPECTIVE)	613	42.03	33.01	33.33
BRSEF (SEXUAL FUNCTIONING)	536	13.77	21.48	0.00
BRSEE (SEXUAL ENJOYMENT)	481	13.65	25.92	0.00
BRST (SYSTEMATIC THERAPY SIDE EFFECTS)	614	22.97	16.10	19.05
BRBS (BREAST SYMPTOMS)	615	17.02	18.48	16.67
BRAS (ARM SYMPTOMS)	615	24.95	23.30	22.22
BRHL (UPSET BY HAIRLOSS)	595	19.16	32.29	0.00
OBR23 (OVERALL BR23 SCORE)	466	454.70	113.50	462.70
EQ-5D	614	0.70	0.29	0.73

SD: standard deviation
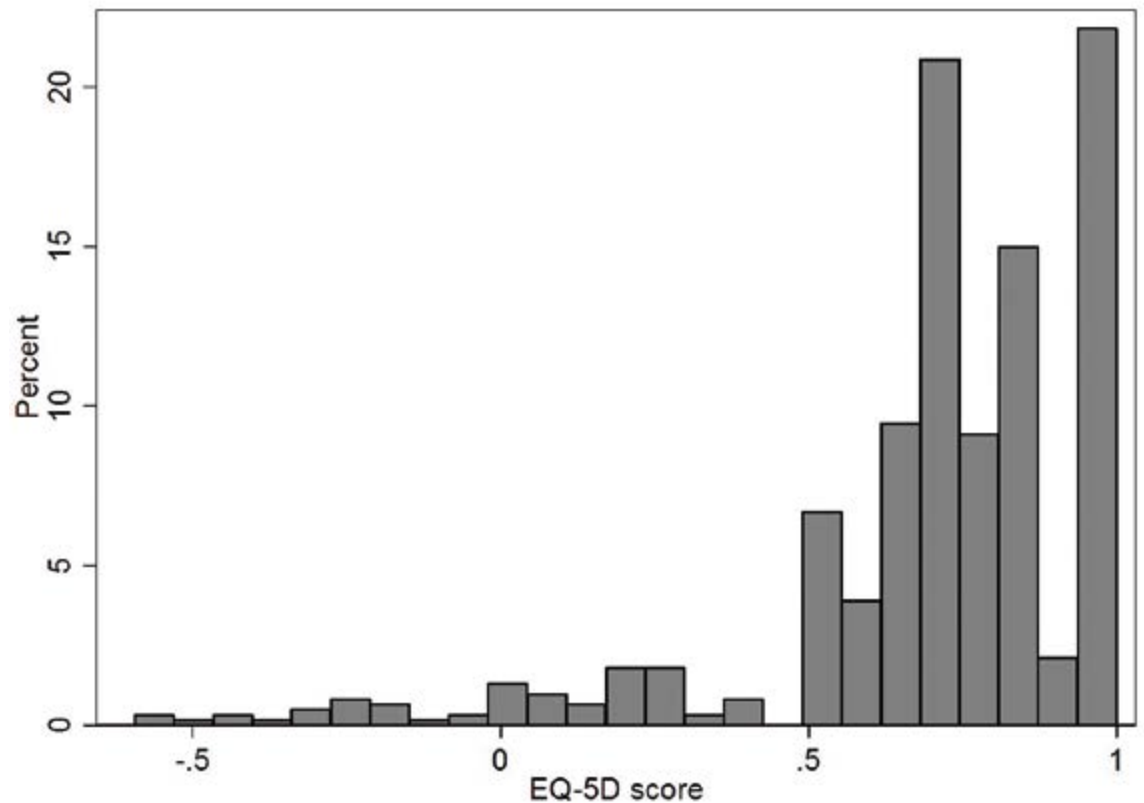
Figure 1. Histogram of EQ-5D values

caution. Also, residuals were proved to be heteroscedastic in each case, hence regression models and backward selection procedures were run with Huber-White sandwich estimate of the variance.

Overall QLQ-BR23 score (OBR23) regression

Because of missing QLQ-BR23 items, the overall OBR23 could be computed only in 466 patients. The mean EQ-5D value of these patients and of those with missing overall QLQ-BR23 was not significantly different. The overall EQ-5D index was missing in only 2 cases. The model used 465 observations.

The explanatory and predictive power of the model was very poor, with adjusted R2 of 0.195; RMSE of 0.262 and AIC of 75.75. The highest EQ-5D value could appear at almost any level of OBR23, and observations around the mean OBR23 score had very large variance of the EQ-5D value.

QLQ-BR23 component scores regression

Next we regressed EQ-5D on the 8 QLQ-BR23 scores separately. The model used 465 observations. The variance inflation factor (VIF) did not show high collinearity for any of the eight BR23 scores. The OLS regression still did not have very impressive goodness-of-fit statistics with adjusted R2, RMSE and AIC equal to 0.298, 0.245 and 19.528, respectively. Three out of eight scores (body image, sexual enjoyment and breast symptoms) were not significant at the 0.05 level. Symptom scores are expected to have a negative effect on EQ-5D, i.e. the smaller the score the better the quality of life, whereas functional scores are expected to have a positive effect on EQ-5D. Among the predictors upset by hair loss score and sexual enjoyment score had the reverse, wrong sign.

QLQ-BR23 component items regression

By regressing EQ-5D on all BR23 items separately, analysis of VIF suggested collinearity be-

tween BR15 and BR16 (Sexual Functioning and Sexual Enjoyment). We have chosen to drop BR16 considering that its derivation is slightly arbitrary (see definition of scores above). Overall, the model resulted in an improved goodness-of-fit with adjusted R2 of 0.4430, RMSE of 0.2157 and AIC of -85.837 (Table 3). A relatively large number of predictors were non-significant. The sign of the parameter estimates were as expected with the exception of BR04 ("Have you lost any hair?"), BR11 ("Did you find it difficult to look at yourself naked?") and BR18 ("Did you have a swollen arm or hand?").

The stepwise backward selection left 9 items in the model, namely: BR1, BR4, BR6, BR11, BR13, BR14, BR18, BR19, BR20. Fitting this model using 516 observations yields adjusted R2 equal to 0.4391 and RMSE equal to 0.2141. Compared to the full model, AIC dropped notably from -85.837 to -116.5737. Again, the same predictors (BR04, BR11 and BR18) had regression coefficients with the reverse sign than expected.

QLQ-BR23 component item levels regression

The previous model required the assumption of interval scale QLQ-BR23 items. The assumption could be eliminated by creating a dummy variable for each level of the items. After omitting BR16 because of collinearity with BR15 (see above), this approach resulted in 22×3 = 66 dummy predictors. Compared to the previous model, a large deterioration in goodness-of-fit could be observed, with an adjusted R2 of 0.4619, a RMSE of 0.21194 and an AIC of -62.83772. On the other hand, this was the first model to predict negative EQ-5D values.

Since no collinearity was detected between the dummies by VIF analysis, we fitted OLS regression with stepwise backward selection starting from the full model of 66 dummy predictors, out of which 26 predictors were left. The model was fitted using 492 observations and yielded largely improved goodness-of-fit with adjusted R2, RMSE and AIC of 0.4936, 0.20587 -132.7386, respectively.

Summary of model results

Table 4 summarizes the results of goodness-of-fit for the above models. In terms of explained variance, predictive fit and AIC, the model with BR23 item levels a predictors and stepwise selection performed the best. Predicted EQ-5D range should be judged comparing to the range of the observed data which is (-0.594; 1). Table 4 shows that only three models gave negative

Table 3. Coefficients of the full model with QLQ-BR23 component items as predictors

	COEFFICIENT	P-VALUE	95% CI	
BR01	-0.053	0.006	-0.090	-0.015
BR02	0.004	0.843	-0.033	0.040
BR03	-0.005	0.796	-0.042	0.032
BR04	0.013	0.416	-0.018	0.043
BR04	0.013	0.416	-0.018	0.043
BR05*	0.011	0.599	-0.029	0.050
BR06	-0.131	0.000	-0.169	-0.093
BR07	0.017	0.182	-0.008	0.041
BR08	-0.017	0.311	-0.050	0.016
BR09	-0.016	0.421	-0.054	0.023
BR10	0.030	0.158	-0.012	0.071
BBR11	0.025	0.120	-0.006	0.056
BR12	-0.024	0.119	-0.053	0.006
BR13	-0.041	0.001	-0.065	-0.016
BR14	0.089	0.001	0.038	0.140
BR15	-0.038	0.155	-0.091	0.015
BR16		?		
BR17	-0.021	0.233	-0.055	0.013
BR18	0.032	0.035	0.002	0.062
BR19	-0.063	0.001	-0.100	-0.025
BR20	-0.021	0.355	-0.066	0.024
BR21	0.014	0.552	-0.032	0.060
BR22	-0.010	0.605	-0.050	0.029
BR23	0.000	0.993	-0.035	0.034
CONSTANT	1.134	0.000	1.017	1.252

CI: confidence interval
* set to 1 if BR04 is 'Not at all'

Table 4. Summary results of goodness-of-fit

PREDICTOR(S)	SELECTION	N	ADJUSTED R^2	RMSE	AIC	PREDICTED EQ-5D RANGE
OVERALL BR23 SCORE	FULL	465	0.195	0.262	75.750	0.34; 1.00
BR23 SCORES	FULL	465	0.298	0.245	19.528	0.24; 1.15
BR23 ITEMS	FULL	470	0.443	0.216	-85.837	-0.02; 1.05
BR23 ITEMS	STEPWISE BACKWARD	516	0.439	0.214	-116.574	0.05; 1.06
BR23 ITEM LEVELS	FULL	470	0.462	0.212	-62.838	-0.21; 1.18
BR23 ITEM LEVELS	STEPWISE BACKWARD	492	0.494	0.206	-132.739	-0.21;1.21

RMSE: root mean squares error, AIC: Akaike's Information Criterion

predictions, but two of them predicted values significantly above 1, as well.

When deciding which model is the recommended mapping function, results of internal validity tests were also taken into account.

Internal validity, recommended mapping function

In order to test the stability of the stepwise backward selection processwhich yielded it, a bootstrap procedure with 200 replications was applied. 14 of the 26 predictors were retrieved less than 70% of the time, and 7 of them were retrieved less than 50% of the time.

The model with BR23 items as predictors and stepwise selection was the second best model according to AIC. Its bootstrap test showed a similar picture: 4 of the 9 predictors were retrieved less than 70% of the time, and 2 of them were retrieved less than 50% of the time.

The results above seem to indicate strong variability in the selection procedures. This hangs a question mark on the applicability of the two models with stepwise selection. The full models with BR23 items and with item levels as predictors were the best models among the remained ones. The latter was better according to AIC and RMSE, while adjusted R2 preferred the first one. Predictive validity of these two models was tested using 10-fold cross-validation. According to

the results, the average increase in RMSE by going from training set predictions to validation set predictions was of significant size (0.025) in case of the model with BR23 item levels as predictors, while it was very small (0.002) in case of the other model.

After all, we favour the full model with BR23 items as predictors for two reasons. Firstly, it performed only marginally worse than the "best fitting" model. Secondly, it was more robust than the others.

DISCUSSION

Our results showed that the expected value of a preference based quality of life measure (EQ-5D) can be reasonably well predicted based on the results of a disease specific quality of life instrument (EORTC QLQ-BR23) in patients with breast cancer. Disease specific instruments generally have the advantage that they are tailored to those aspects of quality of life that are mostly affected by the specific disease, thus they are usually more sensitive to changes in quality of life of patients with the specific disease than the generic instruments. Therefore, these questionnaires are widely used in studies on outcomes in patients with a specific disease. With the use of the mapping function developed in this study it is possible to translate the results of existing and future studies in which the QLQ-BR23 questionnaire is used to the utility scale of EQ-5D, and use these estimates in economic analyses.

There are many studies reporting mapping between EORTC QLQ-C30 onto EQ-5D; most of them applied OLS regression [9-12]. Concerning the heavily skewed sample distribution of EQ-5D, the same pattern was reported by Crott and Briggs in a sample of female patients with locally advanced breast cancer with good baseline health status. The ceiling effect (skewness toward 1 /perfect health/) and the lack of data from the lower region of the scale (below zero) of EQ-5D is often problematic when building a mapping model regressing EQ-5D overall score on any non-preference based instruments [9]. Therefore, the predictive power of the mapping models can be characterized by how much they are capable of giving predicted scores equalling 1 or below 0. Our recommended function performed well in this respect. Nevertheless, OLS has limitations in general to give good predictions in the extreme regions when the outcome variable is so much skewed as EQ-5D index is. A potential statistical alternative could be censored least absolute deviations (CLAD) regression, which has not been widely applied, but showed a better performance than OLS in a study of mapping SF-12 onto EQ-5D [13]. However, it is not self-evident that CLAD performs better than OLS when a disease specific instrument is mapped onto EQ-5D. In a recent publication OLS performed better than CLAD in mapping Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) onto EQ-5D [14]. A study was published recently, in which EORTC QLQ-30 and EORTC QLQ-BR23 questionnaires were mapped onto EQ-5D [15]. EORTC-30 performed better than EORTC QLQ-BR23. In our view, the results of this study need to be interpreted cautiously, because the authors used only the component scores but not the component items as predictors. Our analysis showed that a mapping function with the component items as independent variables had a much better performance.

Although we tested the robustness of our results by internal validation, it would be a particular interest to externally test the validation of the proposed function in a different series of breast cancer patients before the function is actually used to estimate utility values for economic analysis.

Our study has some limitations. The relatively large mean squares error and low R2 statistics indicate that the model cannot be used to predict EQ-5D index of an individualpatient, just to predict the expected value of a group of patients based on their QLQ-BR23 results. This is generally true for any mapping function, nevertheless in quite a few mapping studies with other instruments higher explained variance was achieved [9].

We used only the specific QLQ-BR23 questionnaire without the general QLQ-C30 questionnaire. BR23 focuses on the specific aspects of breast cancer related to quality of life and does not directly assess the domains which are included in the EQ-5D. This already theoretically limits the possibility to map it onto EQ-5D. Nevertheless, our recommended model still maps QLQ-BR23 onto EQ-5D reasonably well, showing that the specific functional and symptomatic items of QLQ-BR23 largely correlate with the aspects of quality of life assessed by EQ-5D. The sign of all scores except for upset by hair loss and sexual enjoyment were consistent with EQ-5D in the model with scores as predictors. When interpreting this result, one needs to consider that if someone did not experience hair loss, or did not have an active sexual life, then the answer to the question about upset by hair loss and to the question about sexual enjoyment were set to their minimum value (i.e. persons with poor quality of life but not experiencing hair loss and not having active sexual life had a low value of the upset by hair loss and of the sexual enjoyment score). Nevertheless, the behaviour of some predictors (BR23 items) was inconsistent (have the opposite sign than the expected) in the recommended final model, too. These were BR04 ("Have you lost any hair?"), BR11 ("Did you find it difficult to look at yourself naked?") and BR18 ("Did you have a swollen arm or hand?").

We used UK tariff valuation of EQ-5D. Recent studies affirmed differences in health-related preferences between countries, indicating the necessity of the estimation of national tariffs [16, 17]. Unfortunately, Hungarian tariff values of EQ-5D are not available. Similarly, preferences of patients with breast cancer might differ by countries, which may restrict the applicability of the mapping function we developed.

CONCLUSIONS

We developed a mapping function of QLQ-BR23 onto EQ-5D which is capable to estimate the expected value of EQ-5D utility value in a group of patients with breast cancer conditional on the answers given to QLQ-BR23 questionnaire.

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Methodology and development of the Polish Dictionary of Quality of Life Terms

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ABSTRACT

Background: Lack of established Polish terminology is a serious limitation of the development of health-related quality of life (HRQoL) studies in Poland. Our goal is to suggest the best translations in order to create the Polish dictionary of QoL terms.

Methods: In February 2012, QoL Special Interest Group of ISPOR Poland Chapter took on the task of preparing Polish dictionary of HRQoL terms. The following steps were planned: (1) preparation of a list of target English-language terms, (2) preparation of a reference list of translations already used in Polish literature, (3) step-by-step translation of English terms by individual experts (4) analysis and approval of proposed translations by Expert Committee, (5) re-analysis of key terms, (6) preparation of pre-final dictionary, (7) reviews by Review Committee, (8) preparation and publication of the final version. Expert Committee was comprised of seven Polish investigators with vast experience in the field of HRQoL studies. Review Committee was formed by three authorities in the field of psychometrics, statistics and epidemiology.

Results: Until June 2013, there were 13 meetings of Expert Committee: three focused on the development of methodology and ten - on analysis and approval of proposed translations. Initially, we identified 1640 English terms from different sources. After removal of duplicates, final English list comprised of 1314 terms. Pre-final version of vocabulary, ready for peer-review, consists of 1051 Polish translations.

Conclusions: We anticipate, that dictionary prepared by the ISPOR Poland Chapter will support practical usage of patient HRQoL in Poland.

INTRODUCTION

A development of a new field of science is generally supported by the publication of dictionaries in order to standardize and popularize professional vocabulary. For example, the development of pharmacoeconomics in Poland was supported by two important publications: dictionary by Orlewska & Czech (2002) [1] and then, lexicon by Lis et al. (2009) [2]. In both prints, proposals of translations of selected quality of life and health state utility terms can be found, but the most of specific terms remains untranslated into Polish.

Lack of established Polish terminology is a serious limitation of the development of health-re-

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lated quality of life (HRQoL) studies in Poland. Our objective was to develop Polish dictionary of terms used in the HRQoL studies. In this paper we present the methodology of the translation process and preliminary results.

MATERIALS AND METHODS

In February 2012, Quality of Life Special Interest Group (QoL SIG) from ISPOR Poland Chapter (Polskie Towarzystwo Farmakoekonomiczne; PTFE) took on the task of preparing Polish dictionary of HRQoL terms. Fig. 1 presents an outline of the project. Eight steps were planned and will be described in details below.

Step 1: Preparation of a list of target English-language terms

First, the list of target English terms was prepared. It was based on following sources: popular English-language HRQoL textbooks [3,4], key words from papers published in leading peer-reviewed journals in the field, ISPOR guidelines concerning patient-reported outcomes, websites of generic HRQoL instruments (Table 1).

Step 2: Preparation of a reference list of translations typically used in Polish literature

The list of translations used in Polish literature was based on pharmacoeconomics [5,6,7,8,9] and psychology textbooks [10,11,12,13], available dictionaries [1,2,14], HRQoL papers published in Polish language, peer-reviewed journals and others [15]. The search was not targeted at any specific terms and the list was treated as a reference point in following steps of translation process.

Step 3: Translation of English terms

A list of English terms was divided among seven members of Expert Committee - Polish investigators with an experience in the field of HRQoL studies or measurement methods education – all of them, PTFE members. Individual English terms were translated by a member picked at random. Experts were obliged to follow the procedure: (1) to perform a targeted search of existing Polish translations of an English term (Google browser was used to identify available scientific publi-

Figure 1. Subsequent stages of a development of the Polish Dictionary of Quality of Life Terms

cations – papers, congress posters or presentations), (2) to refer to results of untargeted search of Polish quality of life terms, (3) to prepare a suggestion of up to three Polish translations, taking into account frequency of usage of a specific Polish translation and a general fit.

Step 4: Analysis and approval of proposed translations by an Expert Committee

Each proposed translation was presented by an author during meeting of an Expert Committee, with discussion over the rationale of translation choice. Experts either accepted the proposition or sought for another Polish term with a better fit.

There were several successive decisions made: (1) all terms will be presented in the singular, (2) expansions of questionnaires abbreviations will be presented in the annex to the dictionary, (3) dictionary will contain generic names of questionnaires in a few cases in which the Polish name is indisputably accepted and widely used (i.e. St. George's Respiratory Questionnaire / Kwestionariusz Szpitala Św. Jerzego).

Step 5: Re-analysis of key terms / Step 6: Preparation of pre-final dictionary

It was planned that key terms, in particular those which yet not had a functioning Polish translation, will be re-examined by the Expert Committee. Before submitting for a review, a list of all terms will be validated internally (in terms of internal cohesion) and externally (in relation to the reference list from untargeted search).

Step 7: Reviews by Review Committee

Review Committee will be formed by at least three authorities in the field of psychometrics, statistics and epidemiology, from outside the PTFE. In the case of lack of agreement, decisions will be made on the basis of consensus.

Step 8: Preparation and publication of the final version

The final version of the Polish Dictionary of Quality of Life terms will be published both in paper and electronic version and widely disseminated.

RESULTS

From February 2012, till June 2013, there were 13 meetings of the Expert Committee: three focused on the development of methodology and ten - on the analysis and approval of proposed translations. Initially, we identified 1640 English terms from different sources. After removal of duplicates, final English list comprised of 1314 terms. Pre-final version of vocabulary, ready for peer-review, consists of 1051 Polish translations.

DISCUSSION

A large number of quality of life terms have been functioning in the Polish language since years. The case is that, usually, there are many Polish equivalents for a single English term. It is a simple consequence of the lack of standardization in this area and the situation in which the Polish researchers are forced to search for Polish terms ad hoc. The project to develop English-Polish dictionary of quality of life terms is

Table 1. Sources of English-language terms to the Polish Dictionary of Quality of Life Terms

SOURCES	NUMBER OF IDENTIFIED TERMS
TEXTBOOKS:	
FAYERS P, HAYS R. ASSESSING QUALITY OF LIFE IN CLINICAL TRIALS (2005)	276
FAYERS P, MACHIN D. QUALITY OF LIFE: THE ASSESSMENT, ANALYSIS AND INTERPRETATION OF PATIENT-REPORTED OUTCOMES (2009)	640
QOL METHODOLOGICAL GUIDELINES ON ISPOR WEBSITE	230
KEY WORDS FROM PAPERS PUBLISHED IN LEADING JOURNALS IN THE FIELD:	
QUALITY OF LIFE RESEARCH (2010 - 2012)	618
VALUE IN HEALTH (2008 - 2012)	141
TERMS SPECIFIC FOR LEADING GENERIC QUESTIONNAIRES:	
SF-36 (HTTP://WWW.SF-36.ORG/)	33
EQ-5D (HTTP://WWW.EUROQOL.ORG/)	30

an attempt to clean up the area and introduce some standardization, by identifying Polish most commonly used and preferred terms. It is worth noting that, still, there is a group of English terms (eg. response shift), which do not have any Polish equivalents, and these concepts are the biggest challenge in the project. Time will tell whether the proposed Polish translations would be adopted among domestic researchers.

Adopted methodology of work on the dictionary has some limitations. In its intention, the dictionary is more democratic than based on the opinion of a single expert. The final decisions of the Expert Committee were made on the basis of the majority. In this way, the dictionary is a kind of a compromise position of many individuals - members of PTFE involved in QoL research and education, as well as researchers from outside the PTFE who created the Review Committee.

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Future steps in the work on the dictionary include a review by the Review Committee, final approval, publication and dissemination. We anticipate, that the dictionary won't meet all the identified needs of researchers. There is still no publication of a lexicon type, containing precise definitions of various concepts. Such a lexicon will be the next task of Polish ISPOR Chapter QoL SIG.

CONCLUSIONS

We anticipate, that dictionary prepared by the ISPOR Poland Chapter will support practical usage of health related quality of life outcomes in Poland.

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Polish Pharmacoeconomic Society activities review 2/2013

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ABSTRACT

Information about current activites at the Polish Pharmacoeconomical Society.

There has been a change to the composition of the Management Board. After the resignation of the Secretary (Anna Zawada) the function was given to one of the Board member, Marcin Czech.

The Sections continue working on their projects.

The Therapeutic Programs, Pharmaceutical Care and Pharmaceutical Law section (TPPCPL) continues working on costs assessment of the adverse events which could potentially be observed during treatment with products used in the Drug Programs.

The Health Related Quality of Life Section continues the work on the dictionary of QoL terminology. An abstract with the methodology described was accepted by ISPOR to be presented as a poster during the European Conference in Dublin.

It is important to mention the success of the Society which organized a Polish –Russian Pharmacoeconomical Forum in Moscow. It was a two-day Forum involving Polish and Russian experts from the pharmacoeconomical area and with participation of Polish and Russian clinical experts and also health authorities' representatives.

The first day was dedicated to pharmacoeconomics and reimbursement issues while the second day was devoted to drugs registration and market access.

During the Forum, Professor Karina Jahnz-Różyk (Former Polish ISPOR Chapter President) and prof. Pavel Vorobiev (President of Russian ISPOR Chapter) presented and discussed the cooperation between both countries in the area of pharmacoeconomics.

Professor Vorobiev discussed the role of pharmacoeconomics in Russia while the Polish experience from last 10 years was shared by dr Joanna Lis, current Polish ISPOR Chapter President.

Polish Ministry of Health representative, Director Artur Fałek, presented the Polish Drug Policy illustrating the way to obtain reimbursement of a new product in Poland. Russian Authorities were represented by Oleg Kulikov from Russian Health Commission who focused his lecture on the legal basis for health insurance in Russia.

The purely pharmacoeconomic topics such as indirect costs (Prof. Marcin Czech) and QALY challenges (L. Bezmelnitsina from Russian Pharmacoeconomical Society and dr Maciej Niewada

as President Elect from ISPOR Chapter Poland) were discussed. Dr Paluchowska presented the direct costs of drugs' induced skin adverse reactions treatment.

There were also some sessions dedicated to specific disease areas. Pharmacoeconomical analysis related to diabetes (Dir. A. Bykov), orphan drugs in mucoviscidosis treatment in Russia (L. Krasnova), biological treatment of psoriasis in Poland (prof. W. Owczarek) and chronic cardiac insufficiency treatment in Russia (F.Ageev) were presented.

Svetlana Zavidova, representing the Russian Association for Clinical Trials Organization, gave a lecture about clinical trials and drugs registration in Russia and Dr Leszek Borkowski, a former President of the Polish Drug Registration Agency, talked about drugs registration process in the European Union.

Pricing principles in Russia were presented by E.Telnova and HTA process in Russia by T. Nizhegorodce while the comparison between HTA in Russia and other European countries was done by M. Hołownia.

Currently the ISPOR Chapter Poland is working on preparation of the next International Conference of Polish ISPOR Chapter which will be held in Warsaw, 5-6 December 2013 and preparing for the Polish/Russian/Ukrainian Forum in Dublin. The Forum will take place during the 16th Annual European ISPOR Congress. It will be moderated by Dr Joanna Lis (ISPOR Poland Chapter President) and participants will discuss changes in drug policy decisions in Poland, Russia, and Ukraine with particular focus on the use of pharmacoeconomic principles in local drug policy decisions. Invited speakers are Prof. Karina Jahnz-Rozyk (Head of Department of Immunology & Clinical Allergology, Military Institute of Medicine, Warsaw, Poland), Prof. Pavel Vorobiev (President, ISPOR Russia Chapter) and Prof. Olha Zaliska (ISPOR Ukraine Chapter President). The speakers will describe how the pharmacoeconomic principles have been applied for effective formulary management, individual patient treatment, drug policy determination, and resource allocation. ∎

PROFESSOR VOROBIEV DISCUSSED THE ROLE OF PHARMACOECONOMICS IN RUSSIA WHILE THE POLISH EXPERIENCE FROM LAST 10 YEARS WAS SHARED BY DR JOANNA LIS, CURRENT POLISH ISPOR CHAPTER PRESIDENT.