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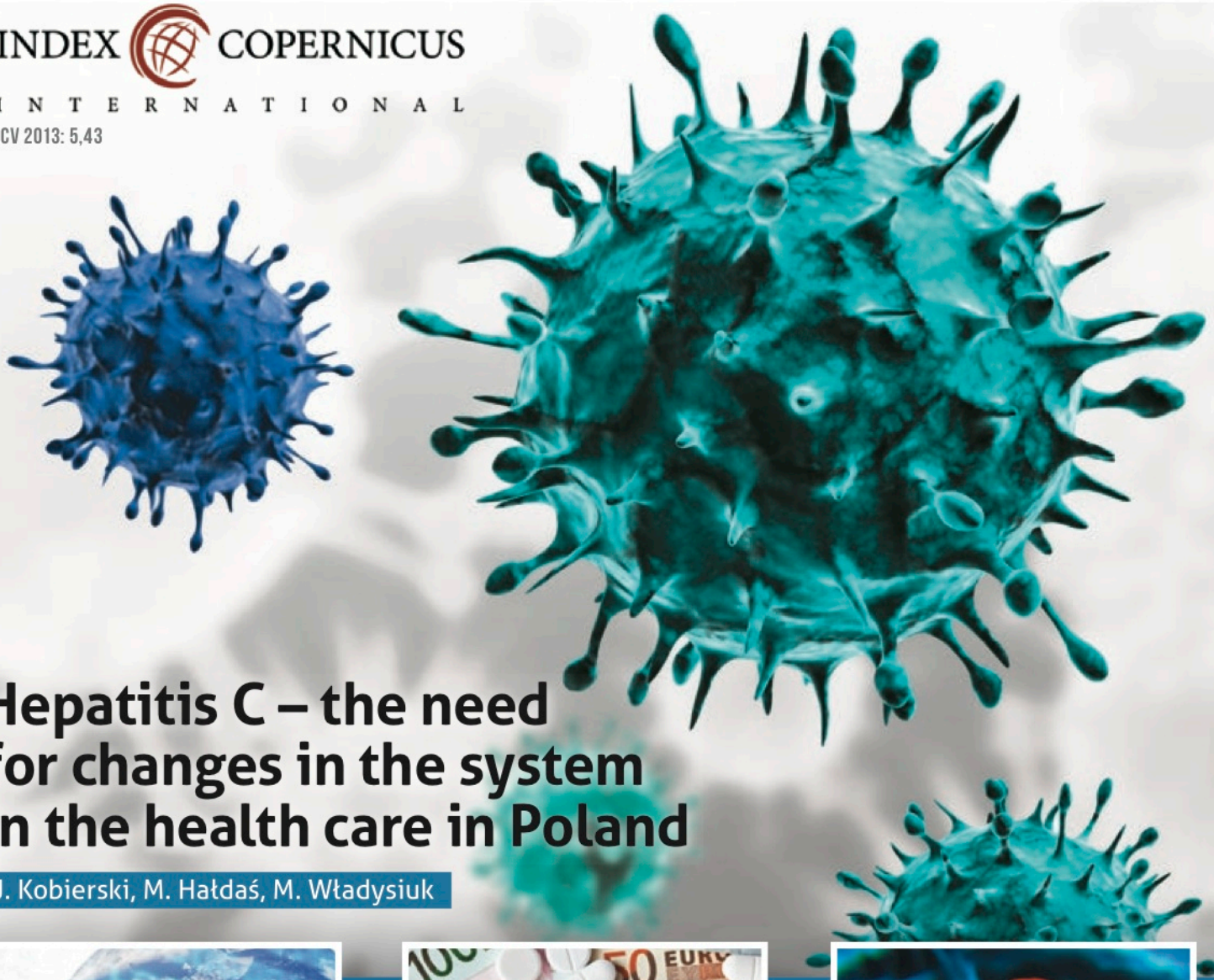

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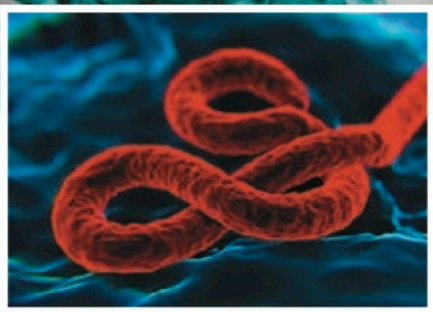

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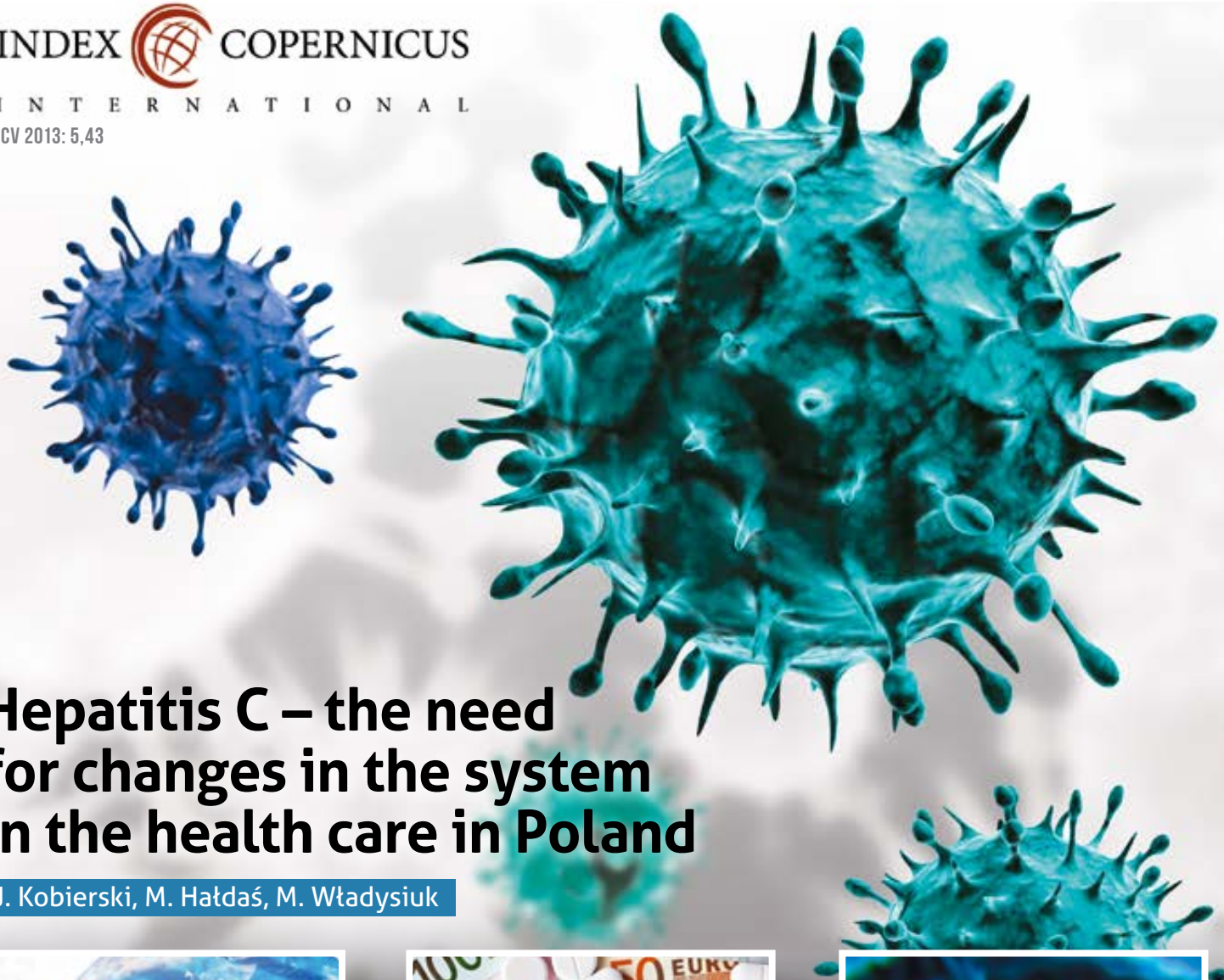

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# Polish Experience in Financial Management of Medicines Market by Public Payer

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*Keywords:*
financial management, reimbursement Act, reimbursing medicines, transparency Directive, new molecules, pharmaceutical market

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## ABSTRACT

**The most important features of medicines market in Poland are presented with the special reference to the terms and conditions of medicines reimbursement. A number of data on value and development of the pharmaceutical market, the value of reimbursement of medicines, changes in the numbers of open pharmacies, are presented also. The processes of decision making on reimbursing medicines in Poland before and after the Reimbursement Act are described in details. The implementation of the Act resulted in the increase of transparency of ways and methods for pricing of medicines, including them into the national health insurance system; the improved financial stability of public payer - gained by the precisely defined part of payer's budget, spent on medicines; patient-oriented approach in introducing new molecules into reimbursement system. The positive impact of the Reimbursement Act on the pharmaceutical market can be noted.**

## INTRODUCTION

The Medicines Reimbursement Act[1] was promulgated in 2011 to implement the Council Directive 89/105/EEC of Dec. 221th, 1988 ("Transparency Directive"), as well as to transform the reimbursement system in Poland in a way that provides the highest possible access to medicines, dietary foods for special medical purposes, and medical devices (hereinafter referred to as "refundable products") according to actual needs of public and financial capacities of public payer. Moreover, the relationships among the enterprises participating in market of refundable products should be clear and fully in accordance with the Transparency Directive. Special attention should be paid to transparency of ways and methods for pricing of products for human use and including them into the national health insurance system[1].

## ORGANIZATION OF MEDICINES MARKET IN POLAND

Continuous progress of medicine and health sciences is the challenge for governments. New technologies and innovations offer new therapeutic possibilities which enable health recovery and in consequence, in longer perspective, the decrease of cost of health care, and decrease of lack of productivity. The costs related to above mentioned changes in medical technologies are a remarkable portion of the budget.

The methods of financing of medicines in Poland have been changed across the history. In 1919-1933 health insurance funds (Kasy Chorych – literally "Sick Cashes") organized the Social Insurance apothecaries and pharmacies[1] providing the access of society to medicines. The Minister of Social Care authorized such apothecaries[2]. After World War II, up to 1997, all medicines and therapies were financed by the State budget, via local authorities (voivodes). In 1997 the 16 independent, regional Sick Cashes (plus 1 for uniformed services) were implemented again. Each Sick Cash was limited to the area of a region (voievodship).

CONTINUOUS PROGRESS OF MEDICINE AND HEALTH SCIENCES IS THE CHALLENGE FOR GOVERNMENTS. NEW TECHNOLOGIES AND INNOVATIONS OFFER NEW THERAPEUTIC POSSIBILITIES WHICH ENABLE HEALTH RECOVERY AND IN CONSEQUENCE, IN LONGER PERSPECTIVE, THE DECREASE OF COST OF HEALTH CARE, AND DECREASE OF LACK OF PRODUCTIVITY.

In 2003 the united National Health Fund was created to finance the whole health care. The National Health Fund is the public payer covering the costs of health services, according to the Act[1] and regulations issued by the Minister of Health[2]. The organization, financing and accounting of costs of health services are defined in details by the regulations of the President of National Health Fund[1]. There are 17 main areas of contracts for services[1] plus contracts for medicines: a) open reimbursement, b) chemotherapy, c) therapeutic programs, d) as a part of the hospitals. The contract is signed up after the open competitions (tenders). The pharmacies and providers (primary health care, family doctors, outpatient specialist clinic et al.) are the main sources of information indispensable for information circulation and accounting system[1,2,3,4]. Electronic medical documentation is widely used in the hospitals, so much more complete data on medicines consumption come to the payer from the hospital reports than from other sources. On the distribution level named "hospital pharmacy" also the separate information is collected on oncological drugs (chemotherapy) consumption; and on the special therapeutic programs i.e. on the types of medicines which are financed separately. According to Polish law "reimbursement" is understood as the return of part or total value of medicines.

The medicines market can be divided into two segments: OTC (over the counter) medicines and Rx medicines; and into three levels of distribution: manufacturer; wholesaler; and retail customer (community pharmacy, hospital pharmacy, or out-of-pharmacy customers). The continuous increase of value of pharmaceutical market was observed in Poland in 2002 – 2013 (Fig. 1).

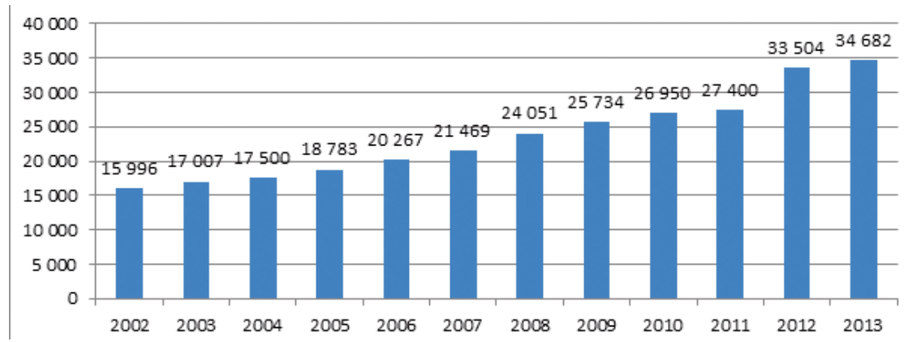


*Figure 1. The value of the pharmaceutical market in the period 2002-2013 (in thousands PLN)*
*Source: Own data based on Pharma Expert annual reports*

The mean annual increase of the pharmaceutical market as a whole (reimbursed medicines, full price medicines and OTC) was approx. 6.2%. The highest increase was observed in 2006 (12%) the lowest one – in 2011 (1.7%). Parallel to the increase of the market the number of community pharmacies was also increased; i.e. the places selling medicines which the public payer was obliged to reimburse full price of medicine or its part. (Fig. 2).

The sharp rise (+62%) of the number of pharmacies in 2006 was related to the end of the pro-

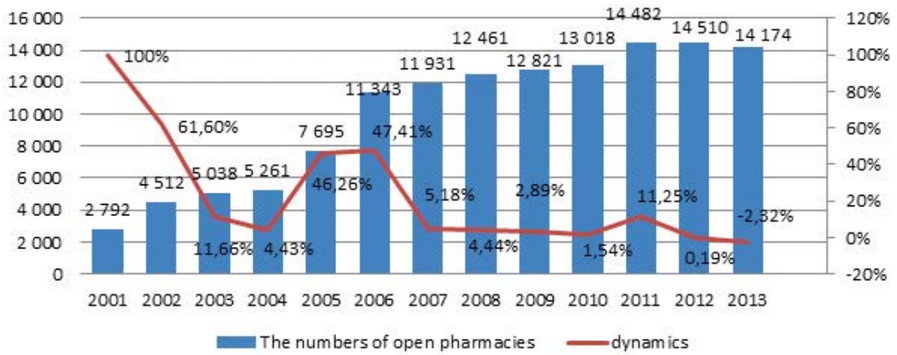


*Figure 2. The number of open pharmacies in 2001-2013*

cess of privatization of pharmacies formerly belonging to state enterprise CEFARM. That forced pharmacists to open new, own, private pharmacies.

The increased number of pharmacies (places selling medicines) was reflected in the increasing share of the cost of drugs in the payer's budget (Tab. 1) and in the positive dynamics of growth of costs in relation to the total budget of the payer.

Between 2004 and 2011 the reimbursement for chemotherapy drugs and therapeutic programs was not set out separately in the National Health Fund's financial plan but fully integrated into the hospital treatment founding.The dynamic changes in pharmaceutical market compared to financial resources in 2004 – 2013 disclosed that the increase of reimbursement of medicines was significantly greater than inflation rate (Tab.2).

*Table 1. The value of reimbursement of medicines in proportion to public payer's budget (in thousands PLN)*

| | 2004 r. | 2005 r. | 2006 r. | 2007 r. | 2008 r. | 2009 r. | 2010 r. | 2011 r. | 2012 r. | 2013 r. | Plan 2014 r. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Therapeutic programs | | | | | | | | | 1730897 | 2001718 | 2321826 |
| Chemotherapy | | | | | | | | | 468478 | 406491 | 516111 |
| Reimbursement (pharmacies) | 6118389 | 6323264 | 6695761 | 6727324 | 7367045 | 8238157 | 8546258 | 8831868 | 6863071 | 7183774 | 8063146 |
| Total reimbursement of medicines | 6118389 | 6323264 | 6695761 | 6727324 | 7367045 | 8238157 | 8546258 | 8831868 | 9062446 | 9591983 | 10901083 |
| Costs of health services | 30487361 | 33003941 | 35965840 | 40122980 | 49348746 | 55038582 | 56643910 | 58224321 | 59875547 | 62077983 | 63643735 |
| Total costs of NHF | 31089631 | 33534053 | 36709475 | 42257315 | 51657798 | 57632663 | 59325751 | 60923073 | 62672399 | 64775011 | 67318117 |
| Costs of reimbursement as % of health services costs | 20,07% | 19,16% | 18,62% | 16,77% | 14,93% | 14,97% | 15,09% | 15,17% | 15,14% | 15,45% | 17,13% |

*Source: NHF data*

*Table 2. The development of pharmaceutical market in Poland in 2004 - 2013*

| Year | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | Plan 2014 |
|---|---|---|---|---|---|---|---|---|---|---|
| Dynamics of budget | 7,86% | 9,47% | 15,11% | 22,25% | 11,57% | 2,94% | 2,69% | 2,87% | 3,35% | 3,93% |
| Dynamics of reimbursement | 3,35% | 5,89% | 0,47% | 9,51% | 11,82% | 3,74% | 3,34% | 2,61% | 5,84% | 13,65% |
| Dynamics of pharmacies' reimbursement | 3,35% | 5,89% | 0,47% | 9,51% | 11,82% | 3,74% | 3,34% | -22,29% | 4,67% | 12,24% |
| Inflation rate | 2,10% | 1,00% | 2,50% | 4,20% | 3,50% | 2,60% | 4,30% | 3,70% | 0,90% | |

*Source: Central Statistical Office and NHF data*

Financing of all health services fulfill the principle of social solidarity, i.e. all citizens pay the compulsory contribution for health insurance[1]. According to Social Insurance Office (ZUS) the levels of contribution stay as high as 9% of 2227.80 PLN (basic).

## MEDICINES FINANCING BY THE PUBLIC PAYER UP TO 2011

BETWEEN 2004 AND 2011 THE REIMBURSEMENT FOR CHEMOTHERAPY DRUGS AND THERAPEUTIC PROGRAMS WAS NOT SET OUT SEPARATELY IN THE NATIONAL HEALTH FUND'S FINANCIAL PLAN BUT FULLY INTEGRATED INTO THE HOSPITAL TREATMENT FOUNDING.

The medicines financing was based on the Minister of Health regulations on two lists of medicines: basic medicines and supplementary medicines. Basic medicines were reimbursed as the lump sum irrespectively from the price of a package , but up to the price limit established by the regulation. The supplementary medicines were reimbursed either up to 30% or 50% but only up to the price limit (reimbursement limit) established by the Ministry of Health. The limits should be updated 4 times a year (every quarter). In practice the limits were updated 1 – 2 times a year. The patient paid the difference between the cost of a medicine and reimbursement sum paid by the public payer. See the following example.

In case when the value of medicine gross price was equal to financing limit, the patient did not pay the difference between them. Financing limit was established on the basis of the lowest price of the medicine (or its equivalent – usually a ge-

| | |
|---|---|
| Price of a medicine (100 PLN) | 100 PLN |
| Financing limit | 80 PLN |
| Patient's fee (lump sum) | 100 PLN – 80 PLN +3,20 PLN = 23,20 PLN |
| Patient's fee 30% | 100 PLN-80 PLN + (80PLN *30%) =20 PLN +24 PLN =44 PLN |
| Patient's fee 50% | 100 PLN-80 PLN + (80PLN *50%) =20 PLN +40 PLN =60 PLN |

neric medicine). Reimbursement limit was bound to the financing limit so it was possible for Minister and public payer to finance new compounds without paying attention to their current market prices. Separation of amounts paid by the budget (payer) from the market development was essential for correct (right) economic development. Reimbursement decisions were made by the Minister of Health with assistance of Medicines Economy Team (see figure below).

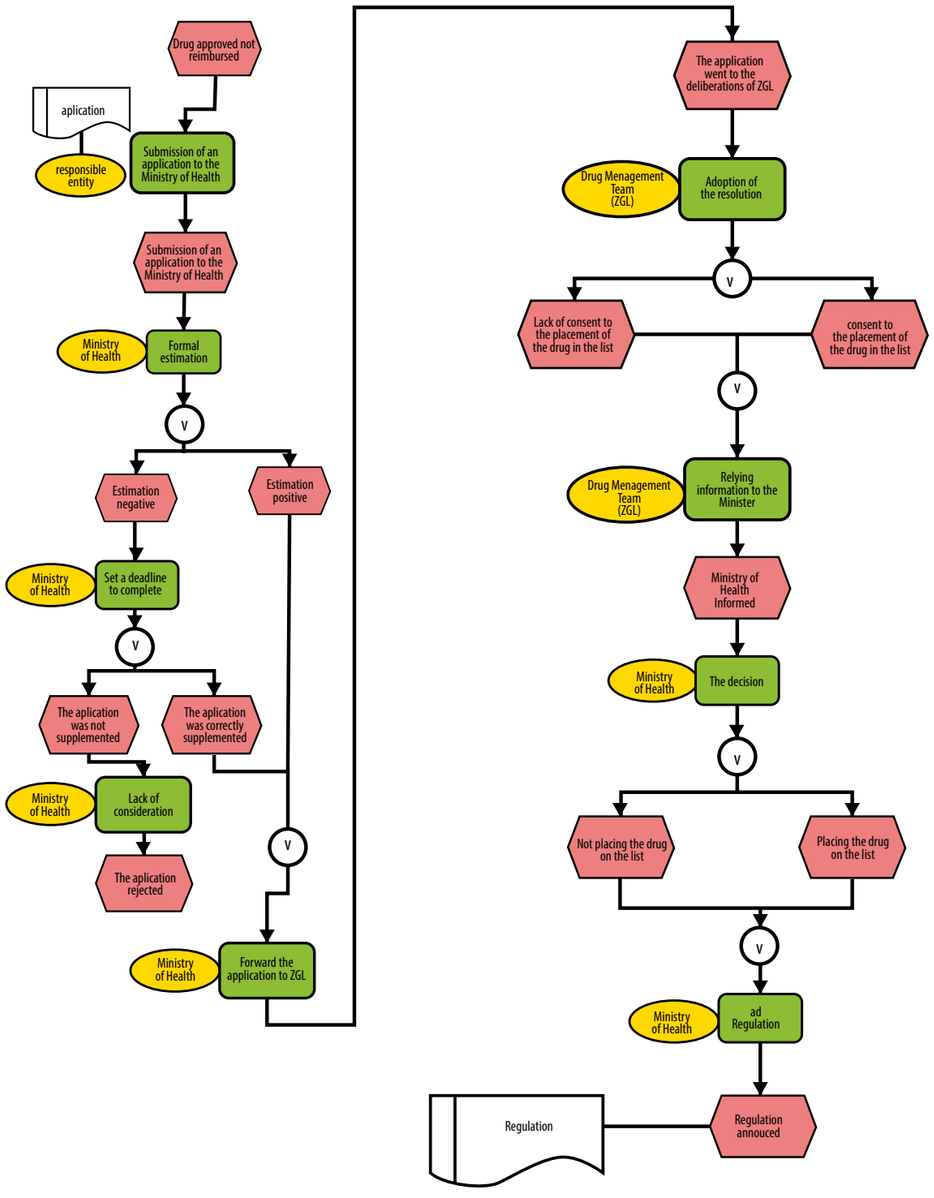


*Figure 3. EPC diagram of information flows in the process of pricing and establishing limits of reimbursement before 01.2012*[1]

On the basis of applications for reimbursement submitted by manufacturers the Team has prepared the opinion/recommendation to the Minister of Health. There was no time limitation for decision making by the Ministry. The decisions on reimbursement were made by the Minister, and published in relevant lists.

## SUMMING UP - FINANCING OF DRUGS BY THE PUBLIC PAYER FROM 01.2012 R TO 12.2013

After promulgation of Reimbursement Act the majority of organizational concepts was not changed. The decree of Minister of Health was the base for three areas of reimbursement: pharmacy reimbursement (community pharmacies); chemotherapy; and therapeutic programs. The changed legislation caused the more dynamic activities of pharmaceutical enterprises by making the administrative procedure more open; systematic updating of Minister Decrees on lists of reimbursed medicines, chemotherapy and therapeutic programs took place every 2 months. It should be mentioned here that during previous six years (since 01.2005 to 12.2011) Minister of Health issued 13 decrees containing above mentioned lists. That is the same number of decrees as issued in two years – 01.2012 to 12.2013. To the end of 2013 the number of reimbursed medicines increased from 2922 medicines (first list) to 3818 (list No XIII). 39 new molecules were introduced into the reimbursement system, including 14 molecules used in chemotherapy. 11 therapeutic programs were modified. The most important changes were as follows:

1. **Diabetology – reimbursement of long-acting insulin analogues (detemir, glargin).**
2. **Cardiology – 5 new medicines (ivabradine, rosuvastatin, ambrisentan, tadalafil rivaroxaban).**
3. **Hepatitis type C – 2 new medicines (boceprevir, telaprevir).**
4. **Sclerosis multiplex - 2 new medicines (fingolimod, natalizumab).**
5. **Epilepsy – new medicine of 3rd generation (retygabine) and for first line – levamicetam, lamotrygin).**
6. **Psoriasis – two therapies with biological medicines (ustekinumab, adalimumab).**
7. **Rheumatic diseases – 3 new biological compounds (certolizumab, toclizumab, denosumab).**
8. **Bronchial asthma – biological medicine omalizumab.**
9. **Food allergy – seven preparations for elimination diet (nutramigen AA, neocate advance, neocate LCP, bebilon pepti 1 DHA, bebilon pepti 2 DHA, nutramigen 1 LGG, nutramigen 2 LGG).**
10. **Nocturnal enuresis in children – 1 medicine (desmopressin).**
11. **Orphan diseases: Pompe's disease – therapy of adult patients; phenylketonuria (21 dietary preparations), Huntington's disease – one medicine (tetrabenazine).**
12. **New molecules reimbursed in oncological diseases:**

1. Prostate cancer – three medicines (abiraterone acetate, degarelix, zoledronic acid),
2. Breast cancer - one medicine of the second line (exemestane),
3. Ovarian cancer - one medicine (bevacizumab),
4. Malignant melanoma – one medicine (vemurafenib),
5. Pancreatic cancer – two medicines (everolimus, sunitynib),
6. Leukemia – four medicines (bendamustin, clofarabine, arsenic trioxide, azacitidine),
7. Lymphoma – one medicine (bendamustine),
8. Multiple myeloma – one medicine (lenalidomid),
9. Renal cell carcinoma – one medicine (pazopanib),
10. Head and neck carcinoma – one medicine (cetuximab),
11. Treatment of pain in cancer patients – one medicine (pregabaline).
12. Treatment of side effects in chemotherapy – antiemetic medicine (aprepitant)

900 new medicines were enlisted in the decrees of Minister of Health since Jan. 2012 to Dec. 2013. The total sum of patients' fees was also tending to decrease at this time. Additional changes in legislation were: the determination of time for making decision by Minister; and the establishment of Economic Commission consisting of experts, which evaluate the rationale for funding (reimbursing) the given technology by the public payer. The decrees are assessed by the public (social) consulting and regularly published on website of Ministry of Health. The information flows in the process of decision making on including medicines into reimbursement were also changed (Fig. 4).

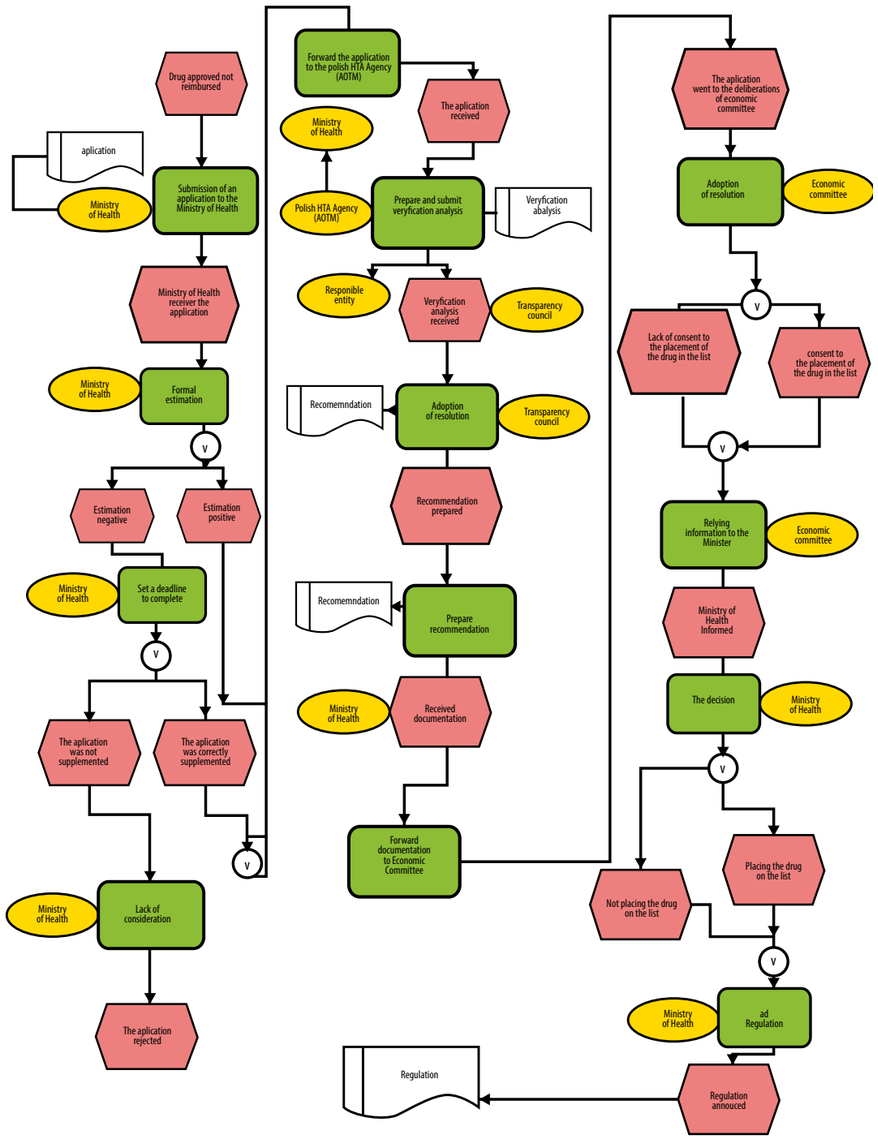


*Figure 4. EPC diagram of information flows in the process of pricing and establishing limits of reimbursement after 01.2012*

## CONCLUSIONS

The expected main objectives of Medicines Reimbursement Act were fully achieved. The main result was the increase of transparency in decision making during reimbursement process, also the increased flexibility and mobility of changes were noted. Additional effect of the Act was the improved financial stability of public payer - gained by the precisely defined part of payer's budget, spent on medicines. Another effect of the Act was the patient-friendly (patient-oriented) approach in introducing new molecules into reimbursement system. The changes in medicines market forced by the Act suggested the positive trend in diminishing the prices of medical technologies, especially those well-established and older ones. Currently the manufacturers are fully informed about terms and timing of considering their applications, and the administrative decision will be made.

In spite of relatively short time (2 years since Jan. 1st 2012) the positive impact of the Reimbursement Act on medicines market can be observed. ■

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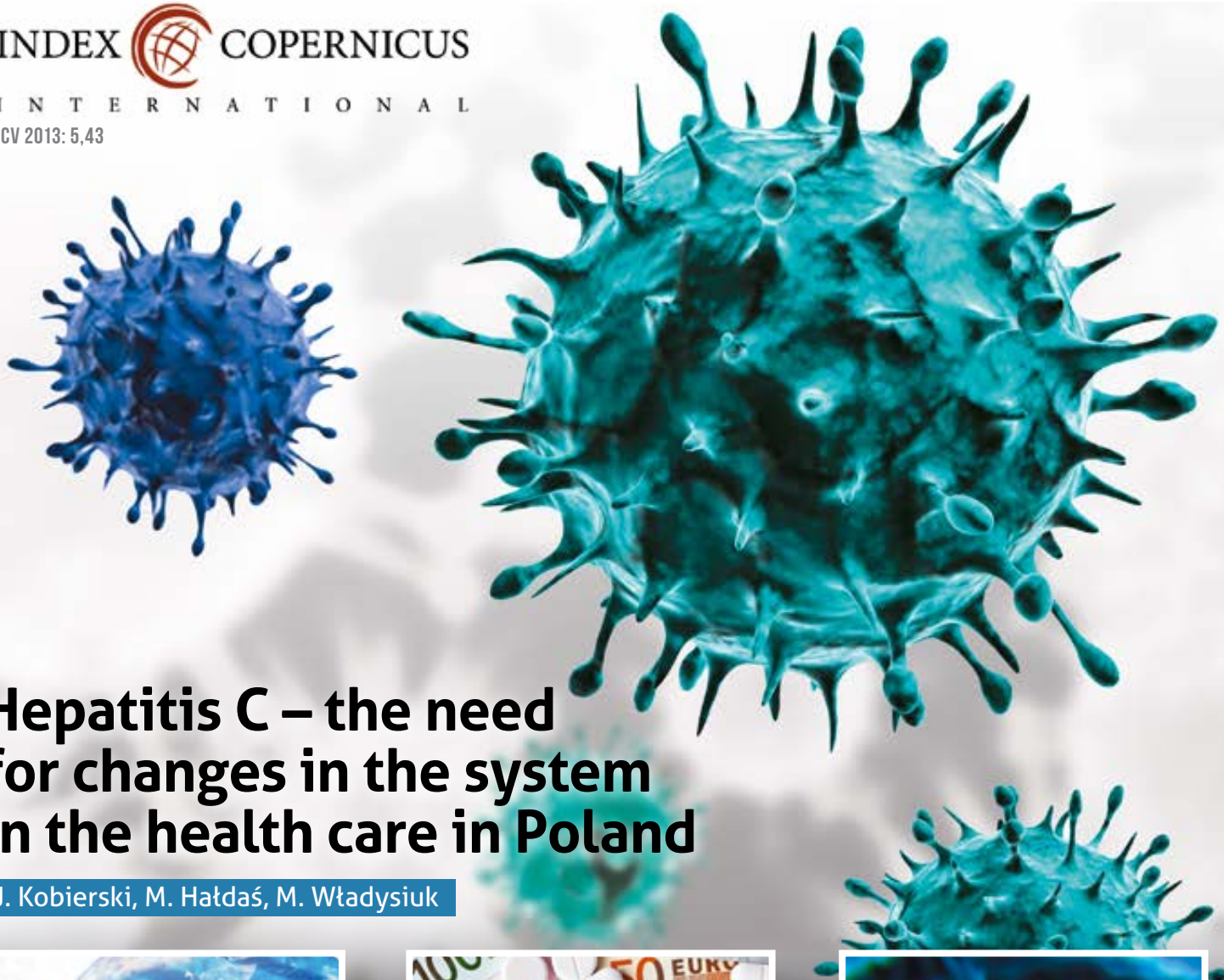

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T.Płusa

**Ebola viral hemorrhagic fever**

# The overview of Agency for Health Technology Assessment recommendations in 2012, and their impact on reimbursement decisions

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*Keywords:*
AHTAPol, Ministry of Health, health technology assessment, Poland, Polish Agency for Health Technology Assessment, reimbursement

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## ABSTRACT

**An introduction of the Reimbursement Act in Poland, which took effect on 1st January 2012, was one of the most important reforms implemented in the Polish healthcare system over the past few years, affecting significantly the pharmaceutical market and its stakeholders.**

***Objective:*** **The aim of this study was to analyse the market access of new, innovative therapies for the Polish patients, after the Reimbursement Act being in force for over one year.**

**The analysis was based on the Overview of the Minister of Health Orders, published on the Polish Agency for Health Technology Assessment (AHTAPol) website. The AHTAPol President and Council for Transparency's recommendations were divided into the positive and negative ones, and they were further divided into their corresponding reimbursement categories: the register of reimbursed medicines, drug programs and the chemotherapy catalogue. The issued recommendations were than compared with the final reimbursement decisions made by the Minister of Health.**

***Results:*** **In the analysed period AHTAPol issued 46 positive / positive subject to conditions recommendations of which: 31 (69%) concerned the medicines available in drug programs, 10 (22%) concerned the medicines available on prescription in pharmacy, and 4 (9%) concerned the products available in chemotherapy catalogue. Most medicines that had been positively recommended were reimbursed from public funds and made available for the Polish patients.**

***Conclusions:*** **Most positively recommended by AHTAPol technologies received positive reimbursement decisions. Receiving a negative recommendation did not imply the negative reimbursement decision.**



## INTRODUCTION

The introduction of the 12th May 2011 Reimbursement of Medicinal Products, Food Products for Particular Nutritional Purposes, and Medical Devices Act (Polish: Dz.U. 2011 nr 122 poz. 696), hereinafter referred to as the Reimbursement Act, which took effect on 1st January 2012, was one of the most important reforms implemented in the Polish healthcare system over the past few years. The Reimbursement Act significantly affected the medicine market parties, including: the payer, providers, beneficiaries, pharmaceutical companies, pharmaceutical wholesalers and pharmacies.

The introduction of Reimbursement Act entailed, among others, that the provisions of EU Transparency Directive are implemented in the Polish reimbursement laws, and the Polish reimbursement laws are adjusted as to correspond to the EU requirements. The objective of Reimbursement Act was both to ensure more transparency in pricing mechanisms and medicinal products reimbursement in Poland, and to rationalize the National Health Fund expenditure. The decision-makers announced greater control over the NHF budget, which would result in creating new funding opportunities for innovative products to be offered to the Polish patients.

As a result of the alterations introduced in 2012, the reimbursement application and assessment procedures have also changed. As stated in the Reimbursement Act, pharmaceutical company is the only entity eligible to apply for product reimbursement, as well as for the increase, decrease or any revision of its official selling price. Furthermore, pharmaceutical company may request to shorten the reimbursement decision expiry period. Applications for product reimbursement and for official selling price increase are one of the most extensive ones, both for the applying party and the institutions assessing them (such as the Ministry of Health and the Agency for Health Technology Assessment). Whether the applications are submitted for original drugs or the generic ones, they contain a set of the HTA analyses, which allows for the assessment of clinical benefits resulting from the use of a drug, as well as financial implications of such reimbursement, both for the payer and the patient[2].

> 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.

The Reimbursement Act defines precisely the reimbursement application scope, its assessment period, as well as each party's, i.e. the Ministry of Health or the Agency for Health Technology Assessment, contribution to its verification.

Pharmaceutical companies seeking reimbursement are required to submit pricing and reimbursement application to the Ministry of Health containing the following information:

- the description of the subject of the application;
- proof of the availability of the drug on the market at the time of the submission of the application;
- the undertaking to ensure continuity of supply, together with an indication of the annual volume of supplies in event of inclusion in the reimbursement;
- data identifying the drug (the name, form, method of administration, type of packaging;
- the authorisation number and a copy of the marketing authorisation decision,
- the EAN ID code or other code corresponding to the EAN code;
- the requested conditions for inclusion in the reimbursement, in particular the indications for which the drug is to be reimbursed; the proposed net sales price; the category of reimbursement availability, the level of payment; the risk-sharing instruments, the period of inclusion in the reimbursement; the draft description of the regimen programme (if applicable);
- the maximum and minimum net sales price of the drug in Poland during the year before the submission of the application;
- the maximum and minimum net sales price during the year before the submission of the application in the EU and EFTA countries in which the drug is reimbursed;
- the daily cost of therapy, average cost of standard therapy, duration of standard therapy separately for each indication;
- information on the expiry of patent protection, including the additional protection certificate and also the expiry of data exclusivity and market exclusivity period[1].

Pharmaceutical companies are obliged to deliver in reimbursement application a justification of the application containing budget impact analysis (BIA) detailing the overall cost to the National Health Found of reimbursing the drug[1].

For a drug which has no reimbursement counterpart in the given indication the following information is also required:

- a clinical analysis, prepared on the basis of a systematic review compared with other medical procedures which can possibly be used in the given clinical condition with respect to the indication for which the application was submitted;
- an economic analysis from the point of view of the entity obliged to finance the drug;
- analysis of the impact on the budget of the entity responsible for financing the drug;
- rationalisation analysis, presented if the analysis of the impact on the budget of the entity obliged to finance drugs with public funds indicates an increase in the cost of reimbursement; this analysis should provide detailing reimbursement solutions to free up public funds[1].
- It should be noted that all analyses must be up-to-date as of the date of application submission, in the scope of efficacy, safety, prices as well as the level and method of financing[1].

The Ministry of Health Minimal Requirements for HTA & the AHTAPol Guidelines in details describe requirements for HTA dossier framework.

According to article 6 Reimbursement Act, drugs are available in specific category of reimbursement. Pharmaceutical companies can apply for reimbursement in the specific category of reimbursement which is the appropriate approach for their drug.

We can distinguish four types of reimbursement:

- drug available in the pharmacy on prescription- the drug is added to the list of reimbursed drugs
- drugs used in a regimen program- kind of reimbursement for high-cost innovative drugs,
- drug used in chemotherapy;
- drug used within the framework of the provision of guaranteed benefits, other than those listed above[1].

In case of the applications submitted with a set of HTA analyses, it is the AHTAPol who is responsible for their assessment. As the advisory body for the Ministry of Health, the AHTAPol is to verify the submitted HTA reports, and issue recommendations for each health technology funding, based on whether the application was positively verified. Agency for Health Technology Assessment operates in accord with the tasks assigned to it by the Minister of Health. In accord with Article 31 c of the 27th August 2004 Act on the Healthcare Provisions and Services Financed from Public Funds (Polish: Dz.U. 2008Nr 164 poz. 1027 ze zm.), the Minister of Health obliges the AHTAPol President to issue recommendations, statements or opinions assessing healthcare provisions and services.

## THE AIM OF STUDY

The aim of this study is to analyze the innovative therapies availability for the Polish patients, after the Reimbursement Act being in force for over one year.

## METHODOLOGY

This analysis was made based on the Overview of Minister of Health Orders, published on the Agency for Health Technology Assessment website.

In 2012, the Agency for Health Technology Assessment (hereinafter AHTAPol) received 132 orders from the Minister of Health. 13 of them were suspended or withdrawn by the Minister of Health, therefore AHTAPol processed 119 orders demanded by the Minister of Health.

Most of these orders, i.e. 68, concerned reimbursement applications (out of this number, 5 applications were suspended). Therefore, there were 63 recommendations analyzed in this work. The AHTAPol President and the Transparency Council recommendations were then divided into the positive and negative ones, and they were further divided into their corresponding reimbursement categories: the list of reimbursed drugs, drug programs, the chemotherapy catalog. The final part of this analysis was to assess

and evaluate the issued recommendations, and relate these to the Minister of Health reimbursement decision, based on the 26th August 2013 Minister of Health Proclamation of the Register of Reimbursed Medicines, Food Products for Particular Nutritional Purposes, and Medical Devices, which came to force on 1st September 2013.

## RESULTS

The AHTAPol is responsible for assessing the reimbursement applications submitted by pharmaceuticals companies of new drugs, as well as price increase applications for existing reimbursed drugs.

AHTAPol assessment is conducted in three phases:

- initial assessment which result is the verification analysis of the clinical and economic data submitted with the reimbursement application. This part of the assessment is to ensure that the analysis were prepare in accordance to law and guidelines;
- opinion of the Transparency Council for the President of the AHTAPol Transparency Council is the independent body within the AHTAPol made up of medical experts, representatives of the Ministry of Health and the National Health Found who's are responsible for ensure clear and transparent process of the assessment and prepare the opinion for President of AHTAPol
- recommendation of the President of the AHTAPol prepare for the Minister of Health taking in to account the opinion of the Transparency Council (at a later stage of the process is used by the Economic Committee as part of the price negotiation with pharmaceuticals companies.).

As previously mentioned in 2012 AHTAPol assessed 63 orders which concerned reimbursement applications. Orders were related to 61 drugs, in the case of 2 products orders differed only EAN code.

***Positive/ conditional positive recommendation***

Based on the analyses conducted in this study, we can conclude that in 2012, AHTAPol issued 46 positive / conditional positive recommendations (Figure 1), of which:

- 32 (69%) concerned the medicines available in drug programs,
- 
- 10 (22%) concerned the medicines available on prescription in pharmacy,
- 
- 4 (9%) concerned the products available in chemotherapy catalog.

Out of 32 positive recommendations issued for the medicines to be reimbursed within drug programs, 18 were not conditioned in any way.

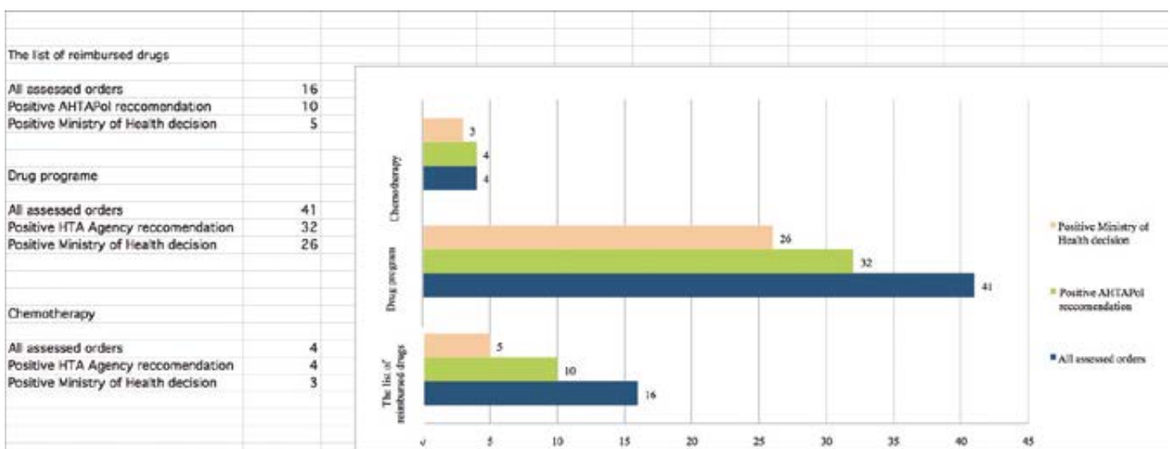


*Figure 1. Summary of Ministry of Health orders, AHTAPol positive recommendation and positive reimbursement decision*

After analyzing the remaining 14 recommendations, it was concluded that the major factor for them being granted conditioned recommendations was that the costs of therapy were too high, which translated into a medicine failing to achieve the acceptable cost-effectiveness. In most cases, the AHTAPol President recommended either extending or proposing a more suitable risk sharing schemes, as to achieve the acceptable cost-effectiveness. In almost all these cases, the Transparency Council statements were consistent with the AHTAPol President recommendations. It was only in case of conestat alfa that there was discrepancy noted. The AHTAPol President recommended this product, based on its evidenced effectiveness and its safety for use. In their opinion, conestat alfa seemed a cheaper and safer alternative to the product now in-use. On the contrary, in their statement, the Transparency Council decided it is unfounded to reimburse this medicine within the drug program, and suggested it is reimbursed subject to conditions within the register of reimbursed medicines[4].

There were 10 positive recommendations issued for the medicines available on prescription in pharmacies. Most of these positive recommendations (6 out of 10) were not subject to any condition for the liable party to meet. In 4 cases, it was noted in the course of this study, that the AHTAPol President did not accept the proposed risk sharing tool (e.g. in case of ivabradine, or recommended to introduce a more suitable one (e.g. (Nutramigen LGG; letrozole). Furthermore, in case of Nutramigen LGG, the AHTAPol President specified the population for which the medicine can be used, and suggested a different apportionment (payment level) than it was proposed by the applicant[5,6].

There were 4 positive recommendations issued for the medicines available in chemotherapy catalog. It was only in one case that the AHTAPol Presidents conditioned their decision on lowering the price of thalidomide to the price of 1 mg of thalidomide, a substance currently financed within the target import. Furthermore, in the course of clofarabine assessment, there was noted discrepancy in the Transparency Council and the AHTAPol President opinions. In their statement, the Transparency Council, declared it is unfounded to reimburse this medicine within the Register of Active Substances Used in Cancer Chemotherapy, while they nonetheless recommended the medicine to be reimbursed within the drug program. The Council also suggested the medicine producer to lower its price as to achieve the acceptable cost effectiveness. The AHTAPol President, on the contrary, did not condition their positive recommendation in any way, and suggested the medicine to be reimbursed in the same reimbursement availability category as proposed by the applicant[7,8].

### *Negative recommendation*

The analysis of 64 orders showed that AHTAPol issued 15 negative recommendations (Figure 2), of which:

- 9 (60%) concerned drugs available in drug programs,
- 6 (40%) concerned drugs available on prescription in pharmacies

Within one of the reimbursement availability categories in Poland, namely drug programs, the AHTAPol President issued 9 negative recommendations. In almost all these cases, the major factor for issuing a negative recommendation was that the clinical analysis was found insufficiently reliable. The AHTAPol President contested the reliability of research results to be assessed in terms of effectiveness and safety for use, hence, the medicine effectiveness and safety were found insufficient. In 5 out 9 cases, the assessed medicines were found cost-ineffective in relation to the limit set in the Reimbursement Act as the limit of cost effectiveness of medicines in Poland. In 2 cases, despite their negative recommendation, the AHTAPol President highlighted it is worthwhile to reimburse eltrombopag and alglucosidase alfa subject to three conditions: that there is a risk division tool introduced, that the drug program is properly monitored, and that the solutions proposed by the applicant are made part of the rationalization analysis[9,10]. The analysis of 6 negative recommendations issued for the products to be reimbursed within the open register showed that in each case, the medicine effectiveness was similar to the effectiveness of medicines already in use and reimbursed within the same register. Hence, there was no evidence that their technology was superior to the technology of medicines already reimbursed from public funds. Furthermore, in two cases (i.e. denosumab, etrabenazine), the applicant did not demonstrate sufficient cost-effectiveness as required by the cost-effectiveness limit mandatory in Poland[11,12]. The analysis of negative recommendations issued for the following products: Lercanidipini hydrochloridum, rotigotine, levetiracetam) showed also that these medicines would generate higher treatment costs than the medicines already reimbursed[13,14,15,16].

### *Ministry of Health decision*

Based on the 26th August 2013 Minister of Health Proclamation of the Register of Reimbursed Medicines, Food Products for Particular Nutritional Purposes, and Medical Devices, which came to force on 1st September 2013, in this study, there were positive and negative recommendations issued by the AHTAPol President, analyzed, along with their impact on final reimbursement decisions.

In Accordance to the Reimbursement Act Minister of Health makes reimbursement decision based on the: position of the Economic Commission, the recommendation of the President of the Agency; the clinical effectiveness and safety of the drug; the relationship between the risks and benefits associated with the treatment; cost ( e.g. versus existing alternative therapies), price competitiveness; the impact on the expenditures of the public payer and patients; public healthcare priorities and finally the level of the cost-effectiveness threshold which is defined as cost of achieving an additional year of life adjusted by quality (QALY) and it is set at an amount of three times the Gross Domestic Product per capita.

Most medicines that were positively recommended or recommended positively subject to some conditions are reimbursed from public funds, therefore available for the Polish patients. Only 12 products were denied reimbursement. In case of products applying to be reimbursed within drug program or chemotherapy catalog, the AHTAPol President's positive recommendation translated into the positive reimbursement decision for most of them.

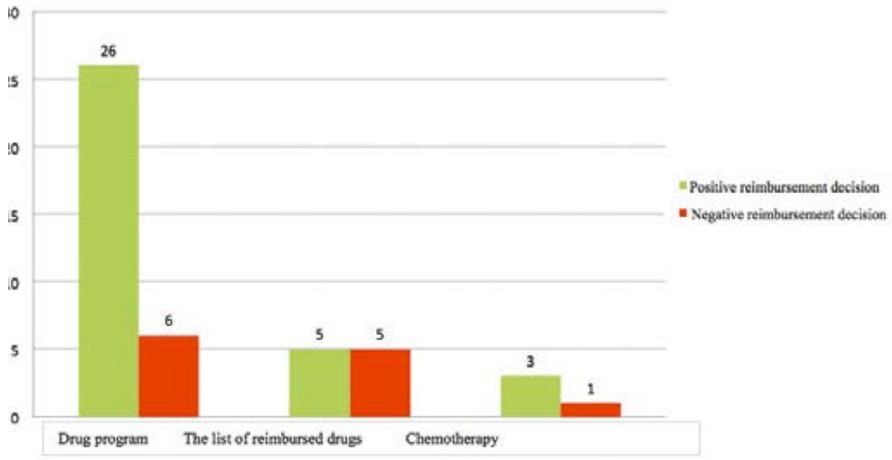


*Figure 2. The number of AHTAPol positive recommendations vs. the reimbursement decisions of the Minister of Health*

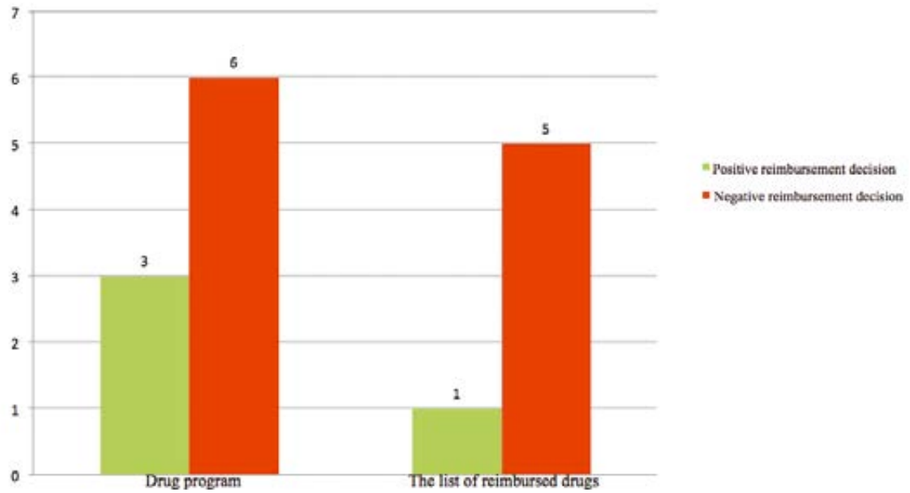


*Figure 3.The number of AHTAPol negative recommendations vs. the reimbursement decisions of the Minister of Health*

The following medicines were decided by the Minister of Health as eligible for reimbursement within drug programs: dasatinib, recommended for use in the chronic myelogenous leukemia treatment, palivizumab recommended for use in the RSV prophylaxis for children with bronchopulmonary dysplasia, and alglucosidase alfa recommended for use in the Pompe disease treatment[10,17,18].

In each recommendation for the above-mentioned products, there were objections to their economic aspects. Dasatinib and alglucosidase alpha turned out to be cost-ineffective, whereas palivizumab generated the rise in incremental expenditure for public payer. Furthermore, the AHTAPol President contested the effectiveness and safety of treatments using the above-mentioned medicines. It was observed that using dasatinib in the treatment category it was applying to, generates greater risk of side effects. The analyses for palivizumab did not demonstrate unequivocal clinical arguments to enlarge children's group to have the medicine recommended, whereas in case of alglucosidase alpha there was provided insufficient scientific evidence that would confirm its impact on the patients' life length and life quality. Despite these shortcomings, in case of alglucosidase alpha, the AHTAPol suggested that it is possible to reimburse this medicine under two conditions: that there are implemented the solutions proposed in the rationalization analysis, and that there is drawn an agreement for risk division. The fact that alglucosidase alpha was eventually decided eligible for reimbursement, indicates that the applicant agreed to these conditions in the course of their negotiations with the Economic Commission[17,18,19].

The Minister of Health also issued a positive reimbursement decision for tetrabenazine, used in the treatment of hyperkinetic motor disorders in Huntington's disease. This medicine was negatively recommended by the AHTAPol President due to the two factors: its high treatment costs (the medicine was cost-ineffective for the price proposed by the applicant), which may be negotiated in the course of negotiations with the Economic Commission though, and the effectiveness and safety of treatment. It was highlighted in the recommendation that this medicine does not affect the natural course of the disease, and causes a number of side effects.

WE HAVE IDENTIFIED TWO STUDIES ON THE SIMILAR SUBJECT. BOTH ANALYSES WERE CARRIED OUT FOR THE PERIOD PRIOR TO THE INTRODUCTION OF THE REIMBURSEMENT ACT.

Based on the above-demonstrated line of argumentation, it appears that the AHTAPol President negative recommendation does not necessarily indicate a negative reimbursement decision, which further evidences that the Agency for Health Technology Assessment is a mere advisory body for the Minister of Health, and the final reimbursement decisions are taken by the Economic Commission and the Minister of Health themselves.

## DISCUSSION

Having analysed the material, one can conclude that the most positively recommended technologies received positive reimbursement decisions. It is worth to emphasize that receiving a negative recommendation does not imply the negative reimbursement decision, which confirms that recommendation of the AHTAPol President is only one of many aspects that are taken into account by the Minister of Health reimbursement decision making.

We can observe a growing role of risk-sharing in decision-making processes, almost all assessed application contain risk sharing scheme proposal. An option to use risk sharing schemes gives pharmaceutical companies a chance to propose better financial conditions to public payer keeping at the same time price confidential.

Among the limitations of the study we can list the fact that only 2012 year was analyzed with a small number of orders (132) assessed by AHTAPol in 2012. To compare, the number of Ministry of Health orders was 352 in 2013 and 292 in 2014. For this reason it would be reasonable to prepare analysis for subsequent years. Analysing the opinions, recommendations, and verifications, that were partly blinded due to data confidentiality can be regarded as another limitation of this study.

We have identified two studies on the similar subject. Both analyses were carried out for the period prior to the introduction of the Reimbursement Act. The first review covered 59 HTA recommendations from September 2007 until October 2008, and the second one referred to all recommendation (285 positions) issued before January 2011[19,20]. In the first study 32 HTA evaluations received negative recommendation, 26 on the grounds of clinical evidence (insufficient clinical efficacy data and poor efficacy or safety was stressed) other 6 concerned non-clinical aspects such as unacceptable cost-effectiveness ratio (ICER), budget impact and risk of off-label use. 27 assessments received positive recommendations with different restrictions e.g. specific subpopulations, need for ICER improvement, lowering a price. ICER was above AHTAPoL threshold in 65% of positive recommendations and below the threshold in 44% of negative recommendations[19].

The aim of the second review was to answer whether ICER (cost per QALY) can be identified as a main criterion for AHTAPol decisions. Authors identified 177 positive and 108 negative recommendations. Clinical efficacy seemed to have the strongest impact on recommendations, but a positive influence on hard endpoints was also clearly reported in 15 negative recommendations and lack of such proven efficacy in 38 positive recommendations. Safety and cost-effectiveness aspects were more often recalled in negative than positive recommendations. According to the results of the study, for the analysed period, no threshold value of QALY as a clear indicator of a decision could be specified.

Based on these examples and our study we can conclude that decision making process regarding pricing and reimbursement is hardly predictable and is based on multi-dimensional process both before and after the Reimbursement Act was introduced.

## CONCLUSIONS

The aim of this study was to analyze the innovative therapies availability for the Polish patients, after the Reimbursement Act being in force for over one year. Based on the analyzed material, i.e. recommendations and reimbursement decisions, it appears that the Polish patients do not have their access to new technologies limited. Most of the positively recommended technologies received positive reimbursement decisions.

It is worth to emphasize that receiving a negative recommendation does not imply the negative reimbursement decision. On the one hand, this can be perceived as an example of insufficient transparency of the reimbursement process. On the other hand however, since the negative recommendation does not end the reimbursement process, this can be perceived as an opportunity for the Polish patients to have a wider access to innovative therapies. ■

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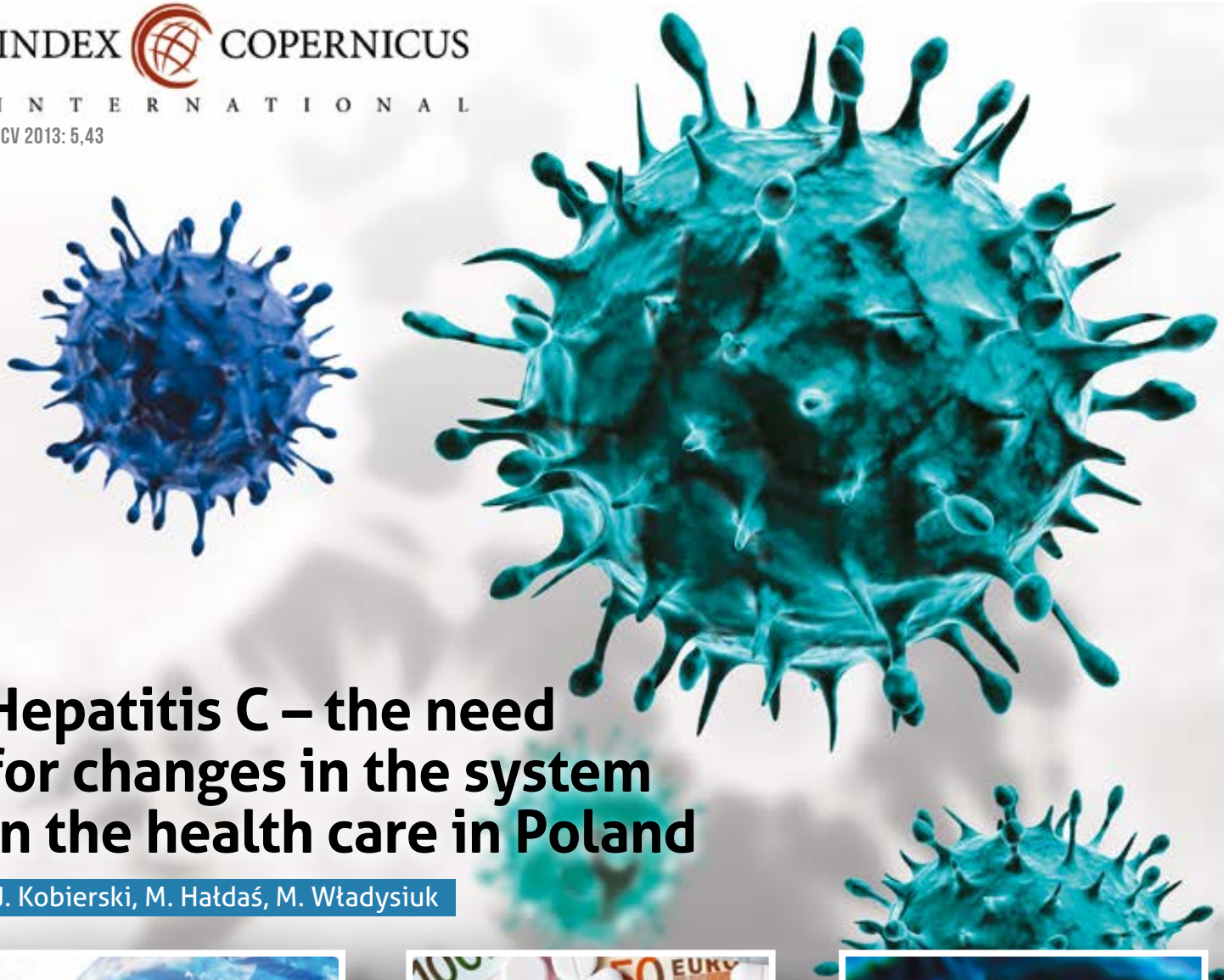

# Hepatitis C – the need for changes in the system in the health care in Poland

J. Kobierski, M. Hałdaś, M. Władysiuk

**Patients Registries - the role of the health system, new trends and hopes for Polish patients - 2nd JHPOR conference, Warsaw March 19th 2015**

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**Polish Experience in Financial Management of Medicines Market by Public Payer**

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**Ebola viral hemorrhagic fever**

# Ebola viral hemorrhagic fever

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*Keywords:*
clinical picture, Ebola virus, management, vaccines

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## ABSTRACT

**Pathogens causing transmissible viral hemorrhagic fevers are therefore classified internationally at the most dangerous hazard level. Most of them may be transmitted through the respiratory tract into human being. For this reason aerosol dissemination of viral pathogens may be considered as biological weapon. The clinical presentation of Ebola virus-infected patients is difficult to distinguish from other infections in the first steps of disease. A rash develops in 25–52% of patients in the first week and hemorrhagic manifestations are noted in some patients after a few days of illness. Tetherin/BST-2 has been identified as an effective cellular factor that prevents Ebola virus hemorrhagic fever as similarly the newly introduced Zmapp. Two proposals vaccines - cAd3-EboV (cAd3) produced by GlaxoSmithKline, and the US National Institute of Allergy and Infectious Diseases and rVSVΔG-EboV-GP (rVSV) produced by NewLink Genetics and Public Health Agency of Canada – were discussed in the last period as effective in prevention of Ebola virus hemorrhagic fever.**

Viral hemorrhagic fevers (VHFs) are a diverse group of illnesses characterized by fever and bleeding diathesis. VHFs are severe viral infections, which can cause haemorrhage, multi-organ failure and high case-fatality rates in humans.

Diseases are caused by lipid-enveloped single-standed RNA viruses from four viral families: Arenaviridae, Bunyaviridae, Flaviviridae, and Filoviridae[1]. They are unified by their potential to present as a severe febrile disease with hemorrhagic symptoms and accompanied by shock, and are capable of causing long-lasting and slow burning epidemics, which can interrupt the normal life, commerce or social structure of a community[2].

These viruses are spread in variety of ways – through blood or body fluid exposure. More of them are transmitted from animals to human by a vector, inhalation or ingestion of excretions or secretions. Most of them may be transmitted through the respiratory tract into human being. For this reason aerosol dissemination of viral pathogens may be considered as biological weapon[1].

Some of viruses are directly transmissible from human to human, and can cause outbreaks, or wider transmission, in non-endemic countries. Pathogens causing transmissible VHFs are therefore classified internationally at the most dangerous hazard level, requiring the highest level of laboratory containment (BSL-4 - biosafety level 4). They are grouped together with other dangerous pathogens, some of which may be deliberately released in acts of bioterrorism[3].



## FILOVIRIDAE – EBOLA (EBOV) AND MARBURG (MARV) VIRUSES

Filovirus infection results in a spectrum of illness, but most recognized infections present as severe acute febrile illness with bleeding into internal cavities and organs. These viruses are unique among human pathogens. They are filamentous, single-stranded, negative-sense RNA viruses. EBOV is genetically and phenotypically similar to MARV, but the viruses are distinct, with little or no natural crossimmunogenicity between them[2].

EBOV is a member of the family Filoviridae in the order Mononegavirales (MNV), and causes a lethal hemorrhagic fever in both humans and non-human primates. Five species of EBOV have been defined to date on the basis of genetic divergence: Zaireebolavirus (ZEBOV), Sudanebolavirus (SEBOV), TaiForestebolavirus (TFEBOV), Restonebolavirus (REBOV), and Bundibugyoebolavirus (BEBOV). ZEBOV, SEBOV, TFEBOV, and BEBOV cause clinical symptoms in humans and non-human primates, while REBOV causes disease only in non-human primates, and not in humans[4].

Electron microscopic studies have indicated that EBOV is morphologically pleomorphic. The genome is approximately 19 kb in length and encodes the viral proteins in the order NP–VP35–VP40–GP/sGP–VP30– VP24–L. The VP40 and VP24 proteins are viral matrix proteins and are associated with the virion envelope [5]. VP40 is the most abundant protein in the virion and plays a key role in virus assembly and budding as viral matrix protein[6].

Hypothesis of Ebola virus transmission at the human-animal interface is based upon observations in outbreaks countries. The virus maintains itself in fruit bats, which spread the virus during migration. Next, infected fruit bats enter in direct or indirect contact with other animals (gorillas, chimpanzees and other monkeys or mammals e.g. forest antelopes) and pass on the infection. Humans are infected either through direct contact with infected bats (rare event) or through contact with infected dead or sick animals found in the forest (more frequent). Secondary human-to-human transmission occurs through direct contact with the blood, secretion, organs or other body fluids of infected persons, especially after handling dead bodies (funerals)[3].

## CLINICAL PICTURE

The typical clinical presentation consists of acute onset of a non-specific febrile illness, including chills, headache, myalgia, nausea/vomiting, and diarrhea. A rash develops in 25–52% of patients in the first week and minor hemorrhagic manifestations are noted in some patients after a few days of illness (petechiae, ecchymoses, bleeding from puncture sites). In many instances, a biphasic pattern can occur, with a brief remission followed by a recurrence of fever and more severe late stage disease. In later stages of the severe forms of illness, patients demonstrate hypotension, shock, mucosal hemorrhages (typically from the gastrointestinal tract) and multi-organ system (particularly renal) failure[1]. Autopsies demonstrate multifocal necrosis. Severe cases are frequently fatal, with ultimate demise attributed to the systemic effects of a septic shock-like syndrome. No licensed or approved specific medical countermeasures exist, making supportive care the cornerstone of patient management[3].

## MANAGEMENT AND TREATMENT

The clinical presentation of filovirus-infected patients is difficult to distinguish from other infections, especially early in the clinical course.

Antibiotics were used to prevent and treat secondary bacterial infections. Acyclovir was used in one patient in the 1976 Zaire outbreak, and ribavirin was given to one patient in Russia. No other employments of antiviral drugs were documented. Analgesics, antipyretics, and antiemetic drugs were typically available and administered as needed. Unfortunately, many patients did not receive any further care. Other symptomatic treatments occasionally available included antidiarrheal drugs, sedatives, and antipsychotic drugs to reduce anxiety and agitation. Oral rehydration was typically preferred to administration of intravenous fluids, partially due to the perceived risk of transmission associated with the use of needles as well as resource constraints. Fluid and electrolyte monitoring and supplementation were universally applied to patients, but these measures were not routinely available during most outbreaks[7].

## ANTIBIOTICS

Tetherin/BST-2 (also known as CD317 or HM1.24) has been identified as an effective cellular factor that prevents human immunodeficiency virus (HIV)[8]. Tetherin/BST-2 also efficiently inhibits the egress of virus-like particles (VLPs) of Marburg virus and Lassa virus and retains VLPs on the cell surface. The sequestration of tetherin/BST-2 in the specific intracellular compartment may be one of the mechanisms of antagonism by Ebola GP. So far, the mechanism by which EBOV glucoprotein (GP) antagonizes tetherin/BST-2 remains unclear. Further investigations are required to understand the mechanism by which EBOV GP counteracts the antiviral function of tetherin/BST-2. It has been reported that high-level expression of tetherin/BST-2 inhibits ZEBOV production even in the presence of GP [9]. Tetherin/BST-2 has great potential for the development of novel antiviral therapeutic strategies against EBOV infection.

The newly introduced ZMapp preparation by Mapp Biopharmaceuticals Inc. is composed of three groups of monoclonal antibodies directed against Ebola virus, but only in relation to the Zaire subtype. It has not yet been fully approved by the FDA (Food and Drug Administration) and the EMA (European Medicine Agency), but it creates a real hope for patients[10,11].

## VACCINES

No specific treatment or vaccine is yet available for Ebola hemorrhagic fever. Several potential vaccines are being tested but it could be several years before any is available. A new drug therapy has shown some promise in laboratory studies and is currently being evaluated. Recently at a meeting in Geneva of 70 scientists, public health and the pharmaceutical industry discussed two proposals vaccines - cAd3-EboV (cAd3) product manufactured by GlaxoSmithKline, and the US National Institute of Allergy and Infectious Diseases (NIAID) and rVSVΔG-EboV-GP (rVSV) product NewLink Genetics and Public Health Agency of Canada. Both vaccines showed 100% efficacy in animal studies[12].

## SUPPORTIVE THERAPY

Various blood products, clotting factors, inhibitors of fibrinolysis (ε-aminocaproic acid) and regulators of coagulation were administered to counteract hemorrhage. Transfusion of blood components included whole blood, packed red blood cells, fresh frozen plasma, and platelets. Clotting factors and other regulators of coagulation administered included fibrinogen, and prothrombin, proconvertin, Stuart-factor and antihemophilic globulin B, and vitamin K. In contrast, anticoagulants (heparin) and rheologic agents (pentoxyfylline) were given in some patients to prevent thrombosis and disseminated intravascular coagulation[1,13].

Support for organ failure, including dialysis, hemofiltration, intubation, and mechanical ventilation was only available for a small number of patients in developed-country settings. ■

ANTIBIOTICS WERE USED TO PREVENT AND TREAT SECONDARY BACTERIAL INFECTIONS. ACYCLOVIR WAS USED IN ONE PATIENT IN THE 1976 ZAIRE OUTBREAK, AND RIBAVIRIN WAS GIVEN TO ONE PATIENT IN RUSSIA.

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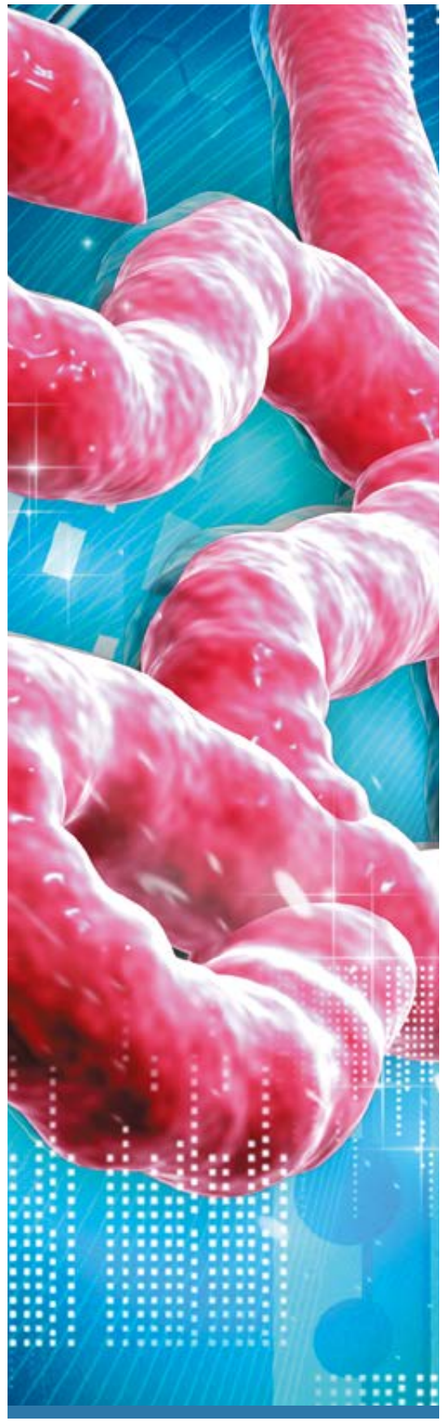

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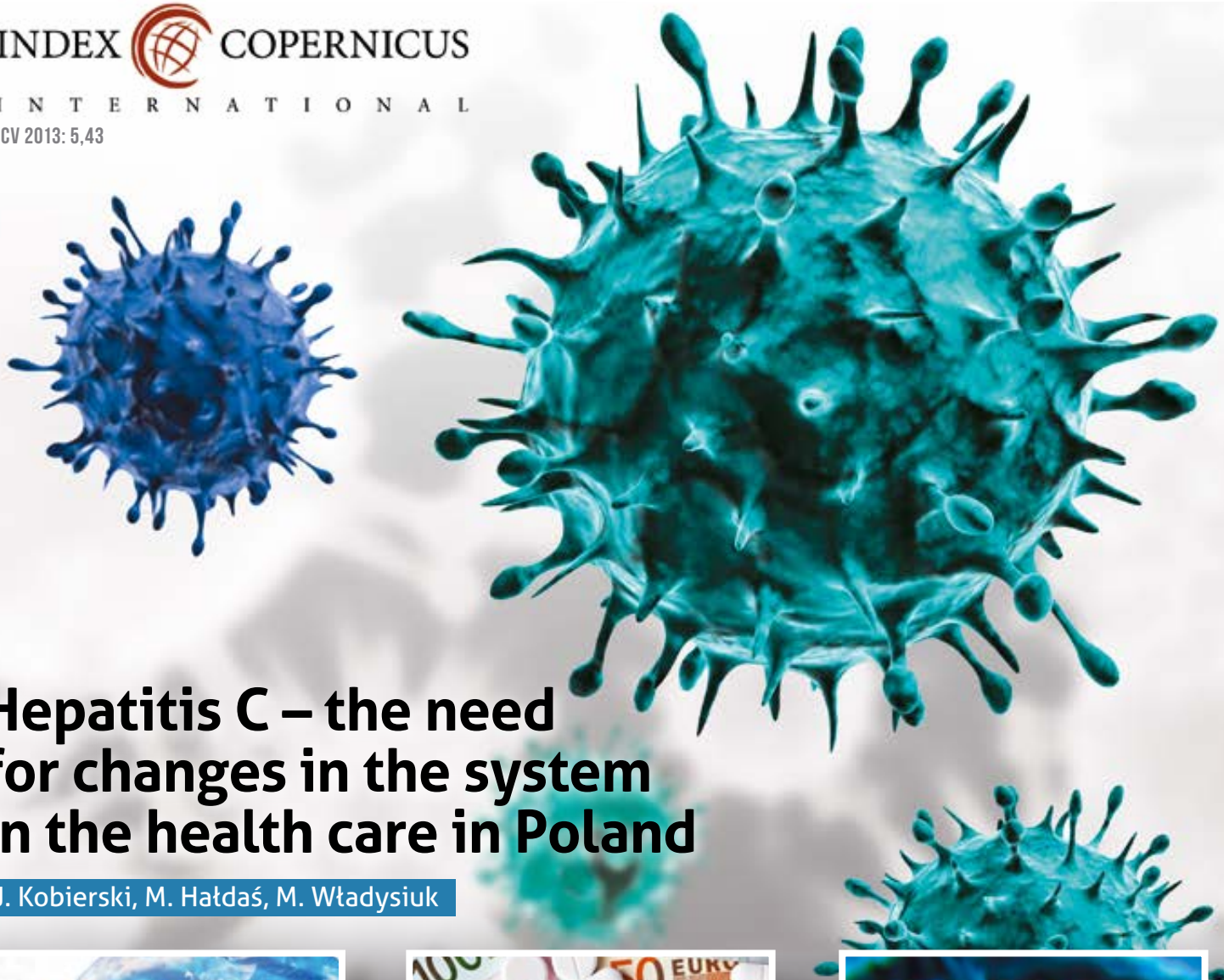

# Hepatitis C – the need for changes in the system in the health care in Poland

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# Hepatitis C – the implications and the need for change in the health care system in Poland

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## ABSTRACT

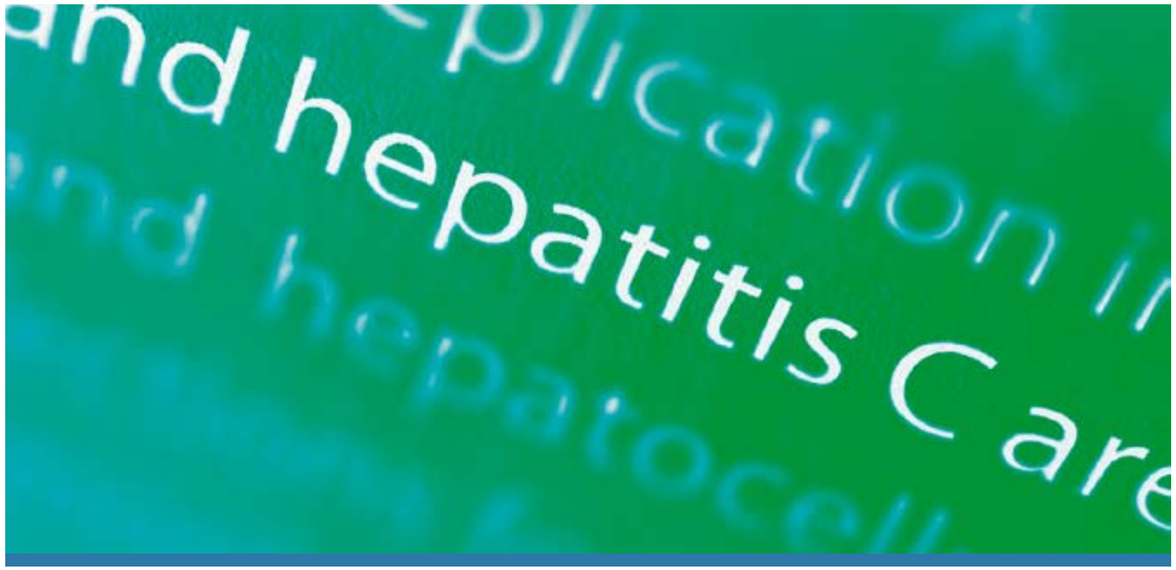
**Hepatitis C is a disease spreading across the world. It is estimated that more than 185 million people are potentially infected with HCV. Each year approximately 350 thousand people die of diseases resulting from HCV. In Poland about 231 thousand people are believed to be infected, with up to 85% of them unaware of their progressive illness. Hepatitis C leads to serious complications in the liver and, consequently, can lead to death. The disease generates appreciable costs associated with the treatment of the complications of HCV in the advanced stages of the disease as well as lost productivity. As there is no vaccine against HCV, hepatitis C treatment is the only way to eradicate the virus. This is now possible with new therapies. This article presents the burden of hepatitis C and its changing dynamics in the context of hepatitis B and HIV in Poland. The natural history, the costs generated by the disease, available current therapies and suggested ways forward are also discussed in the article.**

## INTRODUCTION

Hepatitis C is an infectious disease caused by the Hepatitis C Virus (HCV), which mainly affects the liver. In the first stage, there is progression of acute hepatitis with necrotic and inflammatory changes rapidly developing in the liver. Acute hepatitis C is asymptomatic in approximately 70-80% cases. Spontaneous elimination of HCV occurs in 14-46 % of patients, mainly in symptomatic patients[1]. If the virus is present in the body for longer than six months, the disease progresses into chronic hepatitis. Chronic hepatitis is characterized by multiple necrotic and inflammatory lesions, which are typically asymptomatic. This is the cause of serious complications in the liver and may lead to hepatocellular carcinoma and eventually to the death of the infected person if left untreated. It is estimated that approximately 85% of patients with HCV are unaware of their disease[2,3]. In these patients the destructive processes take place covertly resulting in patients being vulnerable to the serious complications of the disease and at the same time being a reservoir for the virus, allowing further spread of the virus[4]. These features make HCV a serious public health problem if left untreated; alternatively there are a few preventative measures in place, which will be discussed in this article.

The problem of HCV infection and hepatitis C is recognised by international organizations, including the World Health Organization (WH) and the European Union Parliament[5,6]. WHO estimates that approximately 2.8% of the global population has anti-HCV antibodies, which translates into more than 185 million people potentially infected. In 10-15% of patients with chronic hepatitis C, cirrhosis of the liver occurs in approximately 20 years' time after the initial infection if left untreated. This can lead to further complications including liver failure and hepatocellular carcinoma, which can result in premature death. Each year approximately 350 thousand people globally die of diseases resulting from HCV infection[5,7]. In developed countries, including Poland, the number of deaths caused by hepatitis C now exceed the number of deaths resulting from infection with HBV (Hepatitis B Virus, which causes hepatitis B) or HIV (Human Immunodeficiency Virus)[8,9].

The majority of HCV cases currently observed in Western Europe have been detected among drug injection users[10]. In Poland, however, the dominating route of transmission is iatrogenic. Minor medical procedures are responsible for up to 80% of all the infections[11,12]. In comparison to other European countries, Poland is characterized by a relatively low detection rate for hepatitis C[2]. The detection of HCV infection usually occurs by chance, e.g. during the pre-donation screening, or when the patient reports to the physician with symptoms of liver disease at an advanced stage. A low level of knowledge about HCV and hepatitis C, as well as the routes of virus transmission, are factors resulting in new infections[13]. This low level of knowledge currently translates into a small number of diagnostic measures being undertaken and the lack of interest of interest among national and regional authorities to implement preventive actions. No less important are the economic consequences of HCV infection, involving the direct costs of treating the disease including its complications as well as indirect costs resulting from reduced productivity and premature withdrawal of patients from the labour market. For these reasons it is increasingly critical for the various authorities in Poland to make changes to the current health policies to reverse this growing trend of new cases of HCV infection and deaths caused by hepatitis C.



## EPIDEMIOLOGY

In patients in whom the disease process is active or has ended, anti-HCV antibodies are detectable. This is used for the initial diagnosis of hepatitis C. To confirm the active viremia it is necessary to determine the genetic material of the virus (HCV RNA) in the blood serum of the patient[11].

As previously mentioned, the WHO estimates that approximately 2.8% of the global population has anti-HCV antibodies, which translates into more than 185 million potentially infected globally. As mentioned, the number of people dying annually of diseases resulting from HCV infection is approximately 350 thousand people; however, this figure will grow in the coming years if patients are untreated and there is a lack of preventative and other measures in place among countries[7,14].

In Europe, the prevalence of HCV ranges from 0.1% to 6% depending on the country. Comparison of the epidemiological status in different countries poses some difficulties due to variations in diagnostic procedures, various definitions of infection, different methodologies used in the various studies, as well as the time when the epidemiological research took place. According to current estimates, the lowest prevalence of the virus (0.1-1%) is in northern Europe. These infections are mainly present among people aged 30-50 years, most frequently associated with needle sharing by intravenous drug users. Higher prevalence rates of HCV, e.g. 2.5-3.5%, are seen in southern Europe, e.g. Spain, Italy, Greece, where in addition to infections transmitted by the intravenous route, a substantial number of infections among people aged over 50 years of age as due to the iatrogenic route of transmission, i.e. they became infected in hospitals. The highest prevalence of the virus ranging from 1.3% to 6% is observed in Eastern Europe, where the infections take place most frequently via the hospital route, i.e. among recipients of blood and organ donation as well as other causes (Figure 1)[15].

Poland appears to have an average ratio of HCV prevalence based on official data with all limitations. Epidemiological studies[16,17], carried out between 2009-2011 and covering 30 thousand patients indicate that the presence of anti-HCV antibodies is approximately 1.9% of the population, which corresponds to approximately 732 thousand people in Poland. However, the complete testing procedure requires a double repetition of the diagnostic approach. Epidemiological studies that use this method indicate that the prevalence of anti-HCV in Poland at a level of 0.95%, translating into approximately 366 thousand people in Poland having contact with the virus in their lifetime. Moreover, to confirm active infection, it is necessary to demonstrate the presence of viral genetic material. The percentage of the Polish population who present with both antibodies and genetic material of the virus is at a level of 0.6%, translating into 231 thousand people with active infection[16,17]. Meanwhile, the population of hepatitis B in Poland is estimated at 1-1.5% (400 to 600 thousand people) [18,19], while those with HIV infection is estimated at 0.07-0.12%, i.e. 27 to 46 thousand people) [29].

The epidemiology of hepatitis C in Poland has been monitored by the National Institute of Public Health - National Institute of Hygiene (NIPH - NIH) since 1997. However, the number of registered cases is likely to be lower than the actual number of infections due to the current low level of reportability. [20] Consequently, this data fails to show the accurate epidemiological situation of hepatitis C in Poland. Bearing this in mind, between 1997 and 2013 NIPH - NIH registered approximately 38 thousand people with HCV infection in Poland[21]. However as stated, approximately 85% of people with hepatitis C remain unaware of their infection explaining the current low rates reported by NIPH-NPH. In the first year of the monitoring, the number of registered cases stood at approximately 1 thousand. In the following year this number was almost doubled, and in 1998-2004 remained at 2 to 2.2 thousand patients. In 2005 there was a sudden increase to approximately 3 thousand recorded cases. The explanation of this phenomenon may be an increase of the public awareness of HCV and an increase in the number of performed diagnostic tests[11]. After a period of growth, the number of registered cases declined in 2009 to the level seen between 1998 to 2004. However, currently there is an upward trend with a total of 2705 new HCV infections reported in 2013. It

IN THE FIRST YEAR OF THE MONITORING, THE NUMBER OF REGISTERED CASES STOOD AT APPROXIMATELY 1 THOUSAND. IN THE FOLLOWING YEAR THIS NUMBER WAS ALMOST DOUBLED, AND IN 1998-2004 REMAIN WITHIN 2-2.2 THOUSAND.

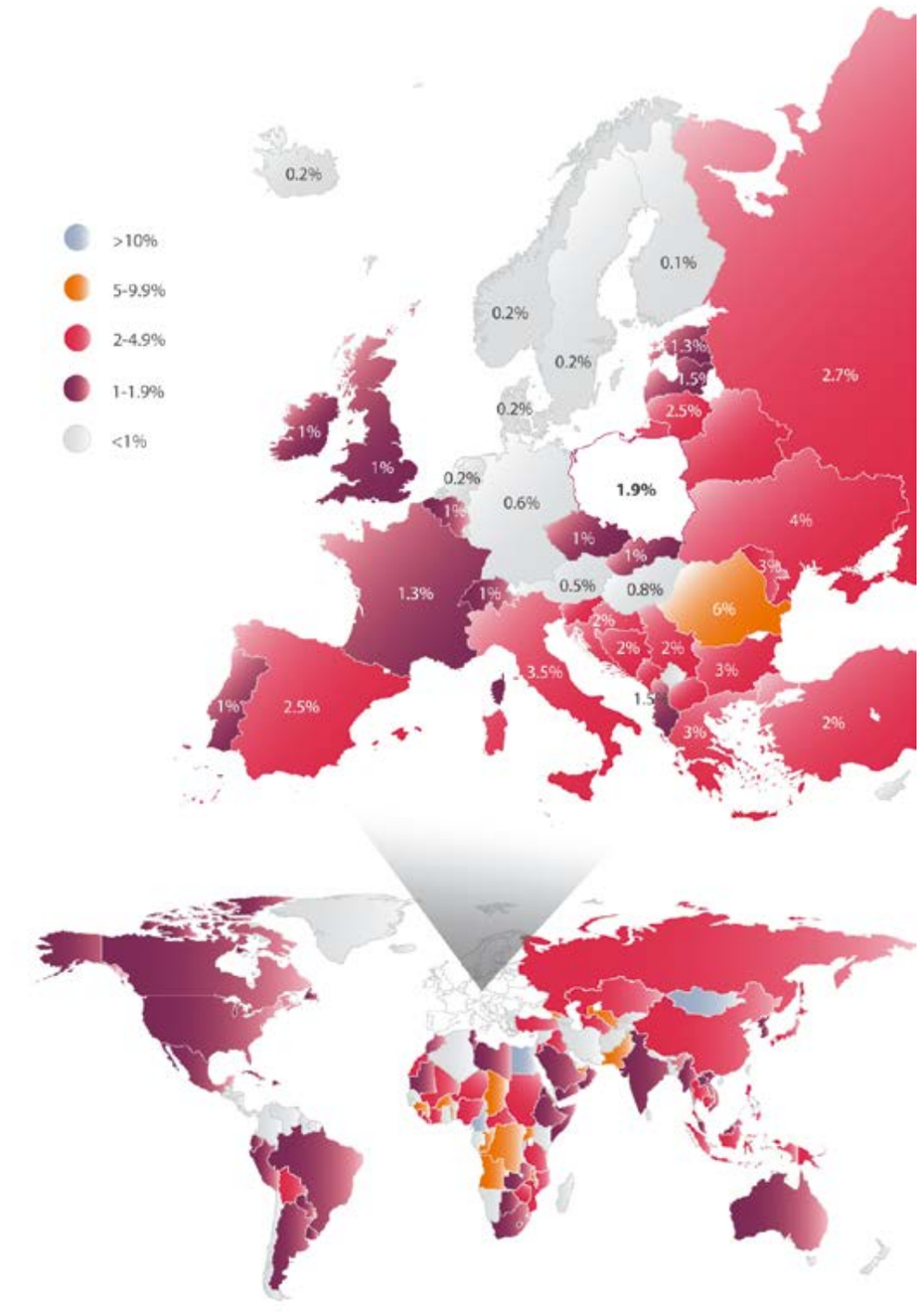



*Figure 1.*
*The estimated prevalence of anti-HCV in the world in 2010* [15,16]

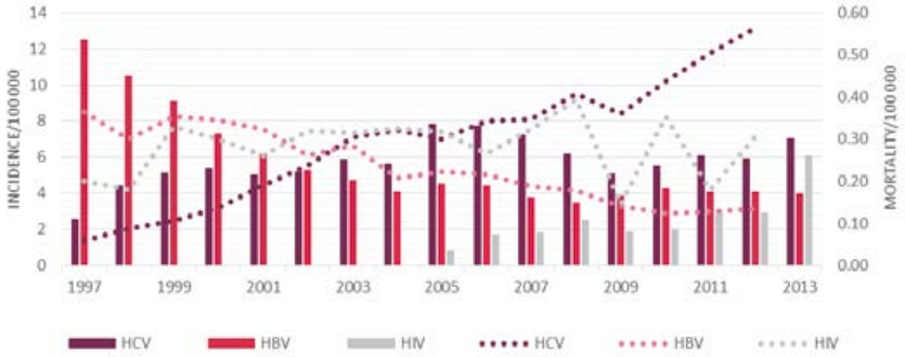



*Figure 2.*
*The dynamics of the HCV, HBV and HIV epidemiological situation in Poland in relation to hepatitis C virus in the context of hepatitis B and HIV*[22,23]

means that there were 7.03 HCV infections per 100 thousand Poles[21].

Meanwhile from the 1980s, thanks to the introduction of a universal system of vaccination for newborns and adolescents, the number of people infected with HBV has been systematically decreasing. In 2013 the number of newly registered cases of hepatitis B in Poland was 1 540 (4.00 per 100 thousand people). Newly registered HIV cases were, in turn, 1163 (3.02 per 100 thousand people)[21].

According to the Central Statistical Office of Poland, the number of deaths due to HCV is systematically increasing. In 2012, 217 people died of hepatitis C in Poland (0.13 per 100 thousand people). That is a 5-fold increase compared to the end of the 1990s. It was also more than the number of deaths caused by infections with HBV or HIV (Figure 2). The number of deaths in 2012 caused by hepatitis B in Poland was 52 (0.13 per 100 thousand people) and AIDS, which is a consequence of HIV infection, 118 (0.31 per 100 thousand people).


*Figure 3.*
*Reported by age group incidences of hepatitis C in Poland* [22]





According to the latest NIPH - NIH data, the majority of the new cases of hepatitis C is observed in the age group 45-59. However, an appreciable number of infections is also recorded in the age groups 25-44 and 60-74 (Figure 3).

This relationship has been present in Poland consistently since the 1990s. In the case of younger patients, infection is usually detected accidentally, e.g. during pre-donation screening. HCV infection can result from an injectable drug episode or from minor procedures breaking the continuity of the tissue, e.g. medical procedures, piercing, tattooing or scarification. In contrast, infections in the elderly are mostly detected during a visit to the physician, caused by the symptoms of developed hepatitis. The infection is most often the result of hospitalizations received before 1990, when the rules for the prevention of transmission of infection were not as restrictive as currently exist, or as a result of a blood transfusion before 1993, when the blood was not routinely tested for the presence of HCV[22]. In addition, men are more often affected by hepatitis C than women. In 2012, the incidence rate in Poland for males was 6.60 per 100 thousand and for women 5.34 per 100 thousand. Moreover, the infection is detected nearly twice as often among urban residents compared with rural ones. In 2012 in Poland, the incidence rates for urban and rural areas respectively were 7.25 and 3.95 per 100 thousand population[21].

HCV exhibits considerable genetic variability. There are six major genotypes of HCV, among which several subtypes can be distinguished. The genotype 7 was also detected, but to date it has been poorly investigated[23]. The prevalence of HCV genotypes varies depending on the geographical area. Genotypes 1-3 occur worldwide, genotype 4 dominates in the Middle East, Central Africa and Egypt, genotype 5 occurs primarily in South Africa, and genotype 6 in Asia[24]. In the extensive epidemiological study conducted by Panasiuk et al. in 2013[25], it was indicated that 86% of HCV infections in Poland in 2011-2012 were genotype 1.

## COURSE AND CONSEQUENCES OF THE DISEASE

Because HCV is a blood-borne virus, the infection can only occur through exposure to infected blood. Most often the infection happens dur-

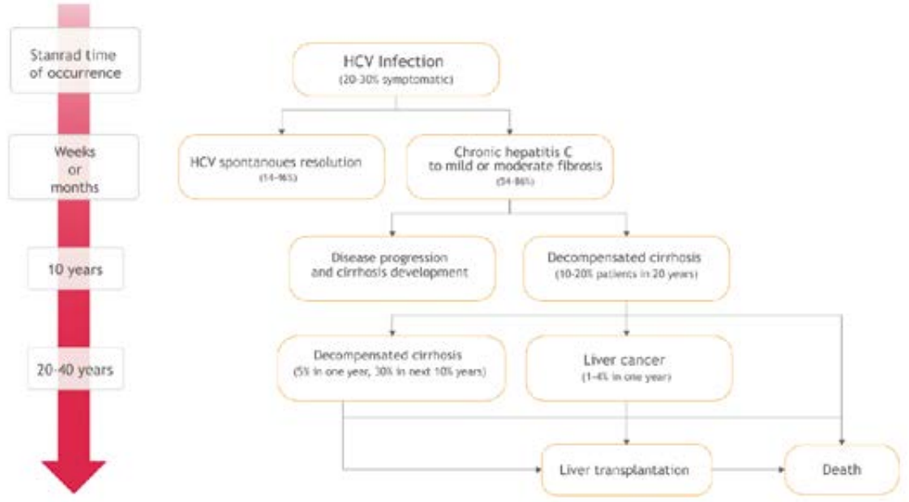



*Figure 4.*
*Natural history of hepatitis C* [1,31]

ing medical procedures and among intravenous drugs users, and are more probable than vertical infections[11,22].

In the second half of the twentieth century, infections in Europe occurred mainly during medical procedures breaking the continuity of the tissues, such as surgical and dental injections and other invasive procedures, as well as through blood transfusions and organ transplants[22]. In the early 1990s after the discovery of HCV in 1989, blood and organ donors began to be examined for the presence of HCV antibodies and viral genetic material. The introduction of new procedures increased the safety of the patients, e.g. appropriate methods for HCV sterilization. This caused a gradual decline in the number of new iatrogenic infections [22,26]. At the end of the twentieth century, infections among intravenous drug users became more common as a result of the sharing of contaminated injecting equipment. This route is the cause of 80% of the registered cases of HCV infection in Europe in 2011[10]. Vertical infections (from mother to child) are also present, most likely perinatal. It is estimated that vertical infections represent 3-10% of all infections in the countries of the European Economic Area[22]. Other possible, but less likely routes of transmission of HCV, may result from such practices as tattooing, piercing, scarification, acupuncture or cosmetic procedures. Infections which result from a day to day contact with an infected person are scarce. In such cases, the transmission of the virus can result from the shared use of personal items such as razors, toothbrushes or nail care accessories contaminated with the HCV infected blood[27]. Infections through sexual intercourse are possible, but very rare. In this case the infection occurs when the mucous membranes continuity is broken [22,28].

In developed countries in Europe 30-60% (depending on the country) of people living with HCV have been infected as a result of intravenous drug use[39]. In Poland, the majority of infections occur during small invasive medical procedures during where safety procedures have been neglected. According to specialists' opinion, iatrogenic events may currently be the cause of 80% of the infections in Poland[11,12].

Initially, hepatitis C usually develops asymptomatically and the ill person is unaware of when and how the infection happened. Therefore, there are inconsistencies related with the description of the natural history of the disease and the average life of the patient is difficult to estimate. However, it is known that the first stage of the illness is acute hepatitis, which is typically asymptomatic, which progresses into the chronic form in between 54 to 86% of cases. Chronic hepatitis, in turn, can run for years without noticeable symptoms, but with accompanied progressive fibrosis of the liver, which may lead to serious complications and potentially to premature death (Figure 4)[1,4,29].

Chronic hepatitis C is accompanied by the presence of genetic material of the virus in the blood for more than 6 months and, as mentioned, develops in between 54 to 86% of patients with acute infections[1]. The probability of the transition to the chronic condition depends on many factors including age, sex, ethnicity, and the course of the preceding acute phase. Spontaneous elimination of HCV at this stage of the disease is sporadic - 0.02% per year. Chronic hepatitis C may be asymptomatic for a long time. However, as a result of the inflammation in this phase, progressive liver damage and impairment of its function occur[29].

The development of disease is associated with progression of liver fibrosis. This process involves replacing the damaged liver tissue elements by connective tissue as a result of ongoing inflammation. Fibrosis leads to the remodelling of the organ and to a significant impairment of its functions. In the early stages, fibrosis develops in the portal and periportal areas. After this, it extends from one area to another one, forming the so-called fibrosis bridges. In the final stages, cirrhosis of the organ occurs. The severity of the liver damage is assessed by performing a biopsy or other equivalent non-invasive methods e.g. Fibrotest or FibroScan, and is determined by using a 5-point scale, where 0 means no change, and 4 - the most severe changes, i.e. cirrhosis. The rate of changes depends on many factors including the age and sex of the infected person, alcohol consumption and the presence of comorbid conditions[29]. However, it is estimated that the development of fibrosis from the stage 0 to 1 occurs in 11.7% of patients within a year of infection. The annual probability of progression to the next stages is 8.5%, 12.0% and 11.6%, respectively[30] (Figure 5). In Poland, patients are mostly diagnosed in the first or the second stage of liver fibrosis (approximately 70%)[31–33].

Cirrhosis is the final stage of liver fibrosis, which occurs in 10-15% of patients with chronic hepatitis C within 20 years from the initial infection. Firstly, HCV may give no symptoms and the liver can function properly. This condition is referred to as a compensated liver cirrhosis. The survival rates for patients with compensated cirrhosis at 3, 5 and 10 years post infection are 96%, 91% and 79% respectively[29]. However, 5% of patients per year and 30% of the patients per 10 years experience decompensation of cirrhosis, which leads to severe complications, such as ascites, bleeding in the upper gastrointestinal tract (as a result of esophageal varices or portal gastropathy) or hepatic encephalopathy[29]. The probability of 5-year survival with decompensated cirrhosis of the liver is much lower, equalling 50% of the cases. It is believed that decompensated cirrhosis is the most common cause of death as a direct consequences of hepatitis[29,34]. Another consequence of chronic hepatitis C is hepatocellular carcinoma (HCC), which affects 1-4% patients with HCV per year. It is estimated that the risk of this cancer is 17 times higher in the case of HCV infection than in cases of uninfected patients. Apart from the consumption of alcohol (20% of HCC) and HBV infection (10-15%), HCV is the main factor favouring the development of this cancer in Europe (60-70% [35]. The average time that elapses from initial infection to the development of HCC is almost 30 years [29]. This cancer is poorly predictive and in most cases leads to death within a few years from diagnosis. It is estimated that the probability of death for people diagnosed with hepatocellular carcinoma and HCV infection is 41-46% per year[36–38].

Advanced cirrhosis and liver failure are the reasons for liver transplantation in many patients. Hepatitis C is the leading cause of the liver transplantation in Poland[39,40] and in other countries, for example, in the USA[41]. According to the Polish

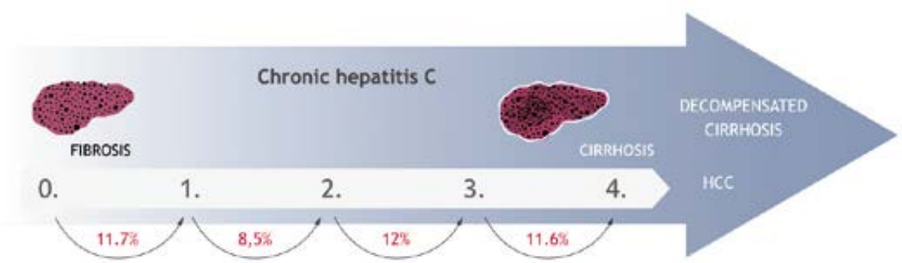



*Figure 5.*
*The annual probability of transition to the subsequent stages of liver fibrosis in patients with hepatitis C*[32]

data, HCV infection or coinfection is responsible for 23-28% of all liver transplantations [42]. Despite the growing number of transplantations, there is still unmet demand at approximately double the number of transplantations undertaken. While the number of grafts resulting from post-inflammatory HCV cirrhosis decreases, the number of transplantations in patients with hepatocellular carcinoma will increase[43]. Unfortunately, the relapse of hepatitis C in patients after the liver transplantation is inevitable, resulting in recirrhosis in 25% of cases within 5 years, which may be the reason for retransplantation[43,44].

Besides the serious complications of liver, hepatitis C may result in extrahepatic disorders, occurring in 1-2% of the infected with HCV. The most common extrahepatic complication is cryoglobulinemia, resulting in symptoms such as fatigue, skin rash, bleeding disorder, arthralgia, Raynaud's symptoms, inflammation of the blood vessels, kidney disorders or peripheral neuropathy. Other observed disorders are membrane-proliferative glomerulonephritis, porphyria cutaneous tarda, lichen planus and vitiligo. In the course of hepatitis C lymphoma and Hodgkin's lymphoma, autoimmune thyroiditis, Sjogren's syndrome and seronegative arthritis are also observed. It is unclear whether these disorders are directly caused by HCV infection or by a chronically stimulated immune response triggered by the inflammation[29].

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**THE PRESENT EPIDEMIOLOGICAL DATA IN POLAND ALLOW TO ESTIMATE THAT ABOUT 3 THOUSAND OUT OF 231 THOUSAND CURRENTLY HCV INFECTED PATIENTS, WILL HAVE TO BE TREATED FOR HEPATOCELLULAR CARCINOMA, AND 20-40 THOUSAND FOR CIRRHOSIS DURING NEXT 30 YEARS.**

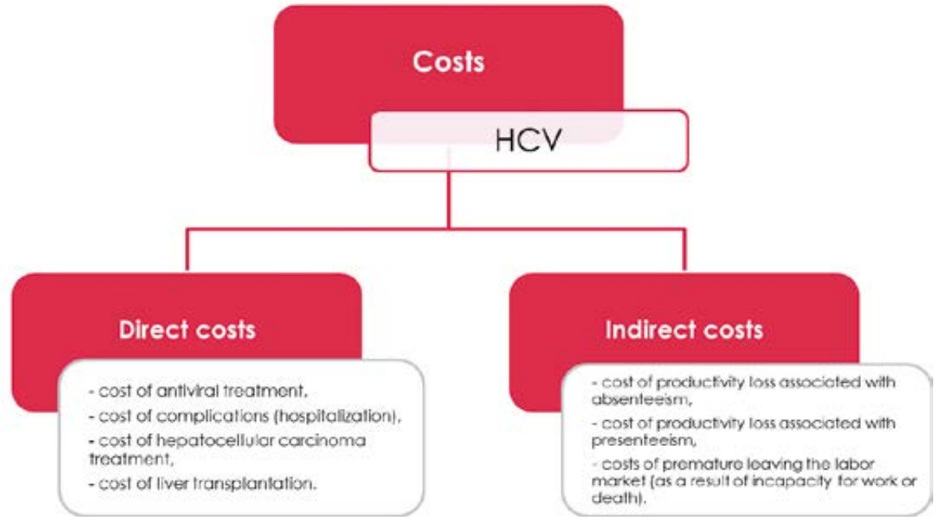


*Figure 6.*
*Types of costs associated with HCV*

Advanced cirrhosis and liver failure are the reasons for liver transplantation in many patients. Hepatitis C is the leading cause of the liver transplantation in Poland[39,40] and in other countries, for example, in the USA[41]. According to the Polish data, HCV infection or coinfection is responsible for 23-28% of all liver transplantations[42]. Despite the growing number of transplantations, there is still unmet demand at approximately double the number of transplantations undertaken. While the number of grafts resulting from post-inflammatory HCV cirrhosis decreases, the number of transplantations in patients with hepatocellular carcinoma will increase[43]. Unfortunately, the relapse of hepatitis C in patients after the liver transplantation is inevitable, resulting in recirrhosis in 25% of cases within 5 years, which may be the reason for retransplantation[43,44].

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## TREATMENT

Hepatitis C is a disease that can be treated effectively. The main goal of the therapy is to achieve a sustained virological response (SVR) to prevent hepatic complications and reduce the mortality by eliminating HCV from the body of the patient [45]. Due to the lack of vaccines against HCV, treating hepatitis C is, in fact, the only way in which the reservoir of potential infections can be reduced[11].

So far, the standard treatment for all patients with chronic hepatitis C has been a non-specific therapy, which consists of stimulating the immune system to the antiviral response for the HCV present in the organism. A combination of pegylated interferon alpha with ribavirin (PegINFα + RBV) has been used as a nonspecific dual therapy[46]. Interferon is responsible for stim-


ulation of the antiviral response while in vitro research has confirmed the activity of ribavirin against some RNA and DNA viruses. Pegylated interferon alpha is administered as a weekly injections and ribavirin is taken orally twice a day. The total duration of therapy can last up to 72 weeks [47–49]. The efficacy of dual therapy PegINFα + RBV strongly depends on the genotype of the virus. For genotypes 2 and 3, an effective cure is achieved in 87% and 77% of patients, respectively[8]. The percentage drops to approximately 56% in the case of genotype 4[50–52]. In the case of genotype 1, identified in nearly 90% of patients in Poland[25], the effective treatment is achieved in only 45% of cases[8]. The use of interferon and ribavirin is associated with serious side effects[53]. The most important side-effects include depression, suicide attempts, anorexia, nausea, anaemia and flulike symptoms[14,48,49]. These side-effects can result in discontinuation of treatment, with estimates that less than 50% of patients complete a course of treatment[46]. This is important as effective therapy requires patients taking at least 80% of the indicated doses for at least 80% of therapy duration[47]. There are also contraindications for combination therapy PegINFα + RBV limiting the population patient population for treatment[48,49].

The second group of drugs used in the treatment of chronic hepatitis C are specific drugs pointed directly against the virus. They are inhibitors of enzymes involved in virus replication. Currently their function is the direct intervention in the process of HCV multiplication. The following drugs are currently registered in Poland: first-generation NS3/4A protease inhibitors boceprevir, telaprevir and second-generation direct-acting antiviral agents sofosbuvir, simeprevir, daclatasvir, ledipasvir tablets[54–59] and recently ombitasvir, paritaprevir, ritonavir and dasabuvir. [60] Many other new substances are in the process of drug registration or at advanced levels of clinical trials.

Boceprevir and telaprevir are aimed at patients infected with the genotype 1. Simeprevir has been tested in patients infected with genotypes 1 and 4 while sofosbuvir can be used for infection of genotypes 1-6. In a population with genotype 1, all drugs are routinely used together with pegylated interferon alpha and ribavirin, in so-called triple therapy. Boceprevir is administered orally, three times a day, telaprevir twice to three times a day, while simeprevir and sofosbuvir are administered once a day. The total duration of the therapy in the case of boceprevir and telaprevir is 48 weeks. Treatment with simeprevir takes less time - 24 weeks, and with sofosbuvir only 12 weeks[54–57]. The use of boceprevir or telaprevir with interferon and ribavirin in naive patients allows to obtain a sustained response at the level of 54-75%, and in patients undergoing treatment again, because of the failure of previous PegINFα + RBV treatment, effectiveness of this therapy is up to 51-67%[61]. Simeprevirand sofosbuvir used in combination with interferon and ribavirin exhibit higher efficiency with cure rates up to 80% and 95% in naive patients[14,46]. It needs to be stressed that sofosbuvir may also be given to patients not eligible for treatment with the use of interferon. In such case it is only used in combination with ribavirin, but then the efficiency is at a level of 50-84%, and the treatment must be extended to 24 weeks[62]. In this group of patients it is also possible to use combination therapy consisting of two specific drugs - sofosbuvir and simeprevir, and optionally ribavirin. Preliminary data indicate that the response to that treatment can be over 90%[63–65]. However, triple therapy, besides the higher efficiency, has the same limitations associated with the comfort and safety as a dual therapy. Patients are still exposed to the adverse events resulting from the use of interferon and ribavirin. Furthermore, especially in the case of boceprevir and telaprevir, there is an additional risk of side effects[14,54,55].

The therapy with combination of ledispavir and sofosbuvir administered for 8 or 12 weeks with or without ribavirin is associated with even higher rate of sustained virological response at a level of 93-96% among previously untreated patients with HCV genotype 1 infection without cirrhosis[66]. The most advanced available therapy with ombitasvir, paritaprevir and ritonavir in combination with dasabuvir is approved for the treatment of genotype 1 chronic hepatitis C virus infection, including patients with compensated cirrhosis. This therapy is dosed orally twice daily for 12 weeks taken with or without ribavirin, except patients with cirrhosis, who should take it for 24 weeks and is effective at a level of 95-100%[60]. For the treatment of genotype 4 chronic hepatitis C patients, this treatment consists of ombitasvir, paritaprevir and ritonavir taken with ribavirin and effectiveness of this therapy is up to 100%[60].





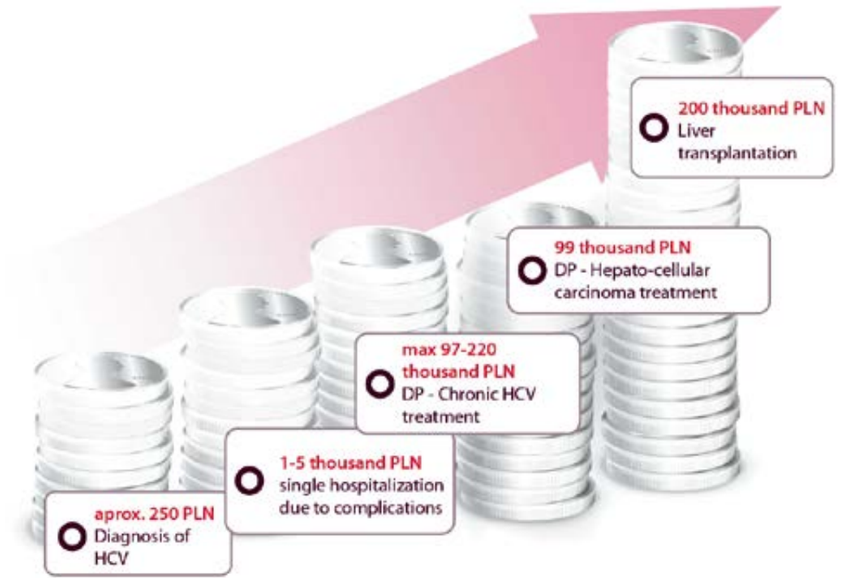



*Figure 7.*
*Treatment costs depending on stage of HCV infection per patient*

## COSTS – DIRECT AND INDIRECT

There are two types of costs: direct and indirect, (Figure 6) and vary depending on HCV stage (Figure 7).

Estimated direct costs associated with hepatitis C treatment in 2013 was 234 million PLN, while annual costs associated with productivity loss due to deaths, permanent incapacity for work, absenteeism and presenteeism computed with the conservative approached 585 million PLN taking into account only currently treated patients and maximum estimation of presenteeism.

Direct costs are calculated as the sum of all health services during one year based on individual data. The largest component of costs per person associated with chronic hepatitis C are for the treatment of severe complications. The estimated cost of one liver transplantation is 200 thousand PLN and annual post-liver transplantation costs are 20 thousand PLN. Costs of drugs during the six months of hepatocellular carcino-

ma drug program are estimated at 99 thousand PLN per patient (Figure 8).

The total costs of drug treatment for HCV are rising each year due to the introduction of new therapies, and in 2013 amounted to approximately 179 million PLN (based on the official report on activities of NHF in 4th quarter 2013 - concluded official data from contracts with hospital valued at 138.5 million). According to Polish National Health Fund data from 2013, 7 111 patients received at least one dose of drugs, sometimes not the full course) within drug program. With the estimated number of 231 thousand infected patient in Poland, this currently equates to a little more than 3% of the possible infected people. In the same year, costs of hospitalizations within diagnosis-related groups system (DRG) equalled 38 million PLN. The estimated cost of hepatitis C liver transplantations (caused by hepatitis C) is approximately 18 million PLN/year in Poland.

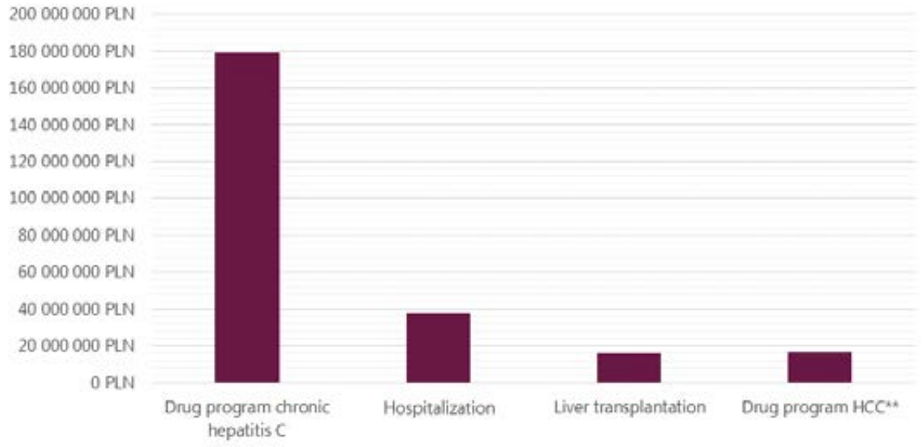



*Figure 8.*
*Annual direct cost estimation of chronic hepatitis C and hospitalization*

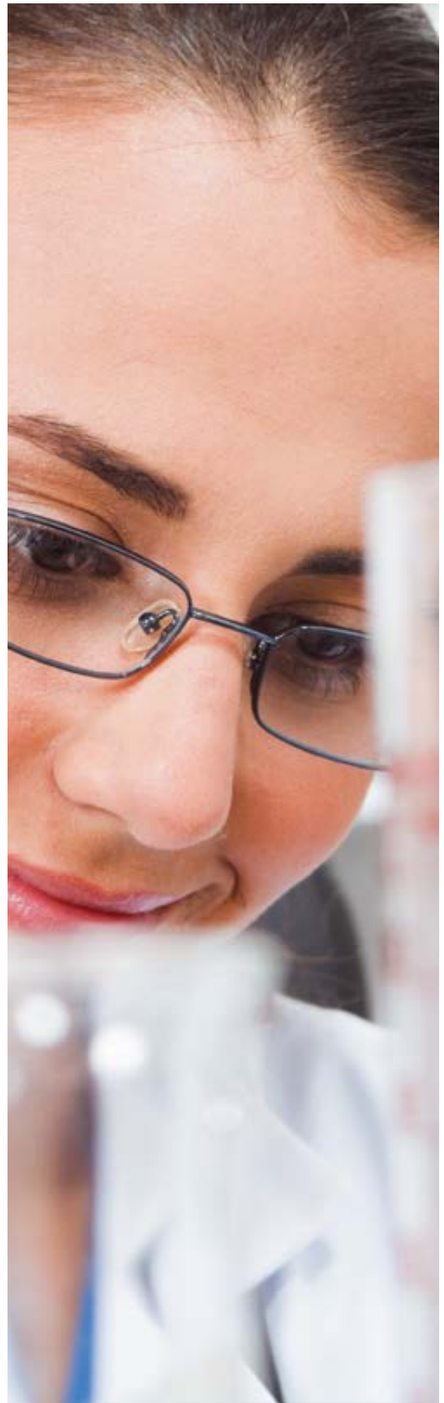
*includes the estimated cost of transplantation, which were the cause of complications of hepatitis C (without cost therapy after transplantation in subsequent years)*
*** the proportion of patients with HCC due to hepatitis C is unknown*

Loss productivity arise from generated by absenteeism and presenteeism. The absenteeism rate is the proportion of absence in time during which the respondent is supposed to work – premature death, sick leave, disability, holidays, family care. The presenteeism rate is the degree to which the health problem affected the respondent's productivity while working, subjectively estimated by the respondent on a scale from 0 to 10 measured for example by WPAI (Work Productivity and Activity Impairment Questionnaire) questionnaire. It can be interpreted as the percent of work not done due to studied condition. The overall work impairment is the sum of work time lost by the respondent due to absenteeism and presenteeism (it is the sum of presenteeism rate multiplied by time spent at work and absenteeism rate). Total annual cost of loss of productivity is approximately 584.8 mln PLN – premature death 53.6 mln PLN, disability – 147.7 mln PLN (data from ZUS together for hepatitis C and B), sick leave – 20.9 mln PLN and maximum estimation of presenteeism for chronic C – 362.5 mln PLN.

## CONCLUSION

The epidemiological data in Poland suggests that 3 thousand out of an estimated 231 thousand patients are currently being treated for hepatitis C infected patients. This translates into an estimated 20-40 thousand people suffering from cirrhosis of the liver during the next 20 years and 4 to 8 thousand patients needing treatment for hepatocellular carcinoma during the next 30 years if these patients remain untreated. For many patients, the only possible treatment will be liver transplantation. However, hepatitis C could now be treated very effectively. Early drug therapy averts serious health consequences for patients as well as reduces the chances of them transmitting the disease to others with cure rates higher than 95% with new therapies. It is recognised that this will appreciably add to drug costs in the early years; however the increased expenditure would be balanced against reduced costs of treating complications in the later years [46]. This could include the potential for discounted prices building on the experiences in other countries negotiated as part of risk sharing schemes for reimbursement [46]. Alongside this, there needs to be co-ordinated preventative activities and changes in treatment in Poland to reduce future infection rates as currently in Poland there are only a few screening activities (also in local governmental programs) and no strategic proposition of shaping the complex approach. If instigated, these could be as effective as actions taken to avoid HBV or HIV infections.

In view of the lack of any hepatitis C vaccination, we believe it is essential for the various national and regional authorities in Poland to take actions to stop the spread of the virus. These activities could be organized into: 1. education and promotion of behaviours that reduce the risk of further infections 2. providing national screening of high risk groups. 3. providing wider access to HCV tests, allowing early detection and diagnosis of the greatest number of people infected in local level. Such actions combined with the availability of effective and safe antiviral therapy could be as efficient as vaccination against hepatitis C, which, as previously pointed out, is non-existent at present. Preventive measures and treatment at early stages would also reduce the costs for the NHF of treating a significant number of patients with serious complications of hepatitis C including cirrhosis and hepatocellular carcinoma. In conclusion, we urge the various authorities in Poland to take prevention and management of HCV seriously, building on ongoing effective strategies for HBV and HIV. ■



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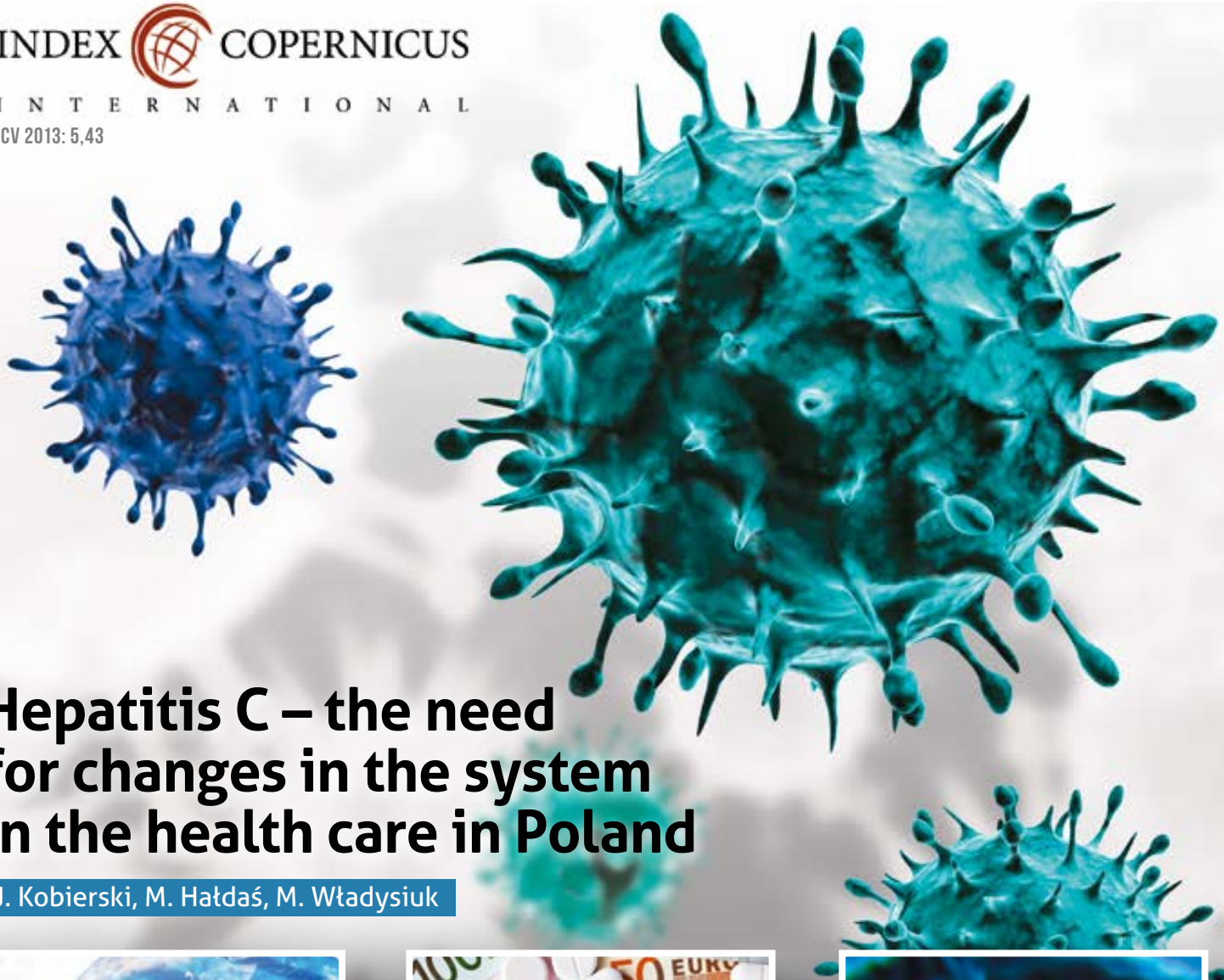

# Hepatitis C – the need for changes in the system in the health care in Poland

J. Kobierski, M. Hałdaś, M. Władysiuk

**Patients Registries - the role of the health system, new trends and hopes for Polish patients - 2nd JHPOR conference, Warsaw March 19th 2015**

A. Fałek et al

**Polish Experience in Financial Management of Medicines Market by Public Payer**

T.Płusa

**Ebola viral hemorrhagic fever**

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# Current treatment options with immunoglobulin G for adult patients with primary immunodeficiency disease in Poland

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IgG, adults, drug program, IVIG, primary immunodeficiency, SCIG

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## ABSTRACT

***Polyclonal immunoglobulin G life-long replacement is a corner stone therapy in patients with primary antibodies deficiency. The evidence of safety and effectiveness of IgG in PAD are strongly documented for reduction and protection for serious infections. There are still limited data for deletion from long term complications as progression of chronic lung diseases, bronchiectasis and damage. Nowadays accelerated progress in IgG products modulation and ways of administration allows for adjustment of this chronic treatment for patients needs and preferences, improving the patients' compliances and quality of life. Intra venous immunoglobulin therapy has been used for many years. There are worldwide accumulating experiences with subcutaneous therapy. The latter can be given by infusion delivery pump, via rapid push or facilitated by pre-infusion of recombinant human hyaluronidase (rHuPH20). The immunoglobulin G life-long replacement is an expensive procedure. In the past in Poland replacement immunoglobulin therapy was provided mainly by pediatricians resulting in a gap with high quality care for adult patients. Awareness of problem of primary immunodeficiency in adult patients provokes the rise of centers which take care of adult patients. To improve the access for immunoglobulin therapy in Poland, a drug program has been introduced for adult patients with primary immunodeficiency. This review paper presents aspects of current immunoglobulin therapy in primary immunodeficiency complying resolutions proposed in Polish health care system.***

## INTRODUCTION

Polyclonal immune globulin products contain mainly immunoglobulins G (IgG) purified from pooled human plasma. In the 1950s, first passive, intramuscular administration of human immunoglobulins for patient with agammaglobulinemia gave a spectacular reduction in the frequency of sepsis and severe bacterial infections[1]. Nowadays patients with primary antibody deficiencies (PAD) require a systematic, life-long immunoglobulin G (IgG) replacement[2-5]. Continuous progress in ways of production, purification of Ig products and advances in the mode of immune globulin administration, give now possibility to tailor the chronic treatment to patients and provider needs and preferences. Both intravenous (IVIG) and subcutaneous (SCIG) IgG are effective and safe. In the past in Poland, due to lack of referral centers dedicated for care of adult patients with PAD, availability of SCIG was especially limited. With the growing knowledge about primary immune deficiencies (PID) in adults and awareness of the problem among physicians and pediatricians, who transfer patients to adults care centers, the new sites providing IgG treatment have been established. Moreover due to implementation of the new therapeutic program for adults' patients with PAD, the standard of care for adults can be improved.

## INDICATIONS

Immune globulin G replacement therapy is a cornerstone of treatment for variety of PIDs. The prevalence and incidence of PIDs remain unclear. In the paper published in 2013 upper estimates suggest that six million people may be living with a PID worldwide. In Europe upper estimate was 638,000 cases, and 15,052 cases are currently registered (2.27 %)[6]. Not all PIDs are equally clinically significant and require IgG substitution. In this paper we mainly consider PIDs with antibody deficiency occurring in adult patients who have been transferred from pediatrics centers or diagnosed in adulthood. The main indication from this point of view is common variable immune deficiency (CVID). It is a complex immune disorder characterized by the impaired B cell peripheral differentiation leading to hipogammaglobulinemia. The disorder involve wide spectrum of symptoms, with majority of subjects affected by recurrent serious infections. The course of disease if untreated deteriorates with age, leading to pulmonary chronic lung disease and irreversible damage. It has to be point out that CVID is a systemic disease with profound immune system deregulation. In 30% of patients with immunodeficiency paradoxically co-exist autoimmune complications and sometimes granulomatous inflammation[7-9]. Moreover patients with CVID are at higher risk of malignancy, mainly but not only lymphoma[10]. To qualify as having CVID, patients have to present with hipogammaglobulinemia (significant reduction in >2 isotypes of serum immunoglobulin (less than 50% lower limit of normal and not simply borderline values)) and defective antibody production. In addition, flow cytometry analysis in CVID should show abnormalities in B cells, such as alterations in memory B cells or isotype switched B cells. Abnormal flow cytometry data are particularly important to confirm a questionable diagnosis[11,12].



Other B cell immune deficiencies for which IgG are indicated includes agammaglobulinemia with classical X-linked (XLA or Brutton's agammaglobulinemia) or autosomal recessive pattern. Hyper IgM syndrome including defects of the CD40 ligand and rare forms caused by defects in enzyme required for the immunoglobulin class switching also lead to IgG deficiency, and are indications for Ig supplementation.

Other immune deficiencies with defects of antibody production include Wiscott-Aldrich syndrome, some cases of DiGeorge syndrome, and patients with sub-class deficiency. In this cases IgG replacement can be indicated despite normal IgG level.

The main issue in patients' treatment is to properly establish diagnosis and verify indication for treatment by clinical immunologist. Replacement Ig therapy should not be given in case of a clinical picture that generally includes borderline immunoglobulin levels, a history of poorly documented pulmonary infections in which etiology is not defined, and a preponderance of chronic rhinosinusitis (often in atopic patients), and chronic fatigue as leading common complaint. According

to some experts' opinion, because the decision to treat or not to treat such patients long-term with immunoglobulin replacement rests on non-functional laboratory assessments, subjects with normal B-cell immunity are often being treated unnecessarily[11].

## AIMS OF IGG THERAPY

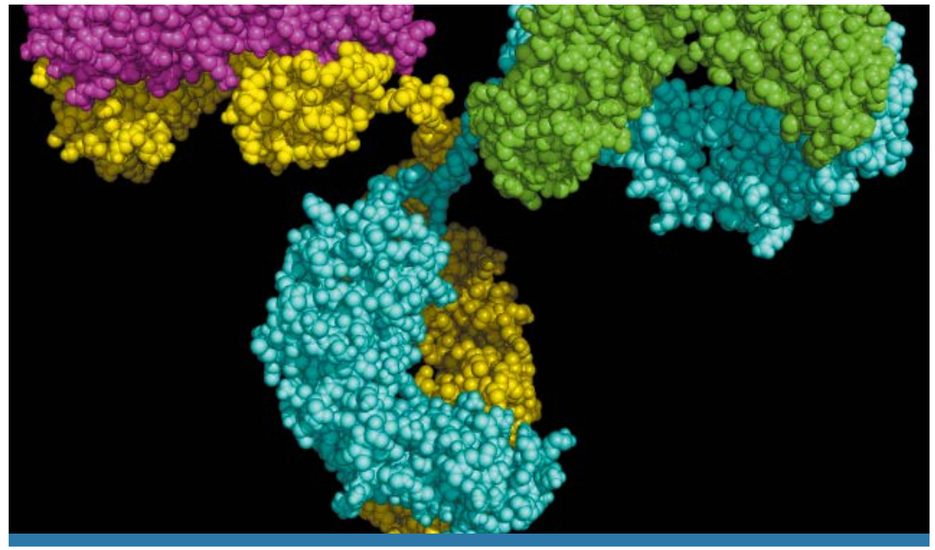
IgG replacement therapy reduces the number and severity of infections, decreases antibiotics use and hospitalizations[13]. The main efficacy end-points in clinical studies of IVIg treatment in PAD are measurement of the rate of serious bacterial infections during regularly repeated administration of the investigational IGIV product in adult and pediatric subjects for 12 months (to avoid seasonal biases) and comparison of the observed infection rate to a relevant historical standard or to a concurrent control group. Secondary endpoints normally include trough total IgG and specific antibody levels, all infections of any kind/seriousness, non-serious infections (total and by category, including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc.), time to resolution of infections, antibiotic treatment (oral, parenteral, oral plus parenteral, prophylactic, and therapeutic), hospitalizations due to infection, episodes of fever, days lost from school and/or work due to infections and their treatment, and additional quality of life measures[14]. The effect of IgG replacement in subjects with hipogammaglobulinemia was so impressive immediately after treatment introduction that placebo-controlled studies have not been performed and are prohibited in PAD. In an retrospective study forty-two (84%) of the 50 patients with CVID had pneumonia at least once before receiving immunoglobulin treatment, and 11 of 42 of these patients had multiple episodes. After treatment with IgG over a mean period of 6.6 +/- 5.2 years (range, <1-20 years), the number of patients experiencing pneumonia significantly decreased to 11 (22%) of 50. In most cases these patients had pneumonia in the first year of immunoglobulin treatment[15]. It is supposed that IgG replacement can slow the progression of chronic lung diseases, although it not have been firmly proven. A prospective study was conducted in 24 adult patients consecutively diagnosed with CVID, with no previous intravenous immunoglobulin (IVIG) treatment. IVIG dose, total serum IgG level, bacterial infection rate, pulmonary function tests (PFTs) and high resolution computed tomography (HRCT) of the thorax were monitored over 2 years. Moreover, outcome data were determined by measurement of chronic pulmonary disease (CPD). IVIG dose variability (205-372 mg/kg/21 days) to obtain the required serum IgG levels was determined. Patients with CPD needed higher doses than those without CPD (p=0.045). A significant reduction in severe and mild infections/patient-year was observed during treatment. Overall, there were no changes in PFTs and HRCT scores in patients without CPD, but both improved in patients with CPD. An increase of over 15% in overall HRCT score was detected in two patients without evidence of impairment in either clinical status or PFT values[16].

Immune globulin therapy has its limitations. It is not effective in the protection from chronic or recurrent sinusitis and does not influence autoimmune phenomena observed in PID patients[17]. Paradoxically granulomatous inflammation or co-existing benign lymphoproliferation have to be treated with immunosuppressive medications. There is no sufficient data for benefits of IgG on the risk and incidences of malignancy in PID.

The matter of debate is the relationship of the dose, trough IgG level and outcome in PAD. According to FDA recommendation for efficacy more data are needed to better understand the quantitative relationships among trough total and pathogen-specific plasma IgG levels and serious infection risk. It is suggested to initiate exploratory analyses of clinical trial data to evaluate the relationship of both serious and nonserious infections to the pharmacokinetic parameters, the total IgG levels, the levels of the various subclasses of IgG and, if possible, the levels of selected specific antibodies such as anti-pneumococcal capsular polysaccharide and anti-Haemophilus influenzae antibodies. The serum IgG level that rises up to 500 mg/dl is commonly acceptable target for the beginning of replacement therapy. However in the healthy population there is a wide range of IgG level that protects from infection. Moreover the impact of trough IgG level on pneumonia incidence was described. In the meta-analysis including seventeen studies with 676 total patients and 2,127 patient-years of follow-up, pneumonia incidence declined by 27% with each 100mg/dL increment in trough IgG (incidence rate ratio, 0.726; 95% confidence interval, 0.658-0.801). Pneumonia incidence with maintenance of 500 mg/dL IgG trough levels (0.113 cases per patient-year) was 5-fold greater that with IgG level of 1000 mg/dL (0.023 cases per patient-year) [18]. In clinical practice it seems to be reasonable to accept as a goal of therapy a "biological" IgG level, individualized for each patient. This is the level obtained by charting patient's infections against IgG levels over time, with addition of change in clinical status and co-morbidites[19]. The concept of targeting individual level is supported by data from 22 years long observation of the cohort of CVID patients. Data were collected prospectively from a cohort of 90 patients with confirmed CVIDs from 1 center. Immunoglobulin doses had been adjusted in accordance with infections rather than to achieve a particular trough IgG level. Doses to achieve infection-free periods were determined and achieved trough levels analyzed. A smaller group of patients with X-linked agammaglobulinemia was analyzed for comparison. Patients with a CVID had a range of trough IgG levels that prevented breakthrough bacterial infections (5-17 g/L); viral and fungal infections were rare. Doses of replacement immunoglobulin to prevent infections ranged from 0.2 to 1.2 g/kg/mo. Patients with proven bronchiectasis or particular clinical phenotypes required higher Ig replacement doses. Patients with X-linked agammaglobulinemia showed a similar range of IgG levels to stay infection-free (8-13 g/L)[20]. This individualized attitude is possible according to rules of Polish Therapeutic Program, as it defines only the minimal target IgG level.

## MODES OF ADMINISTRATION

IVIG therapy has been used from many years. For years, experience with SCIG therapy has been accumulating. The latter in Poland was limited mainly to pediatrics population due to already mentioned limitations in regulations of health care system. The diversity in SCIG usage is observed not only in Poland, but also among other European countries. Both types of IgG replacement are equally effective and have their own advantages and disadvantages. It is crucial to implement therapy according to patients' needs and preferences leading to improvement in quality of life. A standard initial dose of IVIG for the treatment of PAD patients is 400 mg/kg (range of 300-500 mg/kg) every three or four weeks. Longer



intervals between doses are not recommended even on maintaining therapy. In Poland, to authors' knowledge, IVIG is a inpatient procedure; the home IVIG therapy, although possibly more cost effective, is not provided. Standard starting doses for SCIG are 100 to 150 mg/kg per week. SCIG therapy can be given by infusion delivery pump, via rapid push or facilitated (IGHy) by preinfusion of recombinant human hyaluronidase (rHuPH20)[21-23]. Neither IGHy nor rapid-push SCIG is yet available in Polish Therapeutic Program (as of January 2015).

The advances in therapy allow to limit sites injections, increase the infusion rate and volume, with preserved safety of treatment. Routinely SCIG once-weekly administration is the most common, although regimens ranging from daily to bi-weekly have been used. Recently approved in Europe and United States for use in adults recombinant human hyaluronidase-facilitated subcutaneous IgG (IGHY) allowed administration every 3 or 4 weeks, similarly to IVIG, using one site (median, 1.09/month), with a mean volume of 292.2 mL. The bioavailability of IGHy measured by area under the concentration versus time curve was 93.3% of IGIV, which is pharmacokinetically equivalent. Systemic reactions were less frequent with IGHy than with IGIV (8.3% vs 25.0% of infusions). Local reactions to IGHy were generally mild to moderate, with a rate of 0.203 per infusion [23]. (wasserman) IGHy seems to be attractive from physicians' and patients' point of view. The extent to which IgHy will be used in future will depend on further real life experiences, long term observation and cost-benefit ratio[22].

## IGG THERAPY AND COST ASPECTS

IgG life-long replacement therapy is a highly expensive procedure. The main cost related to IgG therapy is the gamma globulin itself. All form of preparations are expensive. According to the Clinical Immunology Committee of the International Union of Immunological Societies and the World Health Organization for manufacturing IVIG it should be extracted from a pool of at least 1000 donors. It should contain minimal IgA and the biochemical modification of IgG molecules should be as little as possible. The preparation should be free from preservatives or stabilizers that might accumulate in vivo[24]. In some European countries and Canada SCIG seems to be less expensive then IVIG[25]. In Canada in 3 year perspective the cost reduction on rapid –push therapy was mainly due to smaller use of hospital personnel. If 75% of patients switched to SCIG, the reduced costs reached $1·962 million or 56% of total budget[26]. A cost-analysis performed to determine whether SCIG is cost-effective compared with IVIG from a French social insurance perspective revealed that direct medical costs ranged from 19 484 euro for home-based IVIG to 25 583 euro for hospital-based IVIG, with home-based SCIG in between at 24 952 euro per year, calculated through a simulation testing different hypothesis on costs drivers. However, costs estimated on the basis of field data collected by a questionnaire completed by a population of patients suffering from agammaglobulinaemia and hyper-IgM syndrome were found to be different, with significantly higher costs for IVIG. This result was explained mainly by a higher immunoglobulin mean dose prescribed for IVIG. While the theoretical model showed very little difference between SCIG and hospital-based IVIG costs, according to authors SCIG appears to be 25% less expensive with field data because of lower doses used in SCIG patients[27]. Economic aspects of SCIG treatment in comparison with previous IVIG therapy were analyzed in phase III pivotal study of IgPro20, an L-proline-stabilized 20% human SCIG in Japan. Switching from IVIG to SCIG reduced markedly productivity loss and hospital-related absenteeism[28].

According to IPOPI survey half of IV recipients would prefer SCIG. SCIG is perceived to perform better on a number of aspects relating to quality of life (convenience, allowing independence and personal freedom) in the survey sample. From patients' perspective the time spent for SC infusion is not perceived as the lost from other activities. Moreover the time required for transportation to the hospital is regained by the patient[29]. One of the aims of new drug program "Treatment of primary immunodeficiency in adult patients" in Poland is improvement of patients' quality of life.

## POLISH THERAPEUTIC PROGRAM FOR ADULT PATIENTS WITH PID

Drug program "Treatment of primary immunodeficiency in adult patients" has been introduced to the Polish health system in 2015. As part of this program following disease entities will be treated with immunoglobulin, according to the ICD-10 code:

- D.80.0 Hereditary hipogammaglobulinaemia
- D.80.1 Non-family hipogammaglobulinaemia
- D.80.3 Selective deficiency of immunoglobulin G subclasses (IgG)
- D.80.4 Immunodeficiency with increased levels of IgM
- D.80.5 Deficiency of serum immunoglobulin antibodies similar to normal or hypergammaglobulinemia
- D.80.8 Other immunodeficiencies with defect prevalence of antibodies
- D.80.9 Unspecified immunodeficiency with predominant antibody defect
- D.81.9 Determined combined immunodeficiency
- D.82.0 Wiskott Aldrich syndrome
- D.82.1 Di George syndrome
- D.82.3 Deficiency response to infection with EB virus
- D.82.8 Deficiency associated with other serious defects
- D.82.9 Indefinite immunodeficiency associated with severe defects
- D.83.0 Common variable immunodeficiency with a predominance of dysfunction or the number of B cells
- D.83.1 Common variable immunodeficiency disorders predominantly related immunoregulatory T cells
- D.83.8 Other common immunodeficiency
- D.83.9 Indefinite common immunodeficiency
- D.89.9 Determined disorders involving the immune mechanism

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.

Drug Program is a guaranteed benefit. The program is done with the use of innovative, expensive active ingredients. Treatment is carried out in selected diseases and includes strictly defined group of patients. The content of each drug program is published as an annex to the notice of the Minister of Health on the list of the Reimbursement of Drugs, Food Products for Special Dietary Purposes and Medical Devices (www.mz.gov.pl)[30]. Description of the program include: patient eligibility for the treatment, exclusion and inclusion criteria of the program, drug regimen, method administration, a list of diagnostic tests performed at the patient's eligibility for the program and necessary to monitor treatment. Eligible patients for drug programs are treated free of charge.

Immunoglobulins are administered intravenously in a hospital or subcutaneously at home. Immunoglobulins home therapy must be initiated in the hospital where the patient is educated in the principles of the home treatment.

The patient is eligible for the program by the Coordinating Team established by the President of the National Health Fund.

Primary immunodeficiencies in adults are rare diseases, and records for this group of patients has not been carried out. Therefore, currently the number of patients remains unknown.

## CONCLUSIONS

The IgG life-long replacement in PAD is an expensive therapy with proven safety and efficacy. The main issue is a well performed diagnosis leading to therapeutic proposals which should be reviewed by the clinical immunologist. It is now possible to tailor the Ig administration route, infusion technique and treatment regime according to patient needs and preferences. It can be supposed that introduction of drug program "Treatment of primary immunodeficiency in adult patients" will help to improve the care of PAD in adults, and to regain data of needs for IgG supplemental therapy in Poland.

### *Disclosers*

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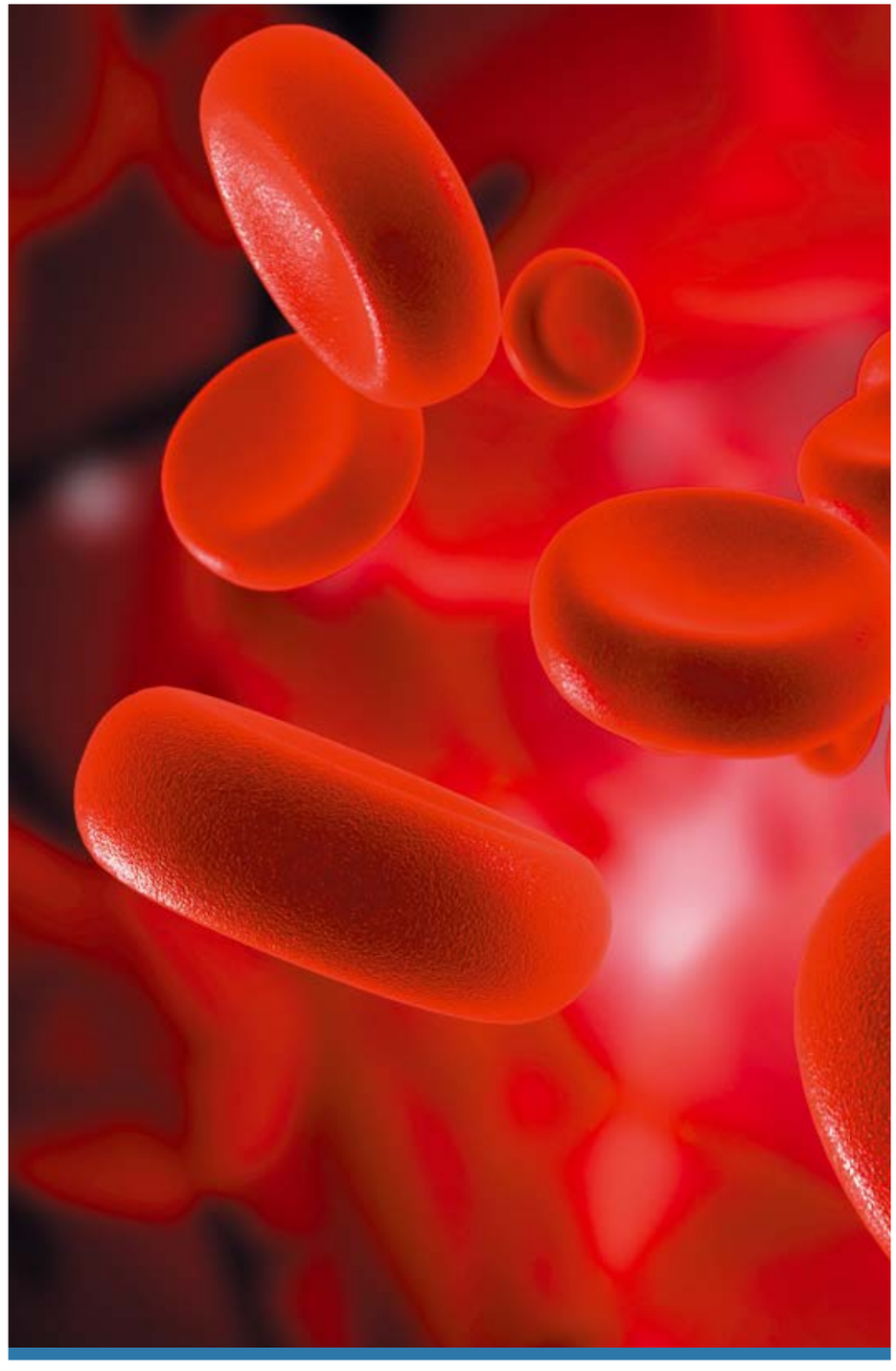

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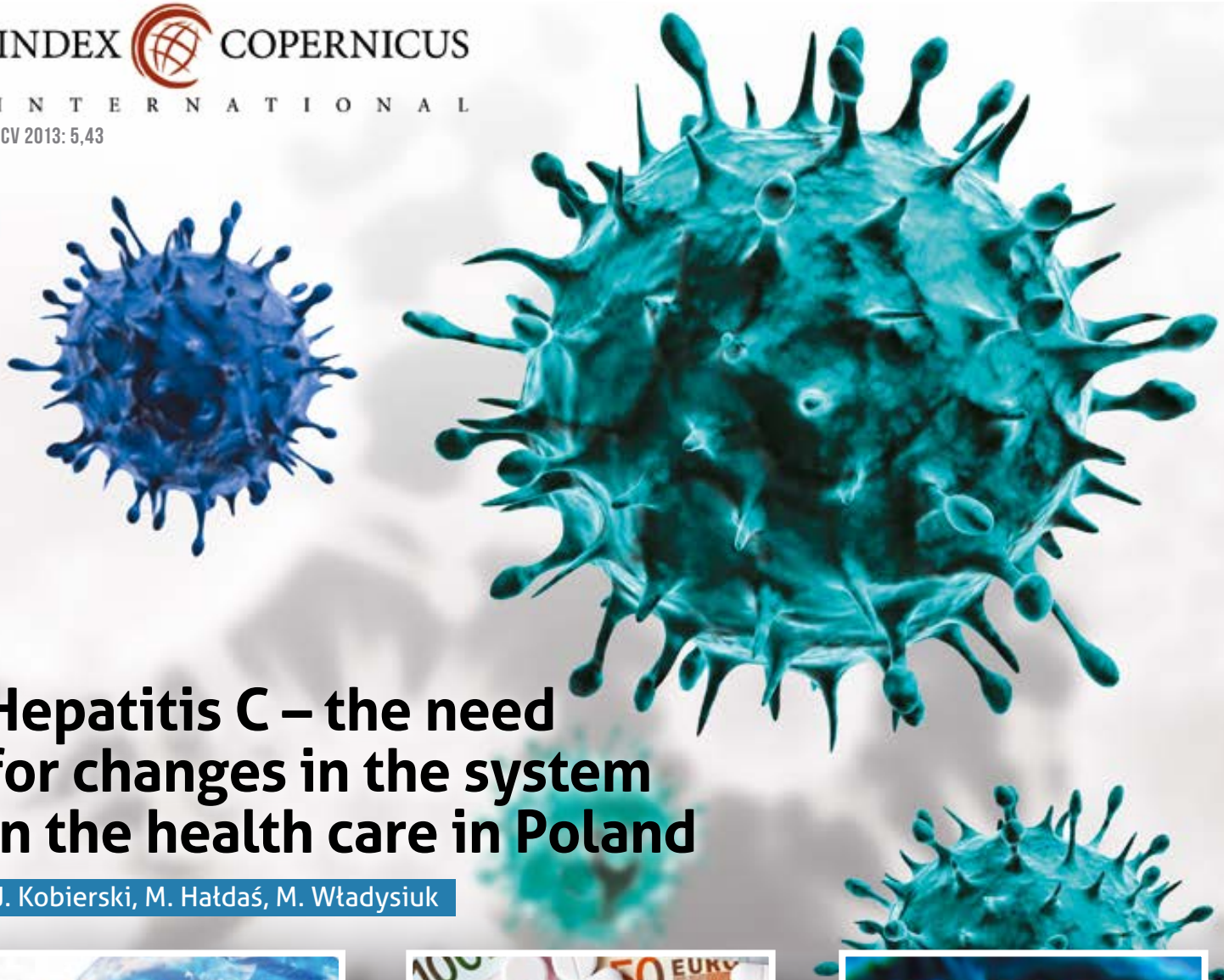

# Hepatitis C – the need for changes in the system in the health care in Poland

J. Kobierski, M. Hałdaś, M. Władysiuk

**Patients Registries - the role of the health system, new trends and hopes for Polish patients - 2nd JHPOR conference, Warsaw March 19th 2015**

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# Generic substitution in the view of pharmaceutical scientists from Polish medical universities

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*Keywords:*
generic substitution, pharmaceutical law, pharmacist

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## ABSTRACT

**Generic substitution is a commonly observed phenomenon in pharmacy. It is promoted as part of the state drug policy and leads to a reduction in expenditure on drugs, facilitates the purchase of medicines by patients and improves compliance. So far researchers have focused on the evaluation of substitution by pharmacists, doctors or patients. The present study investigates the opinion of Pharmaceutical Faculties employees. The respondents acknowledge the importance of generic substitution; nevertheless they do not have a clear opinion on the effectiveness and safety of generic products. The respondents' experience may have had a significant impact their opinion, especially of those working in the community pharmacies. The studies is part of a broader framework of the national debate on generic substitution. Undoubtedly the approach to generic substitution is one of the contemporary challenges of the pharmaceutical law.**

## INTRODUCTION

Generic substitution is the term applied to the substitution of a prescribed branded drug with a different form of the same active substance[1]. This method is used for the optimization of the costs of medicines. The retrenchment on substitution may be used to reimburse innovative molecules. Such conclusion inspired the legislators who passed a new Polish law in 2012[1,2]. According to the legislature, pharmacists are obliged to inform the patient about the possibility of purchasing a cheaper and refundable substitute of a given drug. To promote generic substitution, The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products was involved, and materials have been sent to patients, pharmacists and physicians[3]. The drawn opinions have been widely discussed issues of pharmacy substitution[4]. The pharmaceutical law provided no possibility of refusing to convert the drug to a cheaper equivalent by the pharmacist, based only on their pharmaceutical knowledge. This is an important difference to the preferred solutions in Western Europe and a challenge for the unification of the Polish legislation with the practice in the European Union[5].





## MATERIALS AND METHODS

The aim of the project, was to gain insight into the opinion of the Pharmaceutical Faculties scientists in Poland, on the economic aspects of generic substitution. The research sample was randomly selected. A questionnaire consisting of 11 cloze and 1 open questions was created and tested for its face and content validity. The Likert Scale and modifications was used. Only non-prejective questions were used. A pilot study on the questionnaire was carried out on 10 respondents. The characteristics of the respondents were created based on the responses to questions about the academic degree or title, and any work experience in a pharmacy. The survey was conducted electronically among academics and didactic teachers. For each of the 10 Polish pharmaceutical departments 50 requests were sent by email. The ethical approval was not required for this study.

## RESULTS

In total, 116 employees of Pharmaceutical Faculties, completed the questionnaire. The study group was diverse in terms of obtained professional degree: 37% of the respondents obtained the professional title of Master, 39% of the doctoral degree, 14% with the post-doctoral title (Assistant Professor) and 6% of professors.

Among academics who participated in the study, 30% are actively practicing as a pharmacist in the community pharmacies.

*Table 1. The structure of respondents by degree*

| | | |
|---|---|---|
| 1 | 37,00% | Master |
| 2 | 39,00% | PhD |
| 3 | 14,00% | Assistant Professors |
| 4 | 6,00% | Professors |
| 5 | 4,00% | No information |

The respondents did not have an unanimous opinion on the effectiveness of generic drugs.In the opinion of almost 50% of the respondents there are differences in efficacy between the innovative drugs and generic products. However, almost the same number of respondents, indicated a lack of such differences. It is worth emphasizing that 61% of respondents did not associate additional therapeutic risks with the conversion of the original on the generic. The responses may

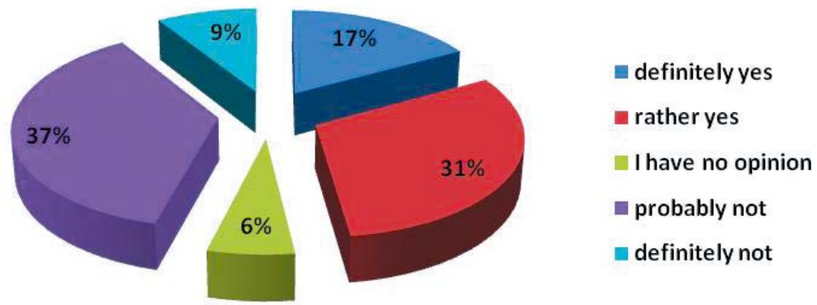


*Figure 1. Are there any differences in efficacy between innovative medicines and generics?*

be related to the professional experience of the respondents. Perhaps patients in pharmacies indicate the differences in the efficacy of drugs in the absence of an increased number of adverse events.

According to 72% of respondents, generic substitution should be promoted as a way of rationalizing the expenditure on drugs; and according to 69% as a way of reducing household spending on drugs. The level of co-payments for drugs in Poland should be considered as too high. Patients, especially the elderly and chronically ailing, may have difficulty in obtaining the necessary medicines. This may have an impact on compliance, which in turn could lead to an increase in health care spending. Commonly known mechanisms should be able to refer patients to hospitals instead of outpatient treatment[6].

An extremely important issue of modern pharmacology is monitoring adverse reactions to drugs. The Polish pharmaceutical law refers to the definition of the adverse effects of the medicinal product - not the active pharmaceutical ingredient. This was reflected in the survey results. 71% of respondents emphasized that the cost of the delivered equivalent should be monitored. The National Health Fund also based on data relating to the possible increased incidence of adverse events.

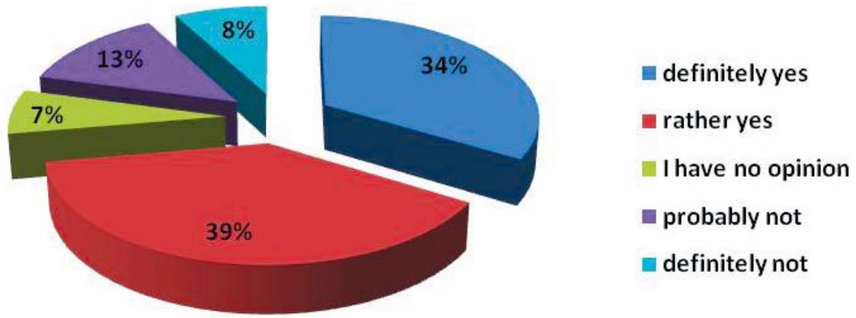


*Figure 2. Should generic substitution be promoted as an opportunity to rationalize expenditure on drugs?*

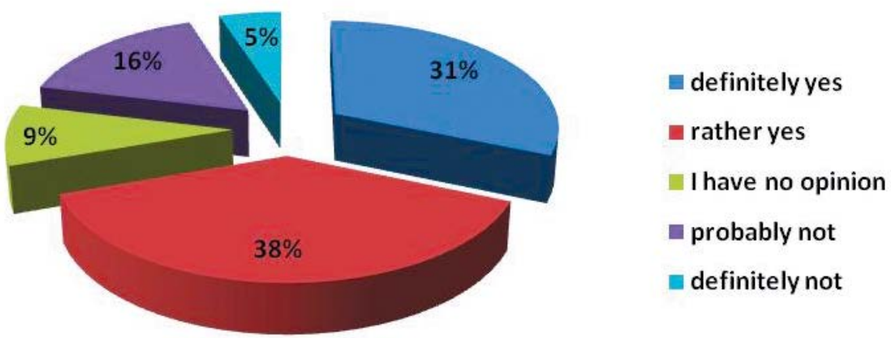


*Figure 3. Should generic substitution be promoted among physicians as a way of reducing household spending on drugs?*



PATIENTS, ESPECIALLY THE ELDERLY AND CHRONICALLY AILING, MAY HAVE DIFFICULTY IN OBTAINING THE NECESSARY MEDICINES.



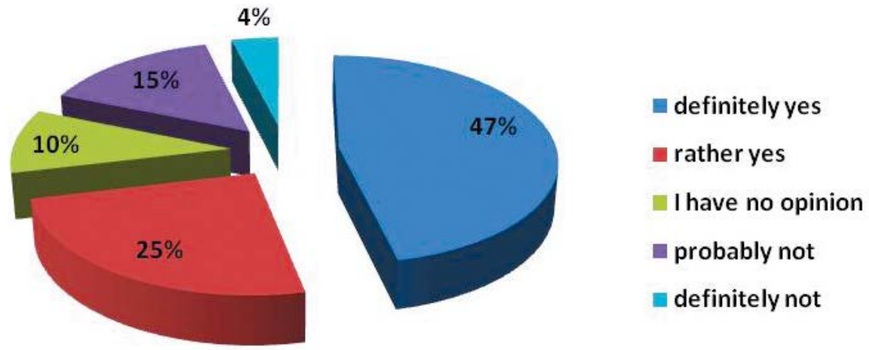


*Figure 4. Should the costs based on data relating to the possible increased number of physician visits, hospitalizations, adverse effects of the delivered equivalent be monitored by the National Health Fund?*

In the opinion of 82% of respondents, the financial surplus obtained on generic substitution, should be used to expand the list of reimbursed drugs. It is worth noting that the introduction of new rules for reimbursement of medicines has led to the introduction of new reimbursed, innovative molecules. However, access to the innovative substances for Polish patients, should be viewed as difficult, particularly when we compare the situation in Poland and the western countries of the European Union.

tures for drugs in hospitals. The adopted drugs available in inpatient care should be divided into 3 categories: A - to be applied by any physician, B - requiring the consent of the chief, C - only with the consent of the Director of Medical devices. This distinction has been widely accepted.

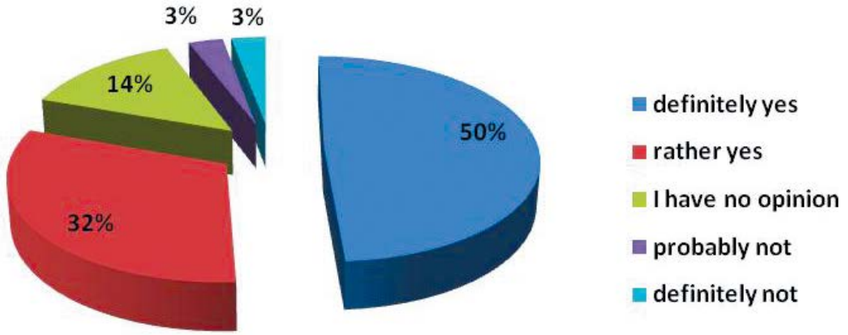


*Figure 5. Should the financial surplus obtained on generic substitution be used to expand the list of reimbursable medicinal substances?*

According to 69% of respondents, generics have to be an important component of hospital formularies. Formularies are now a commonly encountered form of rationalization of expendi-

72% of respondents believe that the pharmacist should be able to refuse to convert the drug to a cheaper generic equivalent if they consider it appropriate in view of the available medical and pharmaceutical knowledge. Nowadays, only physicians have complete freedom in the process of prescribing. Pharmacists were obliged by law to inform patients about the possibility of purchasing a cheaper substitute drug. Nevertheless they cannot legally refer to their pharmaceutical

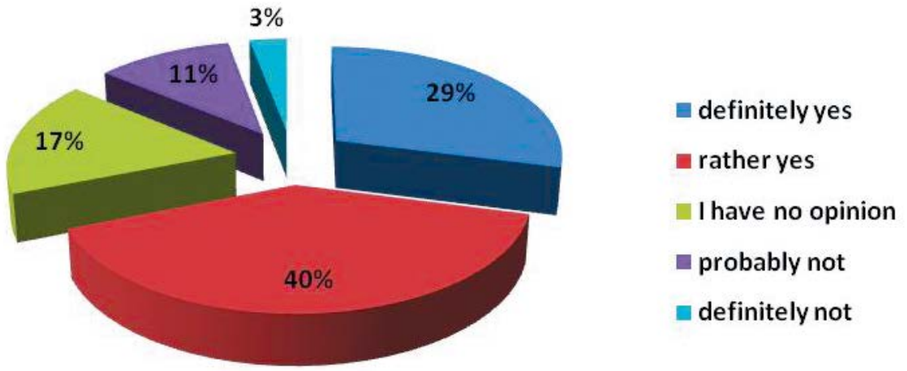


*Figure 6. Should generics be widely used in hospitals (as an important element of hospital formularies) leading to the rationalization of expenditure on drugs?*

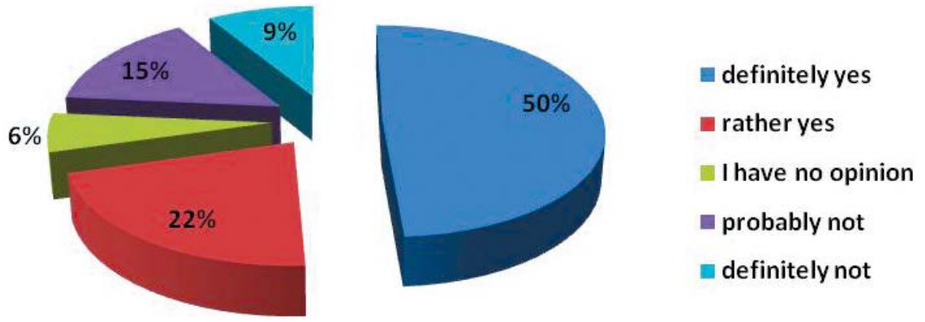


*Figure 7. Should the pharmacist be able to refuse to convert the drug to a cheaper generic equivalent if they considers it appropriate in view of the available medical and pharmaceutical knowledge?*

knowledge, even if the used drug has a narrow therapeutic index and conversion should not take place. In Europe, various countries have prepared pharmacy substitution standards for determining such issues. The legislature did not provide for the possibility of introducing the Good Pharmacy Practice: a document containing a description of the procedures to facilitate the use of the pharmacists' knowledge for the benefit of patients.

## DISCUSSION

Substitution is a relatively well-explored phenomenon in the pharmaceutical market. One of the global challenges facing pharmacology is the unification of the law. The process of harmonization is ongoing within the countries of the European Union. Different countries have different regulations on legal issues related to generic medicines and the process of substitution. Undoubtedly the approach to generic substitution is one of the contemporary challenges of the pharmaceutical law[7]. There have also been considerable debates about bioequivalence and generic substitution of certain critical care drugs. Substitution is an important phenomenon, especially for patients suffering from chronic illnesses. One study investigated the attitudes of patients suffering from epilepsy to substitution. More than 70% of the patients were concerned with the effectiveness of generic antiepileptic drugs and 68% of the patients were not comfortable receiving generics to treat epilepsy. About 87% of the patients thought that their antiepileptic drug should only be substituted by a generic with their consent, and 64% of the patients believed that substitution should only take place with the consent of their doctor[8]. Other studies came toquite similar conclusions. Substitution may result in a reduction in compliance. Personal interviews with 174 Norwegian patients (50–80 years) who had had their brand-name antihypertensive drug generically substituted, were conducted using a semi-structured questionnaire. The study shows that generic substitution can be an additional factor in poor drug adherence in hypertensive patients and contributes to concerns and confusion among the patients[9]. Similar conclusions were also drawn by researchers from Australia. For patients, the price is not the most important feature. Ill people appear to have a strong commitment to a specific medicine product. The findings show that customers with poor awareness of generic prescription medicine, when offered a substitute, were likely to become confused and suspicious. Pharmacists, on the other hand, experienced frustration due to the mistrust and annoyance their customers displayed[10]. The differences in efficacy between the original and generic drugs are confirmed by scientific research. It seems to be a reasonable argument that the payer should consider the pharmacotherapy cost based side effects. Of 671 patients treated with branded lamotrigine, 187 patients (27.9%) switched to a generic, and 51 of these patients (27.5%) switched back to the branded medication. The switch to generic lamotrigine was significantly associated with an increased number of physician visits and hospitalizations[11]. One of the main arguments for substitution is saving measures; however, empirical research shows a different trend. A careful analysis demonstrates the only a part of the substitution process leads to cost saving policies. Finland proves to be a good example of the above mentioned issues. The study analysed the economic assessment of substitution focusing on the impact of reference pricing and extension of generic substitution on the daily cost of antipsychotic drugs in Finland during the first year after its launch. Furthermore, the additional impact of reference pricing on prior implemented generic substitution is assessed. Reference pricing and the extension of generic substitution produced substantial savings on antipsychotic medication costs during the first year after its launch, but the intensity of the impact differed between active substances. Furthermore, results suggest that the additional cost savings from reference pricing after prior implemented generic substitution, are comparatively low[12].

## CONCLUSIONS

***According to the respondents:***

1. Substitution is the way to rationalize expenditure on drugs.
2. There are differences in efficacy between the drugs and generic companies.
3. The use of generics is not associated with an increased risk of side effects.
4. The costs relating to the possible increased incidence of adverse events deriving from the use of the counterpart should be monitored by the National Health Fund.
5. The financial surplus obtained on generic substitution should be used to expand the list of reimbursed drugs.
6. Generic substitution should be promoted among physicians as a way of reducing the spendings on drugs.
7. Generics should be an important component of hospital formularies.
8. The pharmacist should be able to refuse the drug exchange for cheaper generic equivalent if they consider it appropriate in view of the available medical and pharmaceutical knowledge.

Experience may have had a significant impact on the opinions of respondents, especially those working in the community pharmacies. Undoubtedly, the approach to generic substitution is one of the contemporary challenges of the pharmaceutical law. The studies represent another part in the national debate on generic substitution. ■

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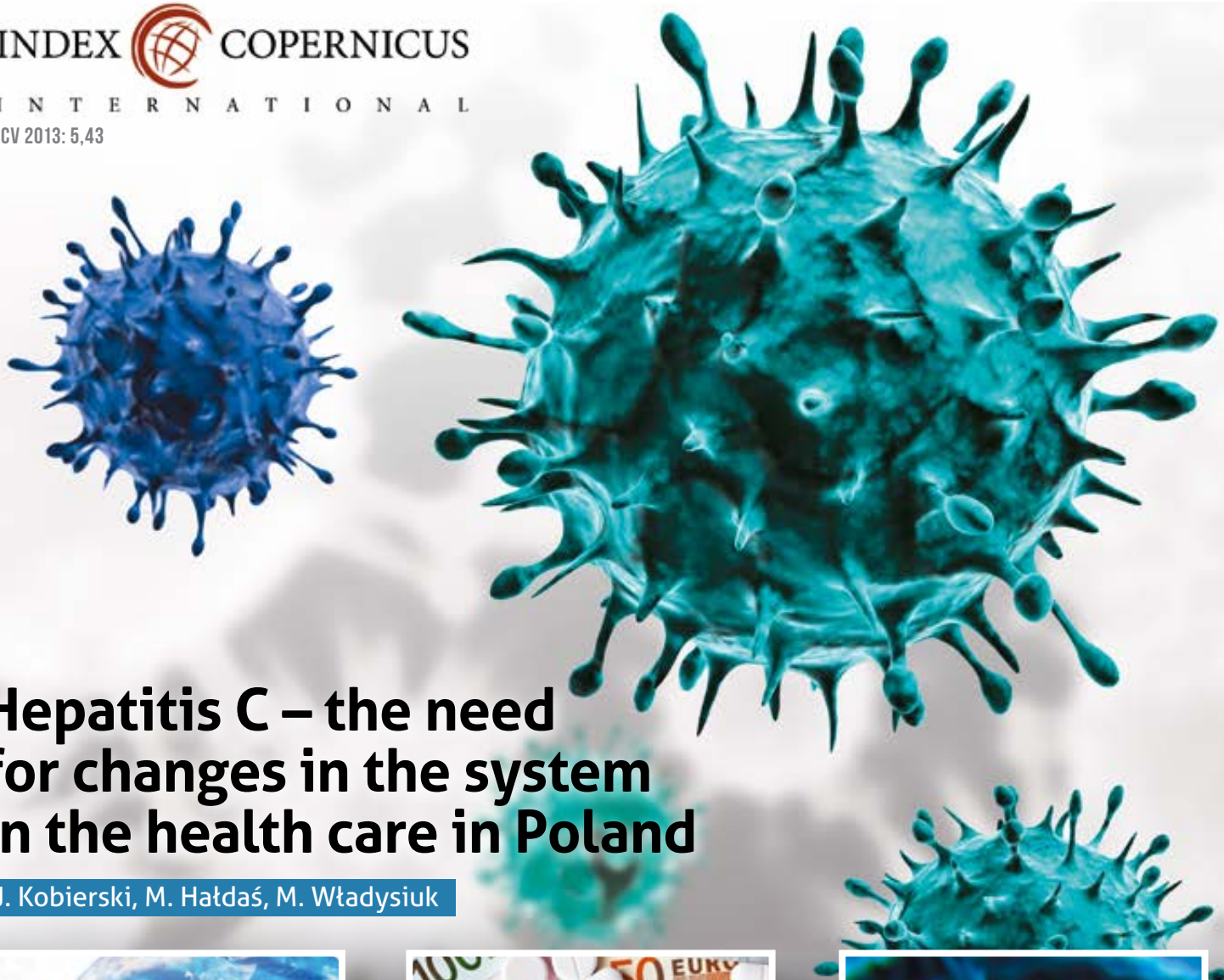

# Hepatitis C – the need for changes in the system in the health care in Poland

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# XYZ-analysis to determine doctors' influence on the pharmacy assortment of OHD in the Podolsky region of Ukraine

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Keywords:
diabetes mellitus (DM) type 2, oral hypoglycemic drugs, XYZ-analysis

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## ABSTRACT

**XYZ-analysis of oral hypoglycemic drugs (OHD) was conducted to determine the effect of individual parameters of the doctors on the formation of pharmacy assortment. It was found that the OHD of the groups X and Y were formed by practitioners under the age of 30 years (47%), with work experience up to 5 years (40%), mostly – endocrinologists (73%), with the second qualifying category (33%), with high qualifying category (27%), and without qualifying category (26%). 14% of these doctors have scientific degree as PhD and associate professor. The group Z was formed by the doctors aged 51-60 years (60%), in 100% of cases there were endocrinologists with 11-20 years of experience on specialty (66%), with the second qualification category (67%), and with the high qualifying category without academic degrees and titles (33%). It has been established that the doctors of Podolsky region of Ukraine who formed groups X and Y were largely committed to the German and French manufacturers, and the doctors who formed group Z were largely committed to the manufacturer of Poland and Ukraine. This indicates a more stable position of manufacturers of Germany and France at the pharmaceutical market of OHD in Podolsky region of Ukraine. It has been established that the cause of these doctors' commitment was the high efficiency of OHD of manufacturers from Germany and France.**

## TOPICALITY

Ukrainian pharmaceutical market has a stable growth rates during last year's (on average on 15-20% per year)[5], this causes the presence of a large number of generics in it, in particular OHD.



THE CALCULATION OF VARIATION COEFFICIENTS FOR THE ANALYZED GROUPS OF DRUGS IS THE BASIS OF XYZ-ANALYSIS. THE SMALLER THE VARIATION COEFFICIENTS, THE GREATER THE COMMITMENT OF THE CONSUMER TO THIS GROUP OF DRUGS



Formation of pharmaceutical assortment of drugs depends on many factors; one of the most important is the demand. OHD are prescription drugs and their demand is formed by doctors that prescribe these drugs. This is determines an interest in the person of physician, his individual characteristics.

## THE PURPOSE:

To identify the influence of individual characteristic of doctors on the formation of pharmaceutical assortment of OHD by XYZ-analysis.

## RESEARCH OBJECTIVES:

1) carry out a sociological survey of practitioners (endocrinologists, therapeutists, family doctors),

2) conduct XYZ-analysis of OHD,

3) analyze the individual parameters of physicians (age, experience, specialization, category, academic degree and title),

4) identify the doctors' commitment to a specific country manufacturer of OHD.

## THE OBJECT OF THE STUDY:

Surveys of practitioners.

## THE RESEARCH MATERIALS:

105 questionnaires of practitioners from Vinnytsa, Khmelnytsky and Ternopol areas (Podolsky region).

## RESEARCH METHODS:

Sociological survey with questionnaires application, XYZ-analysis of OHD, analysis of individual parameters of practitioners according to questionnaires, frequency analysis of doctor's commitment to certain countries producers of OHD.

Questionnaire of a sociological survey included 19 questions. These questions described individual parametrs of doctors (age, experience, specialization, category, academic degree and title), the international nonproprietary name (INN) and trade names of OHD that are prescribed by these doctors, doctors' commitment to certain countries-producers of the OHD, the reasons for such commitment, accounting the patients' purchasing power.

The calculation of variation coefficients for the analyzed groups of drugs is the basis of XYZ-analysis. The smaller the variation coefficients, the greater the commitment of the consumer to this group of drugs[1,3]. Category X (coefficient of variation to 10%) includes drugs that are less susceptible to fluctuations in demand, their sale are easily predicted. Such drugs are characterized by high possibilities of sales forecast. For such drugs must be kept optimal reserves in pharmacies and apply methods of demand forecasting models and optimal sizing of the stock. Category Y (coefficient of variation is 10-25%) involves the drugs with some fluctuations in demand and medium sales forecast. Category Z (coefficient of variation greater than 25%) comprises the drugs with non regular consumption, their demand/sales cannot be predicted, trend any absence, low sales forecast accuracy. These include drugs that are brought to order or those which just appeared on the market and recently went on sale[2,4].

XYZ-analysis was implemented in three stages:

1. Determination of the coefficient of variation of the analyzed OHD
2. Grouping of OHD in accordance with the increase in the coefficient of variation
3. Drug distribution over categories: X, Y, Z.

The coefficient of variation was calculated as the ratio of the standard deviation to the arithmetic mean of the measured values of drugs by the formula:

$V = \sigma/x$, where

V- coefficient of variation

σ - standard of deviation

x - arithmetical mean

*Table 1. Coefficients of variation of OHD*

| | Trade name | Value of the coefficientof variation | Results of XYZ-analysis |
|---|---|---|---|
| 1 | Glucophage tablets (t.) 500 mg №30, № 60; 850 mg, № 30, № 60; 1000 mg, № 30, № 60 | 0,53 | x |
| 2 | Dianorm-M t № 60 | 0,71 | |
| 3 | Victoza solution for injections of 6 mg/ml cartridge 3ml, № 1, № 2 | 1,37 | |
| 4 | Diaformin ® Pharmak t. 500 mg № 30; t. 850 mg № 30, t. 1000 mg № 30, № 60 | 1,79 | |
| 5 | Glucovance t. 500 mg+2,5 mg № 30; t. 500 mg+5 mg № 30 | 2,04 | |
| 6 | Siofor t. 500 mg № 60; t. 850 mg № 60; t. 1000 mg № 30, № 60 | 2,08 | |
| 7 | Amaryl t. 2 mg № 30; t. 3 mg № 30; t. 4 mg № 30 | 2,13 | |
| 8 | Maninil t. 3,5 mg № 120; t. 5 mg № 120 | 2,33 | |
| 9 | Glibomet t. № 40 | 2,38 | |
| 10 | Ongliza t. 2,5 mg № 30; t. 5 mg № 30 | 2,38 | |
| 11 | Glurenorm t. 30 mg № 60 | 2,77 | |
| 12 | Diabeton MR t. 60 mg № 30 | 2,85 | |
| 13 | Metfogamma t. 1000 mg № 30, № 120 | 2,86 | |
| 14 | Pioz t. 15 mg № 28; t. 30 mg № 28 | 2,86 | |
| 15 | Glikomet t. 500 mg № 100 | 3,57 | |
| 16 | Yanumet t. 550 mg № 28; t. 900 mg № 28; t. 1050 mg № 28 | 3,57 | |
| 17 | Januvia t. 25 mg № 14, № 28; t. 50 mg № 14, № 28; t. 100 mg № 14, № 28 | 3,57 | |
| 18 | Diaglizid MR t.30 mg № 30, № 60 | 4,55 | |
| 19 | Diapirid t. 2 mg № 30; t. 3 mg № 30; t. 4 mg № 30 | 5,71 | |
| 20 | Amapirid t. 2 mg № 30; t. 3 mg № 30; t. 4 mg № 30 | 7,14 | |
| 21 | Dianormet t. 500 mg № 30; t. 850 mg № 10, № 30; t. 1000 mg № 30 | 7,14 | |
| 22 | Dibizid M t. № 60 | 7,14 | |
| 23 | Duotrol t. № 30 | 7,14 | |
| 24 | Metformin Sandoz t. 500 mg № 30, № 120; t. 850 mg № 30, № 120 | 7,14 | |
| 25 | Oltar t.1 mg № 30, № 60, № 90, № 120; t. 2 mg № 30, № 60, № 90, № 120; t. 3 mg № 30, № 60, № 90, № 120 | 7,14 | |
| 26 | Tripride t. № 30 | 7,14 | |
| 27 | Glibenclamide Pharmak t. 5 mg № 50, № 100 | 10,58 | y |
| 28 | Diaglizid t. 80 mg № 30, № 60 | 10,58 | |
| 29 | Pioglar t.15 mg № 30, № 100; t. 30 mg № 30, № 100 | 14,28 | |
| 30 | Glutason t.15 mg № 28; t. 30 mg № 28; t. 45 mg № 28 | 14,28 | |
| 31 | Glimepiride-Lugal t. 2 mg № 30; t. 3 mg № 30; t. 4 mg № 30 | 14,29 | |
| 32 | Diabrex t. 1 mg № 30; t. 2 mg № 30; t. 3 mg № 30; t. 4 mg № 30 | 16,67 | |
| 33 | Glirid t. 2 mg № 30; t. 4 mg № 30 | 28,57 | z |





## RESULTS OF THE RESEARCH

When analyzing questionnaires of the doctors it has been divide all OHD into 3 groups (X,Y and Z) and obtained the following results (Table 1).

It has been found that the groups X are formed by 26 OHD with variation coefficients from 0,53 to 7,14; group Y – by 6 OHD with variation coefficients from 14,28 до 16,67; group Z – by only 1 OHD with variation coefficient 28,57.

*Table 2. Characteristics of doctors by individual parameters*

| № | Parameters | Number of doctors prescribed drugsgroup X, Y (%) | Number of doctors prescribed drugsgroup Z (%) |
|---|---|---|---|
| 1 | Age (years) | | |
| | to 30 | 47 | 20 |
| | 31-40 | 20 | 20 |
| | 41-50 | 6 | 0 |
| | 51-60 | 27 | 60 |
| 2 | Experience of work(years) | | |
| | to 5 | 40 | 0 |
| | 6.10.2015 | 13 | 34 |
| | 1.11.2020 | 20 | 66 |
| | 21-30 | 27 | 0 |
| 3 | Specialization | | |
| | endocrinologists | 73 | 100 |
| | therapeutists | 14 | 0 |
| | family doctors | 13 | 0 |
| 4 | Category | | |
| | higher | 27 | 33 |
| | first | 14 | 0 |
| | second | 33 | 67 |
| | has not | 26 | 0 |
| 5 | Academic degree and title | | |
| | PhD, associate professor | 14 | 0 |
| | doctor of science, professor | 0 | 0 |
| | has not | 86 | 0 |

It was interesting to describe physicians who form this assortment of OHD according to individual indicators (age, experience, specialization, category, academic degree and title) (Table 2).

It was found that the OHD of the groups X and Y were formed by practitioners under the age of 30 years (47%), with work experience up to 5 years (40%), mostly – endocrinologists (73%), with the second qualifying category (33%), with high qualifying category (27%), and without qualifying category (26%). 14% of these doctors have scientific degree as PhD and associate professor. The group Z was formed by the doctors aged 51-60 years (60%), in 100% of cases there were endocrinologists with 11-20 years of experience on specialty (66%), with the second qualification category (67%), and with the high qualifying category without academic degrees and titles (33%).

Doctors' commitment to a certain country-manufacturers of OHD has been studied (Table 3).

*Table 3. Degree of practitioners' commitment to a country-manufacturers of OHD*

| № | Country-manufacturer of OHD | Number of doctors that are prescribed OHD of groups X, Y (%) | Number of doctors that are prescribed OHD of group Z (%) |
|---|---|---|---|
| 1 | Ukraine | 40 | 49 |
| 2 | Germany | 93 | 28 |
| 3 | France | 60 | 28 |
| 4 | Austria | 14 | 14 |
| 5 | Poland | 14 | 63 |
| 5 | India | 7 | 0 |

It has been established that the doctors of Podolsky region of Ukraine who formed groups X and Y were largely committed to the German (93%) and French (60%) manufacturers, and the doctors who formed group Z were largely committed to the manufacturer of Poland (63%) and Ukraine (49%). At the same time, only 14% of the doctors who formed groups X and Y were committed to the Poland and Austria manufacturers and 40% – to the Ukraine manufacturers.

## DISCUSSION

The calculation of variation coefficients for the analyzed groups of drugs is the basis of XYZ-analysis. The reasons of differences in the values variation of coefficients could have been caused by doctor's commitments to certain drugs, doctors' experience, interests, drugs belonging to known producing firms, presence/deficit of drugs in the pharmaceutical market; medical representatives' work with doctors, publications in specialized magazines, etc.

It has been found that the group X includes OHD that have the highest sustainable preference of doctors: Glucophage, Dianorm-M, Victoza, Diaformin® Pharmak, Siofor, Glucovance, Amaryl, Maninil, Glibomet, Ongliza, Glurenorm, Diabeton MR, Metfogamma, Pioz, Glikomet, Yanumet, Januvia, Diaglizid MR, Diapirid, Amapirid, Dianormet, Dibizid M, Duotrol, Metformin Sandoz, Oltar, Triprayd. Group Y had some tendencies of preferences and was formed by the following OHD: Glibenclamide Pharmak, Diaglizid, Pioglar, Glutason, Glimepiride-Lugal Diabrex. Group Z was formed by only one drug Glirid.

In group description the groups of the doctors who prescribed oral hypoglycemic drugs in groups X and Y no differences were revealed in individual parameters, which allowed to combine them in one group. Individual parameters of the doctors who formed X and Y groups were the following: age was 30 years (47%), work experience was up to 5 years (40%), in 73% of cases they were the endocrinologists, 33% of them had the second qualification category, 27% – the highest, in the 26% – without qualification category. Approximately 14% of these doctors have PhD degree and academic title of associate professor. Individual parameters of doctors who formed the groups Z were following: age was 51-60 years (60% of cases), they were endocrinologists (in 100% of cases) with experience in the specialty 11-20 years (66% of cases), 67% of them had the second qualification category, 33% of them had a higher qualification category and in 100% of cases they were without scientific degrees and titles.

Results of the survey of practitioners show stable position of Germany and France manufacturers of doctors that are prescribed OHD: 93% Germany manufacturers and 60% France manufacturers form groups X and Y of OHD. In comparison with the manufacturers of these drugs of Germany and France the manufacturers Ukraine, Poland and Austria had unstable position in the pharmaceutical market of Ukraine Podolsky region: 40%, 14% and 14%, respectively of odoctors that are prescribed OHD of groups X, Y.

RESULTS OF THE SURVEY OF PRACTITIONERS SHOW STABLE POSITION OF GERMANY AND FRANCE MANUFACTURERS OF DOCTORS THAT ARE PRESCRIBED OHD: 93% GERMANY MANUFACTURERS AND 60% FRANCE MANUFACTURERS FORM GROUPS X AND Y OF OHD.

The cause of such distribution, in the opinion of the respondents, is the high efficiency of OHD of groups X and Y (80%), rare adverse reactions (60%), presence of these OHD in state treatment standards (33%), constant presence of these OHD in pharmacies (27%) and their affordability (7%).

## CONCLUSIONS

1. OHD of X and Y groups were formed by younger practitioners with shorter work experience, mostly endocrinologists of the second qualification category without academic degrees and titles; Z group were formed by only older endocrinologists with longer work experience of the second qualification category without scientific degrees and titles.
2. The main reason for the commitment of doctors to OHD manufacturers of Germany and France was a high efficacy of these drugs.
3. A more stable position of manufacturers of Germany and France in the pharmaceutical market of Podolsky region of Ukraine.
4. Most of the physicians in selecting OHD take into consideration the purchasing power of the population. ■

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# Can We Determine the Optimal Cycle Length for Which Half-Cycle Correction Should Always Be Applied?

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## ABSTRACT

***Objective:*** **The aim of the study is to measure the influence of cycle length and progression rates on differences between final results obtained using different approaches concerning time of transition to another state in Markov models (at the beginning, at the end of the cycle or half-cycle correction – HCC) and to estimate an optimal cycle length for which HCC should always be applied.**

***Methods:*** **A hypothetical, two-state Markov model was built. Assuming different progression rates, four methods concerning time of transition were compared. For each rate, the threshold values were determined, i.e. the maximal cycle length for which the difference between HCC/'life-table' (LT) method and 'beginning'/'end' methods were not greater than 5%. Cycles longer than the estimated threshold are assumed to imply the application of HCC/LT.**

***Results:*** **Under few assumptions, the threshold cycle length for annual progression of 0.05 was 1 year or 2 years, for 5% and 0% discount rate, respectively. The threshold cycle lengths became shorter for lower progression rates (2 weeks for 0.90 rate). The results obtained for single intervention cannot be easily repeated for incremental outcomes; however, some general relationships can be determined.**

***Conclusions:*** **Choice of the time of transitions in the model may have a significant impact on the findings of economic evaluations. For cycles shorter than 2 weeks, HCC/LT does not appear necessary. However, it should be applied for cycles longer than 1 year. We were unable to make a recommendation for cycles between 2 weeks and 1 year.**

## INTRODUCTION

Medical decision making is supported by pharmacoeconomic analyses, which are usually based on modeling of health effects and costs. A common tool used in such analyses are Markov models, which enable the progress of the diseases to be simulated throughout the lifetime of patients[1,2]. One of the problems that arise whilst modeling long-term costs and health outcomes utilizing Markov models is the choice of transition time between health states. Once a specific cycle length is adopted, it allows to change the status of disease (progression, regression or death) only at specific time points, which does not always adequately reflect the course of disease in real life[1]. Various approaches can be adopted, i.e. transitions at the beginning or at the end of the cycle and more accurate methods like half-cycle correction (HCC), 'life-table' method (LT), or Simpson's method[3,4]. The half-cycle correction and the 'life-table' method are equivalent in some situations: if costs/utilities are equal in each cycle and there is no discounting[4]. Despite some limitations[4,5], the most common method used in economic evaluations, which is also recommended by some of national HTA agencies[6–9], is half-cycle correction.

The practical implementation of the half-cycle correction and 'life-table' method has been described in other publications [1,4].

Our aim is to review information concerning various approaches to choosing time of transition, accuracy of these methods and to establish whether there is an optimal cycle length for which HCC/LT should always be applied.

## METHODS

We developed a simple two-state Markov model (alive or dead) in order to analyze the influence of cycle length on differences between analyzed methods.

The time horizon was set to be lifetime, the discount rate was 0–5% and costs/utilities were held constant in time.

Assuming different death probabilities (0.05–0.90 annually), we compared four approaches:

- transitions at the beginning of the cycle ('beginning'),
- transitions at the end of the cycle ('end'),
- half-cycle correction,
- 'life-table' method.

Half-cycle correction is made to transitions either at the beginning or at the end of the cycle. The method of calculations differs slightly between those two assumptions, however in both cases identical results are obtained. In case of progression at the end of the cycle, HCC is implemented by cutting off the first half of the first cycle. If the horizon of the analysis is shorter than lifetime, patient/cohort's life must be modeled one cycle longer then the assumed time horizon and the results for the first half of the additional cycle must be added to cumulative results. In case of progression at the beginning of the cycle, HCC is implemented by adding half of a cycle at the beginning of the analysis. If the horizon of the analysis is shorter than lifetime, this action will result in overestimation of the results, therefore, an additional correction must be made by cutting off second half of the last cycle.

Both of the described methods result in the same final outcomes, so we use the same outcomes for HCC when comparing it with both 'beginning' and 'end' methods.

The 'life-table' method is implemented by calculating number of patients staying in particular state as a mean number of patients staying in this state at the beginning and at the end of the cycle (arithmetic mean, i.e. assuming linear progression).

The key issue concerned with the use of different methods is establishing the time points when costs/health effects are calculated (discounting time). For 'beginning' and LT method we assumed that there are no costs/effects incurred in cycle 0 (cycle, in which no discounting is applied). For 'end' method we assigned full cost to the cycle 0 and for HCC method we assigned half of these costs to the cycle 0 (Table 1). Such procedure is coherent with practical approach in pharmacoeconomic models.

*Table 1. Amount of costs/health effects in cycle 0 and 1*

| Cycle | Beginning | End | LT | HCC |
|---|---|---|---|---|
| 0 | 0 | $c$ | 0 | $0.5c$ |
| 1 | $\frac{c(1-q)}{(1+r)^1}$ | $\frac{c(1-q)}{(1+r)^1}$ | $\left(\frac{c+c(1-q)}{2}\right)\frac{1}{(1+r)^1}$ | $\frac{c(1-q)}{(1+r)^1}$ |

$t$ – cycle length in years

$q$ – progression probability (per cycle)

$c$ – costs/effects of 'alive' state (per cycle)

$r$ – discount rate

We assumed progression probabilities to be constant in time. For each probability the threshold values were determined, i.e. the maximal cycle lengths for which the differences between half-cycle correction/'life-table' method and 'beginning'/'end' methods were not greater than 5%. We propose that cycles longer than the estimated threshold should imply the application of HCC/LT.

Furthermore, influence of applied assumptions (cost/utilities and death probabilities variability, number of health states in the model) on the obtained results and consequences of relaxing them were analyzed. Additionally, we studied the relationship between threshold cycle lengths and incremental results, and made an attempt to provide general conclusions concerning incremental cost-effectiveness ratios (ICERs).

All calculations were performed using Microsoft Excel® 2007.

## RESULTS

### *General relations between cycle length, death probability and the method of calculation*

The problem of calculating costs / health effects for a cohort of patients may be illustrated by graphs which link survival curves with costs/utilities. Such graphs may be created for every state, however in more complicated models this is an incredibly laborious task. The final result (i.e. total costs, expected survival) would be the sum of areas under the curves.

A mathematical approach to the problem of calculating the area under the curve would be solving a corresponding integral. When discrete Markov models are used, the approximate area is calculated as the sum of areas of respective rectangles. All four methods ('beginning', 'end', HCC, LT) provide approximate outcomes, which become more accurate as smaller rectangles are used. Using Markov models language, it means that the shorter cycle is chosen, the more accurate outcomes are obtained. It is intuitive: if a short cycle is used, we are able to describe more precisely the moments of transitions between states. The illustrative results for probability of death equal to 0.5 are presented on Figure 1.

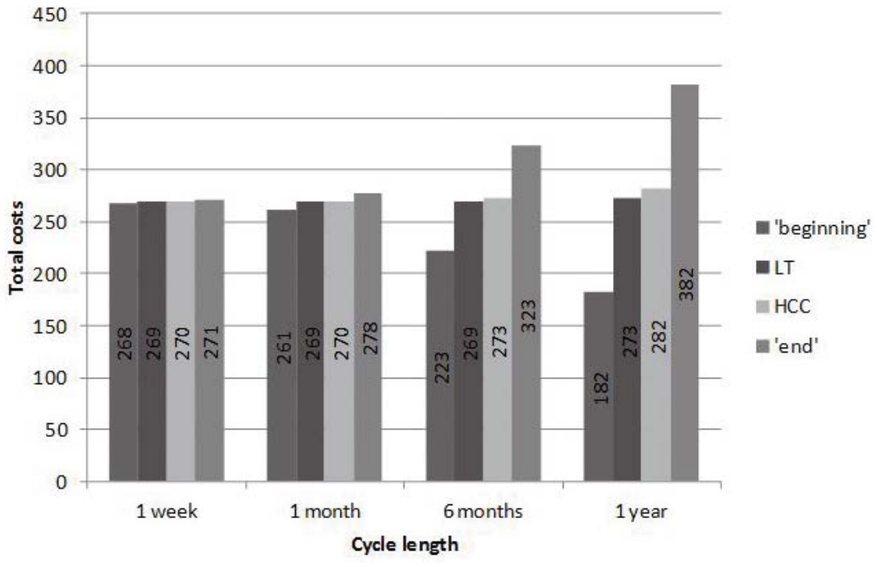


*Figure 1. Comparison of differences in total costs between methods for various cycle lengths*
*Assumptions: progression rate – 0.5, annual cost for 'alive' state – 200, annual cost for death state – 0, discount rate 5%. The exact result (calculated using integrals) is 269.56.*

If the horizon of analysis is finite (i.e. not lifetime), the accuracy of the approximation depends also on the slope of the curve (progression probabilities in Markov models). The steeper the slope, the less precise the approximation of the area (results for several slopes are presented on Figure 2).

In case of lifetime horizon the differences between 'beginning', 'end' and HCC methods are associated with the differences in approach to cycle 0. As a result, the difference between results obtained using different methods is equal to the difference obtained in cycle 0 and does not depend on the progression probability (provided it is constant). However, the percentage difference between results obtained using HCC and 'beginning' / 'end' methods depends on the probability because the total outcomes are strictly related to the probability of transition. For example, assuming annual costs of 'alive' state equal to 200, discount rate 5% and progression probabilities equal to 0.7 or 0.8 the differences between total outcomes for HCC and other methods are 100 for both probabilities of death and the percentage differences are 56% and 68% for probabilities 0.7 and 0.8, respectively.

As far as LT method is concerned, the difference between total results for this method and for 'beginning' / 'end' is associated not only with cycle 0, but also with other cycles. Moreover, the percentage differences for LT vs 'beginning' method and LT vs 'end' method are in general not equal.

However, it may be easily shown that percentage differences between costs/effects for LT and 'beginning' / 'end' method in any single cycle are constant and, as a result, equal to the percentage differences for total costs/effects (Table 2).

The same results may be obtained for any other cycle.



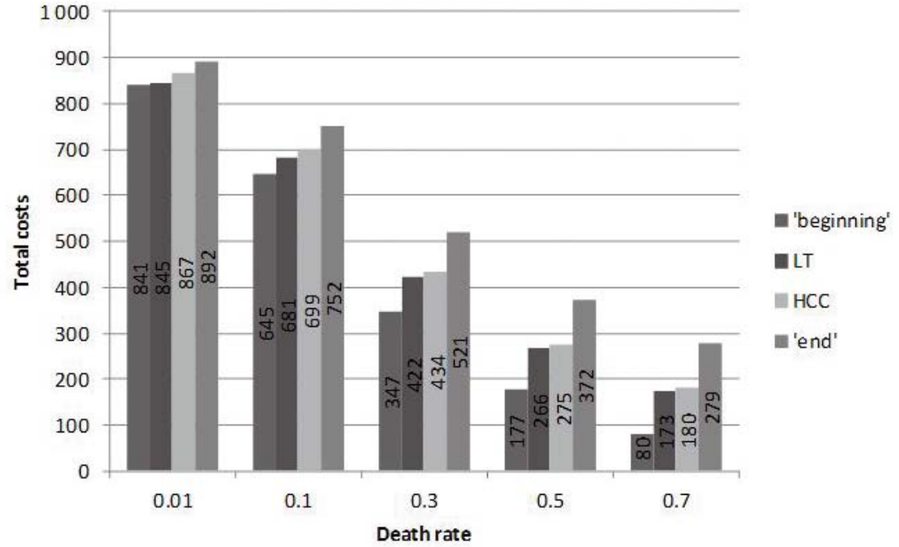


*Figure 2.Compariso n of differences in total costs between methods for various progression rates*
*Assumptions: horizon 5 years, cycle length 1 year, annual costs 200, discount rate 5%.*
*The exact results (obtained using integrals) are 866.32, 697.16, 428.30, 262.96, 159.34 .for rates 0.01, 0.1, 0.3, 0.5, 0.7, respectively*

| Cycle | Number of patients in 'alive' state | | | Costs | | |
|---|---|---|---|---|---|---|
| | Beginning | End | LT | Beginning | End | LT |
| 0 | - | $n$ | - | - | $c^{end} = nc$ | - |
| 1 | $n(1-q_l)$ | $n(1-q_l)$ | $\frac{n(1-q_l)+n}{2}$ | $c^{beg} = \frac{n(1-q_l)c}{(1+r)^l}$ | $\frac{n(1-q_l)c}{(1+r)^l}$ | $c^{LT} = \frac{n(1-q_l)+n}{2}\frac{c}{(1+r)^l}$ |

$l$ – cycle length

$q_l$ – death rate for single cycle

$c$ – costs of 'alive' state

$r$ – discount rate

$c^{LT}/c^{beg}/c^{end}$ – costs of single cycle for LT/'beginning'/'end' method

$$\frac{c^{LT} - c^{beg}}{c^{LT}} = \frac{q_l}{2 - q_l}$$

$$\frac{c^{end} - c^{LT}}{c^{LT}} = \frac{2(1+r)^l - 2 + q_l}{2 - q_l}$$

*Table 2. Percentage differences in single cycle results between LT and 'beginning' / 'end' methods*

The percentage differences between results obtained using different methods do not depend on the magnitude of costs / health effects. In the example described above annual costs of the 'alive' state were assumed to be 200; however, under the assumptions made previously, any other cost would provide the same results for percentage differences. Therefore the results described further are general, and the only important assumptions are two-state model and constancy of costs/utilities and progression probabilities in time.

### *Threshold cycle lengths depending on death probabilities*

In Table 3 threshold cycle lengths for various transition probabilities are presented. The threshold was defined as the cycle length for which the difference between HCC and 'beginning' / 'end' methods is equal to 5% or the cycle length for which the maximum of differences between LT and 'beginning' / 'end' methods is equal to 5%. Following the results obtained earlier, adopting the cycle length shorter than the threshold provides results which differ by less than 5% (more accurate approximation). Differences between HCC and 'beginning' / 'end' methods do not depend on the discount rate (in lifetime horizon). However, the relative difference is smaller if lower discount rate is used. As a result, if the discount rate is lower, the threshold cycle length will be longer. For LT method, both differences and relative differences depend on discount rate (as a result of calculation in Table 2).

### *Threshold cycle lengths for costs/utilities that are not constant*

Costs/utilities are often not constant in time[10-12]. In Table 3 the comparison of threshold cycle lengths is presented for HCC for constant utilities and utilities depending on age (using the age-specific multipliers according to Polish tariff [13] and hypothetical 50% decrease of utility at the age of 55). As expected, the thresholds for decreasing utilities are slightly lower, the largest differences are observed for the slowest

THE PERCENTAGE DIFFERENCES BETWEEN RESULTS OBTAINED USING DIFFERENT METHODS DO NOT DEPEND ON THE MAGNITUDE OF COSTS / HEALTH EFFECTS. IN THE EXAMPLE DESCRIBED ABOVE ANNUAL COSTS OF THE 'ALIVE' STATE WERE ASSUMED TO BE 200; HOWEVER, UNDER THE ASSUMPTIONS MADE PREVIOUSLY, ANY OTHER COST WOULD PROVIDE THE SAME RESULTS FOR PERCENTAGE DIFFERENCES.





*Table 3. Threshold cycle lengths depending on progression rate*
**) assumptions: discount rate – 5%, initial age – 50 †) for age ≥ 55 utility equal to 0.5*

| Annual probability of transition | Threshold cycle length (days) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | LT | | | HCC | | | Decreasing utilities (HCC vs 'beginning' / 'end' method) * | | |
| | Discount rate = 5% | Discount rate = 3.5% | Discount rate = 0% | Discount rate = 5% | Discount rate = 3.5% | Discount rate = 0% | Constant utilities | Polish tariff (13) | Decreasing utilities † |
| 0.05 | 240 | 299 | 712 | 365 | 425 | 712 | 362 | 352 | 253 |
| 0.1 | 177 | 207 | 346 | 237 | 261 | 346 | 237 | 234 | 180 |
| 0.2 | 112 | 124 | 163 | 134 | 142 | 163 | 134 | 134 | 117 |
| 0.3 | 80 | 85 | 102 | 90 | 93 | 102 | 90 | 90 | 84 |
| 0.4 | 60 | 63 | 71 | 65 | 67 | 71 | 65 | 65 | 64 |
| 0.5 | 46 | 48 | 53 | 49 | 50 | 53 | 49 | 49 | 49 |
| 0.6 | 36 | 37 | 40 | 38 | 38 | 40 | 38 | 38 | 38 |
| 0.7 | 28 | 29 | 30 | 29 | 29 | 30 | 29 | 29 | 29 |
| 0.8 | 21 | 22 | 23 | 22 | 22 | 23 | 22 | 22 | 22 |
| 0.9 | 15 | 15 | 16 | 16 | 16 | 16 | 16 | 16 | 16 |

progression probabilities. Similar results and dependencies may be obtained for LT method.

### *Incremental results*

The challenging problem to determine the threshold cycle length occurs also when investigating incremental outcomes. The key issue is the fact that there are differences between two interventions associated with progression probabilities and cost/utilities varying over time. Concluding from what was shown before, when the outcomes are calculated for single intervention the costs/utilities of health states do not influence the percentage differences between methods. However, if incremental results are calculated, the total amount of costs / health effects for separate interventions is crucial and therefore any change of the cost/utility of health state results in changes in incremental costs/effects. For example, assuming 1 month cycle, death probability – 0.5 for intervention, and 0.7 for comparator, discount rates – 5% for costs and 3.5% for utilities and utility of 'alive' state – 0.85 we obtain following percentage differences between ICERs (HCC vs 'beginning' / 'end'):

- 2.2% for annual costs of intervention and comparator equal to 400 and 200, respectively,
- 2.7% for annual costs of intervention and comparator equal to 700 and 200, respectively,
- 1.0% for annual costs of intervention and comparator equal to 700 and 600, respectively.

However, in case of comparison of HCC and 'beginning' / 'end' methods, after making a few assumptions, it is possible to observe some general conclusions for ICER calculation. Suppose that a new treatment option is to be compared with standard practice (we will refer to them as intervention vs. comparator). We assume that:

1. the initial cohort distribution among health states and the utilities for each health state are the same for both options,
2. probability of death (progression) is lower for assessed intervention than for the comparator,
3. annual costs of health states for assessed intervention are higher than annual costs of the states for comparator.

The first assumption implies that incremental QALY (quality-adjusted life years) will be the same for all three methods[14]. The second assumption implies that the percentage difference between costs of intervention for analyzed methods is lower than the respective difference for comparator. Under these assumptions the percentage difference between ICERs obtained using the analyzed methods is not higher than the minimum of two percentage differences between total costs: for the intervention and for the comparator (Table 4).

If annual costs of health states for the intervention are lower than annual costs for the comparator (assumption 3 is not satisfied) the last inequality from Table 4 does not hold and the previously made conclusion about ICERs is not true. However, if assumption 3 is not satisfied and annual costs of health states for the intervention are low enough to make the total costs of intervention be lower than total costs of comparator (by balancing the additional costs associated with lower progression probability), the ICERs are negative. In this case intervention dominates the comparator and there is no point in analyzing percentage differences between them. If the total costs of intervention remain higher than total costs of comparator, the percentage difference between ICERs may become large even in case of low percentage differences between costs. The example of such situation is presented in Table 5. The difference between ICERs for HCC and other methods is 27.6%, despite the difference between total costs being not higher than 5%.

| |
|---|
| $c_i^{hcc}$ / $c_i^{beg}$ – total costs obtained with HCC / 'beginning' method<br>$e_i^{hcc}$ / $e_i^{beg}$ – total QALY obtained with HCC / 'beginning' method |
| $\frac{c_i^{hcc} - c_i^{beg}}{c_i^{hcc}} = p_i$, $\quad \frac{c_c^{hcc} - c_c^{beg}}{c_c^{hcc}} = p_c$ |
| $ICER^{hcc} = \frac{c_i^{hcc} - c_c^{hcc}}{e_i^{hcc} - e_c^{hcc}}$, $\quad ICER^{beg} = \frac{c_i^{beg} - c_c^{beg}}{e_i^{beg} - e_c^{beg}}$ |
| $p_c > p_i$ (conclusion from assumption 2) |
| $c_i^{hcc} > c_c^{hcc}$ (conclusion from assumptions 2 and 3) |
| $e_i^{hcc} - e_c^{hcc} = e_i^{beg} - e_c^{beg}$ (conclusion from assumption 1) |
| $\frac{ICER^{hcc} - ICER^{beg}}{ICER^{hcc}} = \frac{(c_i^{hcc} - c_c^{hcc}) - (c_i^{beg} - c_c^{beg})}{c_i^{hcc} - c_c^{hcc}} = \frac{p_i c_i^{hcc} - p_c c_c^{hcc}}{c_i^{hcc} - c_c^{hcc}} \leq p_i$ |
| The last inequality is true only if the numerator is positive. This condition is equivalent to inequality:<br>$p_i c_i^{hcc} - p_c c_c^{hcc} = (c_i^{hcc} - c_i^{beg}) - (c_c^{hcc} - c_c^{beg}) > 0$<br>The above inequality holds, because:<br>• differences between total costs do not depend on the death rate (as it was explained earlier)<br>• annual costs of health states for intervention are higher than annual costs of health states for comparator (assumption 3), so the difference between total costs for intervention is also higher than respective difference for comparator |

*Table 4. Percentage difference between ICERs obtained from HCC and 'beginning' method*
*The same results may be obtained for comparison between HCC and 'end' method.*





| Category | Method | Intervention | Comparator | Intervention vs Comparator |
|---|---|---|---|---|
| Annual costs | - | 530,000 | 800,000 | - |
| | | Results | | |
| Total costs (per 1 patient) | Beginning | 692,490 | 640,490 | 52,000 |
| | End | 736,657 | 707,157 | 29,500 |
| | HCC | 714,574 | 673,823 | 40,750 |
| | Percentage difference | 3.1% | 5.0% | 27.6% |
| QALY (per 1 patient) | Beginning | 1.133 | 0.689 | 0.444 |
| | End | 1.204 | 0.760 | 0.444 |
| | HCC | 1.169 | 0.725 | 0.444 |
| | Percentage difference | 3.0% | 4.9% | 0.0% |
| ICER | Beginning | - | - | 117,126 |
| | End | - | - | 66,447 |
| | HCC | - | - | 91,787 |
| | Percentage difference | - | - | 27.6% |

*Table 5. Large difference between ICERs for specific costs data*
*Assumptions: 1 month cycle, probability of transition – 0.5 for intervention, 0.68 for comparator, discount rates – 5% for costs, 3.5% for utilities, utility of 'alive' state – 0.85*

Generally, the smaller the difference between total costs of intervention and comparator, the higher the difference between ICERs, namely when

$$c_i^{hcc} - c_c^{hcc} \to 0$$

then the percentage difference between ICERs increases rapidly:

$$\frac{ICER^{hcc} - ICER^{beg}}{ICER^{hcc}} = \frac{p_i c_i^{hcc} - p_c c_c^{hcc}}{c_i^{hcc} - c_c^{hcc}} \to \infty.$$

The results obtained for incremental results for HCC cannot be easily generalized for LT method, as the assumption of the same initial cohort distribution among health states and the same utilities for each health state for both options does not imply that incremental QALY will be the same for LT and 'beginning' / 'end' method.

## DISCUSSION

There is no general rule concerning the necessity of using half-cycle correction depending on cycle length. The ISPOR Good Research Practice recommend applying HCC in all cost-effectiveness analyses[15]. The guidelines provided by HTA agencies which mention this method do not precisely state when HCC should be used[6–9]. Therefore various approaches are adopted in economic analyses [16–19].

For a simple, 2-state Markov model it seems that in case of 2-week cycles or shorter half-cycle correction is unnecessary. The cycles shorter than thresholds result in differences between methods of less than 5%, which seems not to have significant impact on final results.

However the results were obtained under few assumptions:

- costs/utilities constant in time,
- progression probabilities constant in time,
- 2-state Markov model.

It is more difficult to calculate the threshold cycle lengths if some of the assumptions are not satisfied. However, it is possible to determine roughly the behavior of thresholds in cases where there are some variations in assumptions.

Costs/utilities are often not constant in time, e.g. utilities may depend on age. In case of relationships between HCC and 'beginning' / 'end' methods: if the costs/utilities decrease/increase, the total outcomes also decrease/increase and as a result the percentage differences increase/decrease which makes the thresholds lower/higher. If the changes are irregular, no general rule may be concluded. The highest variations, comparing with results for constant cots/utilities values, were observed for lower death probabilities. Furthermore, in practice progression probabilities are almost never constant. In case of relationships between HCC and 'beginning' / 'end' methods: if a probability of transition to state which is cheaper (or has lower utility) increases in time, the total results decrease and as a result the percentage differences increase which makes the thresholds lower. Similar conclusions can be made for opposite situations and LT method. Usually models consist of more than two states and some probabilities increase and other decrease. In such situations no general rule may be concluded.

If the model consists of more than two states it is difficult to make general conclusions about threshold cycle lengths. In order to make general rules, all possibilities of transitions between states should be analyzed and it would be complicated for multi-state models. When economic evaluations of health technologies are conducted, the key outcomes are usually ICERs and budget impact. Calculating the threshold cycle lengths for ICERs is a challenging problem. We made an attempt to analyze the relationship between threshold cycle lengths obtained for single interventions and the percentage differences between ICERs obtained using different methods. We showed that under a few assumptions, the percentage difference between ICERs obtained using different methods is not higher than the respective percentage differences between total costs for two compared interventions. However, there are situations when, despite low differences between total costs, the differences between ICERs are considerably high.

All the calculations and conclusions were made for lifetime horizon. However, if all the assumptions made at the beginning are satisfied, the results may be generalized for finite horizon models.

We did not identify other researches concerning the problem of conditions under which half-cycle should always be applied. Naimark et. al.[20] provided an explanation of half-cycle correction method. However, the authors did not make any specific recommendation when the correction should be used. Barendregt[4] outlined a few limitations of the method and suggested 'life-table' as alternative approach to be used in economic modeling. Another solution was suggested by Taylor et. al.[5], namely choosing as a time of transition the moment when half of the events occurs in each cycle. The authors indicated also the situations when the half-cycle correction use would not be justified, e.g. when patients use drugs which are bought at the beginning of cycles.

The main limitation of the study is a set of assumptions adopted in order to determine threshold cycle lengths. The set is very rarely satisfied in practice. However, skipping any of the assumptions significantly complicates the calculations and an appreciable number of possibilities need to be analyzed. An attempt was made to provide some general effects associated with relaxing some of assumptions as a pragmatic way forward.

Another limitation is applying the half-cycle correction to all costs/utilities in model. It is not always justified, e.g. there exists some costs that are incurred at the beginning of each period[5].

ALL THE CALCULATIONS AND CONCLUSIONS WERE MADE FOR LIFETIME HORIZON. HOWEVER, IF ALL THE ASSUMPTIONS MADE AT THE BEGINNING ARE SATISFIED, THE RESULTS MAY BE GENERALIZED FOR FINITE HORIZON MODELS.

## CONCLUSIONS

Choice of the time of transitions in the model may have a significant impact on results. For cycles shorter than 2 weeks HCC/LT method does not seem to be necessary. However, HCC/LT method should always be applied for cycles longer than 1 year. For cycles between 2 weeks and 1 year, we were unable to make a general recommendation. ■

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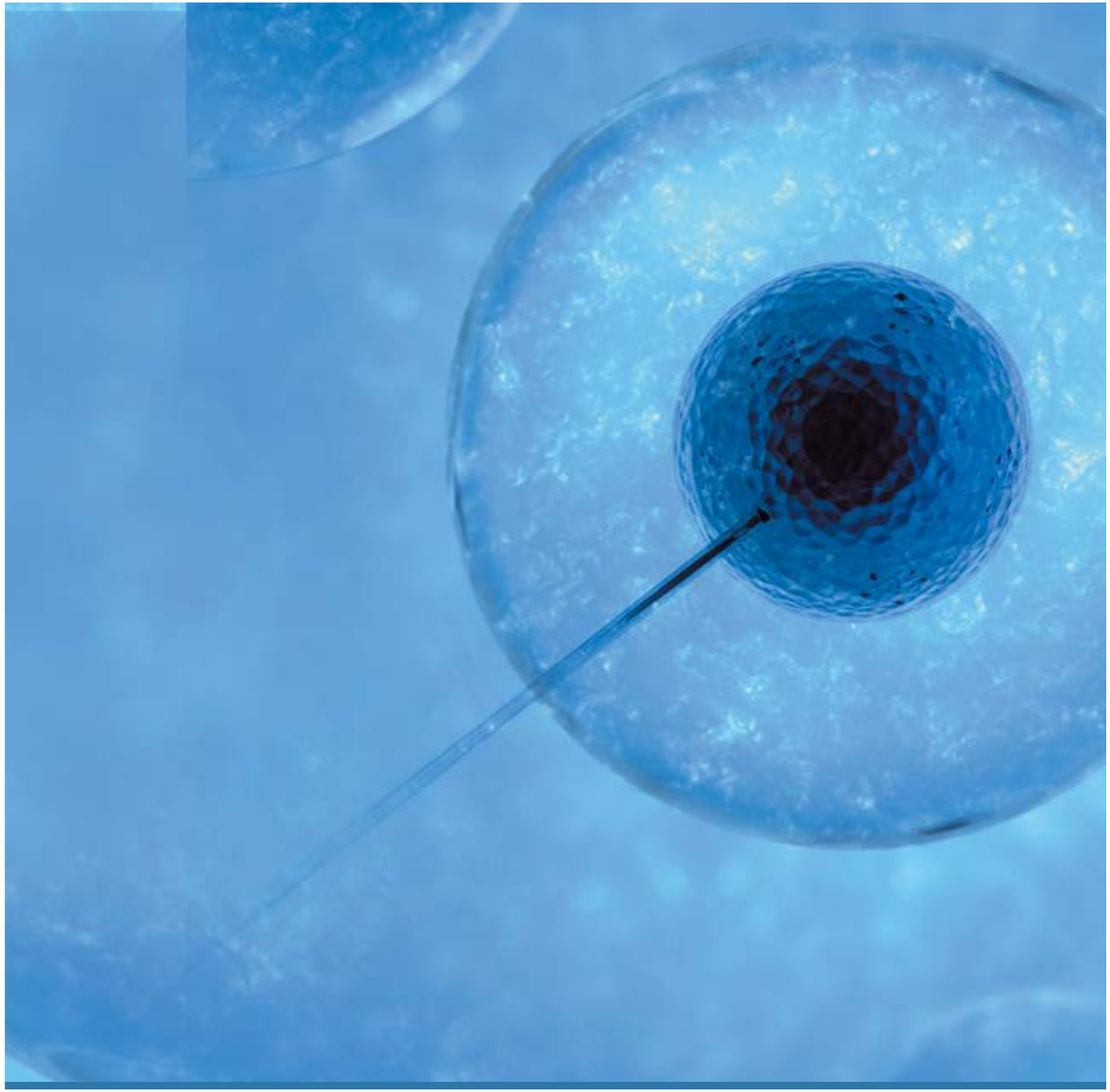

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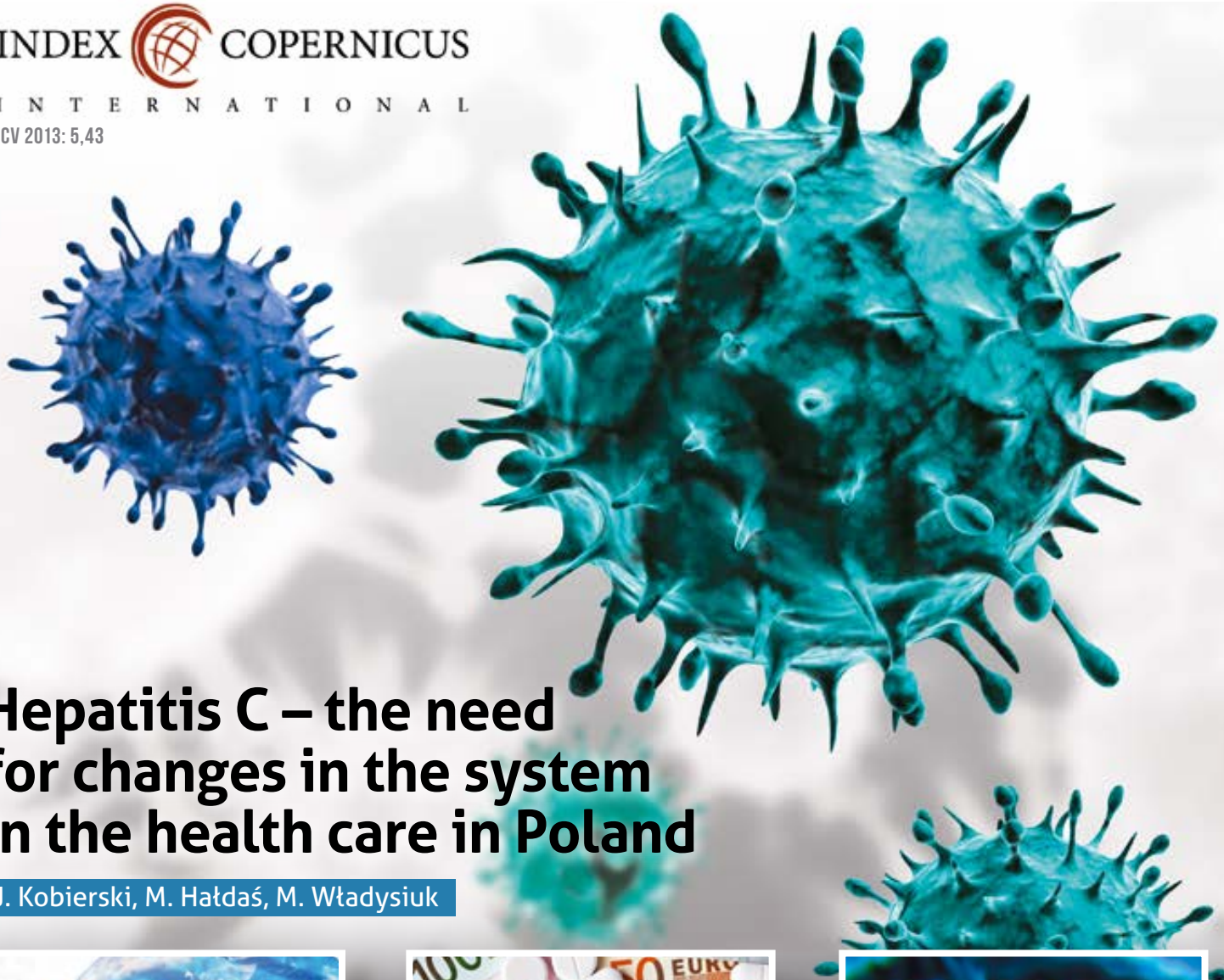

# Hepatitis C – the need for changes in the system in the health care in Poland

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**Patients Registries - the role of the health system, new trends and hopes for Polish patients - 2nd JHPOR conference, Warsaw March 19th 2015**

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**Polish Experience in Financial Management of Medicines Market by Public Payer**

T.Płusa

**Ebola viral hemorrhagic fever**

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# Can We Determine the Optimal Cycle Length for Which Half-Cycle Correction Should Always Be Applied?

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*Keywords:*
Markov models, life-table method, cost-effectiveness, cost-utility, half-cycle correction

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## ABSTRACT

***Objective:*** **The aim of the study is to measure the influence of cycle length and progression rates on differences between final results obtained using different approaches concerning time of transition to another state in Markov models (at the beginning, at the end of the cycle or half-cycle correction – HCC) and to estimate an optimal cycle length for which HCC should always be applied.**

***Methods:*** **A hypothetical, two-state Markov model was built. Assuming different progression rates, four methods concerning time of transition were compared. For each rate, the threshold values were determined, i.e. the maximal cycle length for which the difference between HCC/'life-table' (LT) method and 'beginning'/'end' methods were not greater than 5%. Cycles longer than the estimated threshold are assumed to imply the application of HCC/LT.**

***Results:*** **Under few assumptions, the threshold cycle length for annual progression of 0.05 was 1 year or 2 years, for 5% and 0% discount rate, respectively. The threshold cycle lengths became shorter for lower progression rates (2 weeks for 0.90 rate). The results obtained for single intervention cannot be easily repeated for incremental outcomes; however, some general relationships can be determined.**

***Conclusions:*** **Choice of the time of transitions in the model may have a significant impact on the findings of economic evaluations. For cycles shorter than 2 weeks, HCC/LT does not appear necessary. However, it should be applied for cycles longer than 1 year. We were unable to make a recommendation for cycles between 2 weeks and 1 year.**

## INTRODUCTION

Medical decision making is supported by pharmacoeconomic analyses, which are usually based on modeling of health effects and costs. A common tool used in such analyses are Markov models, which enable the progress of the diseases to be simulated throughout the lifetime of patients[1,2]. One of the problems that arise whilst modeling long-term costs and health outcomes utilizing Markov models is the choice of transition time between health states. Once a specific cycle length is adopted, it allows to change the status of disease (progression, regression or death) only at specific time points, which does not always adequately reflect the course of disease in real life[1]. Various approaches can be adopted, i.e. transitions at the beginning or at the end of the cycle and more accurate methods like half-cycle correction (HCC), 'life-table' method (LT), or Simpson's method[3,4]. The half-cycle correction and the 'life-table' method are equivalent in some situations: if costs/utilities are equal in each cycle and there is no discounting[4]. Despite some limitations[4,5], the most common method used in economic evaluations, which is also recommended by some of national HTA agencies[6–9], is half-cycle correction.

The practical implementation of the half-cycle correction and 'life-table' method has been described in other publications [1,4].

Our aim is to review information concerning various approaches to choosing time of transition, accuracy of these methods and to establish whether there is an optimal cycle length for which HCC/LT should always be applied.

## METHODS

We developed a simple two-state Markov model (alive or dead) in order to analyze the influence of cycle length on differences between analyzed methods.

The time horizon was set to be lifetime, the discount rate was 0–5% and costs/utilities were held constant in time.

Assuming different death probabilities (0.05–0.90 annually), we compared four approaches:

- transitions at the beginning of the cycle ('beginning'),
- transitions at the end of the cycle ('end'),
- half-cycle correction,
- 'life-table' method.

Half-cycle correction is made to transitions either at the beginning or at the end of the cycle. The method of calculations differs slightly between those two assumptions, however in both cases identical results are obtained. In case of progression at the end of the cycle, HCC is implemented by cutting off the first half of the first cycle. If the horizon of the analysis is shorter than lifetime, patient/cohort's life must be modeled one cycle longer then the assumed time horizon and the results for the first half of the additional cycle must be added to cumulative results. In case of progression at the beginning of the cycle, HCC is implemented by adding half of a cycle at the beginning of the analysis. If the horizon of the analysis is shorter than lifetime, this action will result in overestimation of the results, therefore, an additional correction must be made by cutting off second half of the last cycle.

Both of the described methods result in the same final outcomes, so we use the same outcomes for HCC when comparing it with both 'beginning' and 'end' methods.

The 'life-table' method is implemented by calculating number of patients staying in particular state as a mean number of patients staying in this state at the beginning and at the end of the cycle (arithmetic mean, i.e. assuming linear progression).

The key issue concerned with the use of different methods is establishing the time points when costs/health effects are calculated (discounting time). For 'beginning' and LT method we assumed that there are no costs/effects incurred in cycle 0 (cycle, in which no discounting is applied). For 'end' method we assigned full cost to the cycle 0 and for HCC method we assigned half of these costs to the cycle 0 (Table 1). Such procedure is coherent with practical approach in pharmacoeconomic models.

*Table 1. Amount of costs/health effects in cycle 0 and 1*

| Cycle | Beginning | End | LT | HCC |
|---|---|---|---|---|
| 0 | 0 | $c$ | 0 | $0.5c$ |
| 1 | $\frac{c(1-q)}{(1+r)^1}$ | $\frac{c(1-q)}{(1+r)^1}$ | $\left(\frac{c+c(1-q)}{2}\right)\frac{1}{(1+r)^1}$ | $\frac{c(1-q)}{(1+r)^1}$ |

$t$ – cycle length in years

$q$ – progression probability (per cycle)

$c$ – costs/effects of 'alive' state (per cycle)

$r$ – discount rate

We assumed progression probabilities to be constant in time. For each probability the threshold values were determined, i.e. the maximal cycle lengths for which the differences between half-cycle correction/'life-table' method and 'beginning'/'end' methods were not greater than 5%. We propose that cycles longer than the estimated threshold should imply the application of HCC/LT.

Furthermore, influence of applied assumptions (cost/utilities and death probabilities variability, number of health states in the model) on the obtained results and consequences of relaxing them were analyzed. Additionally, we studied the relationship between threshold cycle lengths and incremental results, and made an attempt to provide general conclusions concerning incremental cost-effectiveness ratios (ICERs).

All calculations were performed using Microsoft Excel® 2007.

## RESULTS

### *General relations between cycle length, death probability and the method of calculation*

The problem of calculating costs / health effects for a cohort of patients may be illustrated by graphs which link survival curves with costs/utilities. Such graphs may be created for every state, however in more complicated models this is an incredibly laborious task. The final result (i.e. total costs, expected survival) would be the sum of areas under the curves.

A mathematical approach to the problem of calculating the area under the curve would be solving a corresponding integral. When discrete Markov models are used, the approximate area is calculated as the sum of areas of respective rectangles. All four methods ('beginning', 'end', HCC, LT) provide approximate outcomes, which become more accurate as smaller rectangles are used. Using Markov models language, it means that the shorter cycle is chosen, the more accurate outcomes are obtained. It is intuitive: if a short cycle is used, we are able to describe more precisely the moments of transitions between states. The illustrative results for probability of death equal to 0.5 are presented on Figure 1.

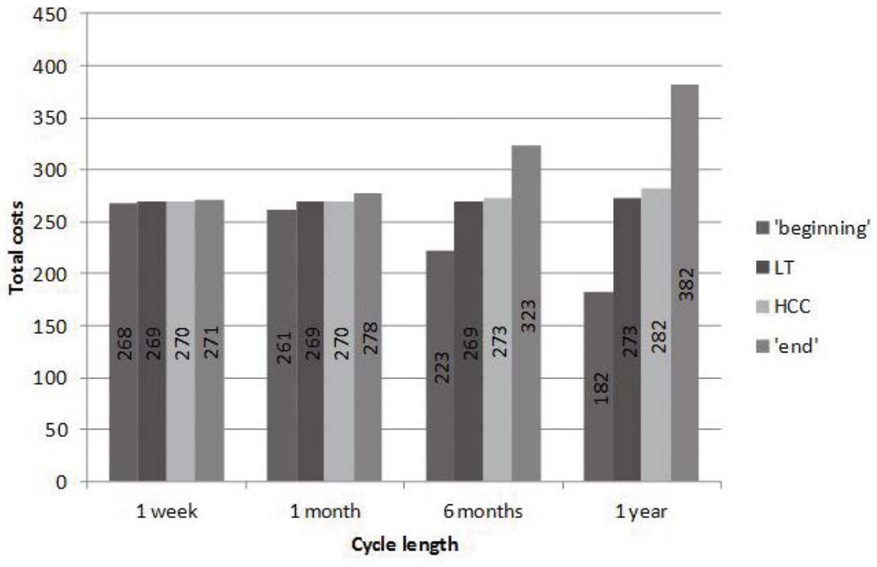


*Figure 1. Comparison of differences in total costs between methods for various cycle lengths*
*Assumptions: progression rate – 0.5, annual cost for 'alive' state – 200, annual cost for death state – 0, discount rate 5%. The exact result (calculated using integrals) is 269.56.*

If the horizon of analysis is finite (i.e. not lifetime), the accuracy of the approximation depends also on the slope of the curve (progression probabilities in Markov models). The steeper the slope, the less precise the approximation of the area (results for several slopes are presented on Figure 2).

In case of lifetime horizon the differences between 'beginning', 'end' and HCC methods are associated with the differences in approach to cycle 0. As a result, the difference between results obtained using different methods is equal to the difference obtained in cycle 0 and does not depend on the progression probability (provided it is constant). However, the percentage difference between results obtained using HCC and 'beginning' / 'end' methods depends on the probability because the total outcomes are strictly related to the probability of transition. For example, assuming annual costs of 'alive' state equal to 200, discount rate 5% and progression probabilities equal to 0.7 or 0.8 the differences between total outcomes for HCC and other methods are 100 for both probabilities of death and the percentage differences are 56% and 68% for probabilities 0.7 and 0.8, respectively.

As far as LT method is concerned, the difference between total results for this method and for 'beginning' / 'end' is associated not only with cycle 0, but also with other cycles. Moreover, the percentage differences for LT vs 'beginning' method and LT vs 'end' method are in general not equal.

However, it may be easily shown that percentage differences between costs/effects for LT and 'beginning' / 'end' method in any single cycle are constant and, as a result, equal to the percentage differences for total costs/effects (Table 2).

The same results may be obtained for any other cycle.



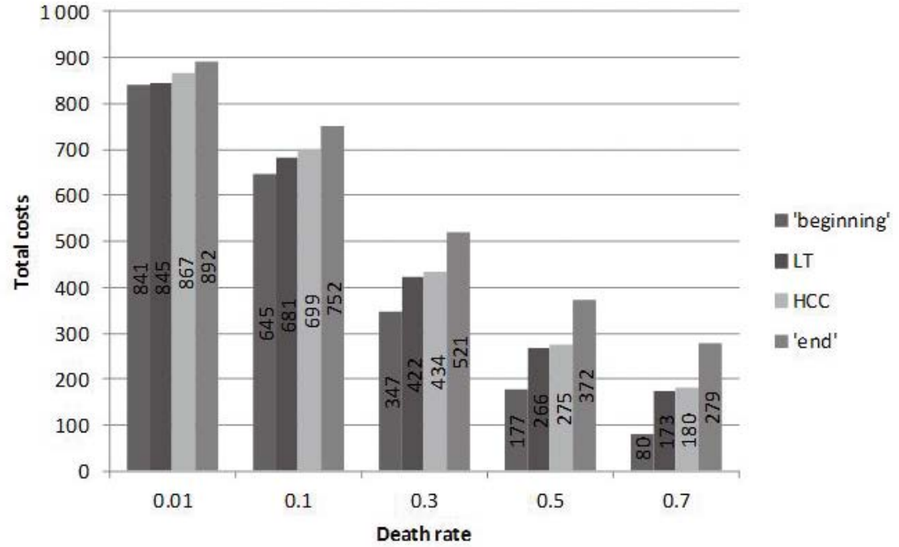


*Figure 2.Compariso n of differences in total costs between methods for various progression rates*
*Assumptions: horizon 5 years, cycle length 1 year, annual costs 200, discount rate 5%.*
*The exact results (obtained using integrals) are 866.32, 697.16, 428.30, 262.96, 159.34 .for rates 0.01, 0.1, 0.3, 0.5, 0.7, respectively*

| Cycle | Number of patients in 'alive' state | | | Costs | | |
|---|---|---|---|---|---|---|
| | Beginning | End | LT | Beginning | End | LT |
| 0 | - | $n$ | - | - | $c^{end} = nc$ | - |
| 1 | $n(1-q_l)$ | $n(1-q_l)$ | $\frac{n(1-q_l)+n}{2}$ | $c^{beg} = \frac{n(1-q_l)c}{(1+r)^l}$ | $\frac{n(1-q_l)c}{(1+r)^l}$ | $c^{LT} = \frac{n(1-q_l)+n}{2}\frac{c}{(1+r)^l}$ |

$l$ – cycle length

$q_l$ – death rate for single cycle

$c$ – costs of 'alive' state

$r$ – discount rate

$c^{LT}/c^{beg}/c^{end}$ – costs of single cycle for LT/'beginning'/'end' method

$$\frac{c^{LT} - c^{beg}}{c^{LT}} = \frac{q_l}{2 - q_l}$$

$$\frac{c^{end} - c^{LT}}{c^{LT}} = \frac{2(1+r)^l - 2 + q_l}{2 - q_l}$$

*Table 2. Percentage differences in single cycle results between LT and 'beginning' / 'end' methods*

The percentage differences between results obtained using different methods do not depend on the magnitude of costs / health effects. In the example described above annual costs of the 'alive' state were assumed to be 200; however, under the assumptions made previously, any other cost would provide the same results for percentage differences. Therefore the results described further are general, and the only important assumptions are two-state model and constancy of costs/utilities and progression probabilities in time.

### *Threshold cycle lengths depending on death probabilities*

In Table 3 threshold cycle lengths for various transition probabilities are presented. The threshold was defined as the cycle length for which the difference between HCC and 'beginning' / 'end' methods is equal to 5% or the cycle length for which the maximum of differences between LT and 'beginning' / 'end' methods is equal to 5%. Following the results obtained earlier, adopting the cycle length shorter than the threshold provides results which differ by less than 5% (more accurate approximation). Differences between HCC and 'beginning' / 'end' methods do not depend on the discount rate (in lifetime horizon). However, the relative difference is smaller if lower discount rate is used. As a result, if the discount rate is lower, the threshold cycle length will be longer. For LT method, both differences and relative differences depend on discount rate (as a result of calculation in Table 2).

### *Threshold cycle lengths for costs/utilities that are not constant*

Costs/utilities are often not constant in time[10-12]. In Table 3 the comparison of threshold cycle lengths is presented for HCC for constant utilities and utilities depending on age (using the age-specific multipliers according to Polish tariff [13] and hypothetical 50% decrease of utility at the age of 55). As expected, the thresholds for decreasing utilities are slightly lower, the largest differences are observed for the slowest

THE PERCENTAGE DIFFERENCES BETWEEN RESULTS OBTAINED USING DIFFERENT METHODS DO NOT DEPEND ON THE MAGNITUDE OF COSTS / HEALTH EFFECTS. IN THE EXAMPLE DESCRIBED ABOVE ANNUAL COSTS OF THE 'ALIVE' STATE WERE ASSUMED TO BE 200; HOWEVER, UNDER THE ASSUMPTIONS MADE PREVIOUSLY, ANY OTHER COST WOULD PROVIDE THE SAME RESULTS FOR PERCENTAGE DIFFERENCES.





*Table 3. Threshold cycle lengths depending on progression rate*
**) assumptions: discount rate – 5%, initial age – 50 †) for age ≥ 55 utility equal to 0.5*

| Annual probability of transition | Threshold cycle length (days) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | LT | | | HCC | | | Decreasing utilities (HCC vs 'beginning' / 'end' method) * | | |
| | Discount rate = 5% | Discount rate = 3.5% | Discount rate = 0% | Discount rate = 5% | Discount rate = 3.5% | Discount rate = 0% | Constant utilities | Polish tariff (13) | Decreasing utilities † |
| 0.05 | 240 | 299 | 712 | 365 | 425 | 712 | 362 | 352 | 253 |
| 0.1 | 177 | 207 | 346 | 237 | 261 | 346 | 237 | 234 | 180 |
| 0.2 | 112 | 124 | 163 | 134 | 142 | 163 | 134 | 134 | 117 |
| 0.3 | 80 | 85 | 102 | 90 | 93 | 102 | 90 | 90 | 84 |
| 0.4 | 60 | 63 | 71 | 65 | 67 | 71 | 65 | 65 | 64 |
| 0.5 | 46 | 48 | 53 | 49 | 50 | 53 | 49 | 49 | 49 |
| 0.6 | 36 | 37 | 40 | 38 | 38 | 40 | 38 | 38 | 38 |
| 0.7 | 28 | 29 | 30 | 29 | 29 | 30 | 29 | 29 | 29 |
| 0.8 | 21 | 22 | 23 | 22 | 22 | 23 | 22 | 22 | 22 |
| 0.9 | 15 | 15 | 16 | 16 | 16 | 16 | 16 | 16 | 16 |

progression probabilities. Similar results and dependencies may be obtained for LT method.

### *Incremental results*

The challenging problem to determine the threshold cycle length occurs also when investigating incremental outcomes. The key issue is the fact that there are differences between two interventions associated with progression probabilities and cost/utilities varying over time. Concluding from what was shown before, when the outcomes are calculated for single intervention the costs/utilities of health states do not influence the percentage differences between methods. However, if incremental results are calculated, the total amount of costs / health effects for separate interventions is crucial and therefore any change of the cost/utility of health state results in changes in incremental costs/effects. For example, assuming 1 month cycle, death probability – 0.5 for intervention, and 0.7 for comparator, discount rates – 5% for costs and 3.5% for utilities and utility of 'alive' state – 0.85 we obtain following percentage differences between ICERs (HCC vs 'beginning' / 'end'):

- 2.2% for annual costs of intervention and comparator equal to 400 and 200, respectively,
- 2.7% for annual costs of intervention and comparator equal to 700 and 200, respectively,
- 1.0% for annual costs of intervention and comparator equal to 700 and 600, respectively.

However, in case of comparison of HCC and 'beginning' / 'end' methods, after making a few assumptions, it is possible to observe some general conclusions for ICER calculation. Suppose that a new treatment option is to be compared with standard practice (we will refer to them as intervention vs. comparator). We assume that:

1. the initial cohort distribution among health states and the utilities for each health state are the same for both options,
2. probability of death (progression) is lower for assessed intervention than for the comparator,
3. annual costs of health states for assessed intervention are higher than annual costs of the states for comparator.

The first assumption implies that incremental QALY (quality-adjusted life years) will be the same for all three methods[14]. The second assumption implies that the percentage difference between costs of intervention for analyzed methods is lower than the respective difference for comparator. Under these assumptions the percentage difference between ICERs obtained using the analyzed methods is not higher than the minimum of two percentage differences between total costs: for the intervention and for the comparator (Table 4).

If annual costs of health states for the intervention are lower than annual costs for the comparator (assumption 3 is not satisfied) the last inequality from Table 4 does not hold and the previously made conclusion about ICERs is not true. However, if assumption 3 is not satisfied and annual costs of health states for the intervention are low enough to make the total costs of intervention be lower than total costs of comparator (by balancing the additional costs associated with lower progression probability), the ICERs are negative. In this case intervention dominates the comparator and there is no point in analyzing percentage differences between them. If the total costs of intervention remain higher than total costs of comparator, the percentage difference between ICERs may become large even in case of low percentage differences between costs. The example of such situation is presented in Table 5. The difference between ICERs for HCC and other methods is 27.6%, despite the difference between total costs being not higher than 5%.

| |
|---|
| $c_i^{hcc}$ / $c_i^{beg}$ – total costs obtained with HCC / 'beginning' method<br>$e_i^{hcc}$ / $e_i^{beg}$ – total QALY obtained with HCC / 'beginning' method |
| $\frac{c_i^{hcc} - c_i^{beg}}{c_i^{hcc}} = p_i$, $\quad \frac{c_c^{hcc} - c_c^{beg}}{c_c^{hcc}} = p_c$ |
| $ICER^{hcc} = \frac{c_i^{hcc} - c_c^{hcc}}{e_i^{hcc} - e_c^{hcc}}$, $\quad ICER^{beg} = \frac{c_i^{beg} - c_c^{beg}}{e_i^{beg} - e_c^{beg}}$ |
| $p_c > p_i$ (conclusion from assumption 2) |
| $c_i^{hcc} > c_c^{hcc}$ (conclusion from assumptions 2 and 3) |
| $e_i^{hcc} - e_c^{hcc} = e_i^{beg} - e_c^{beg}$ (conclusion from assumption 1) |
| $\frac{ICER^{hcc} - ICER^{beg}}{ICER^{hcc}} = \frac{(c_i^{hcc} - c_c^{hcc}) - (c_i^{beg} - c_c^{beg})}{c_i^{hcc} - c_c^{hcc}} = \frac{p_i c_i^{hcc} - p_c c_c^{hcc}}{c_i^{hcc} - c_c^{hcc}} \leq p_i$ |
| The last inequality is true only if the numerator is positive. This condition is equivalent to inequality:<br>$p_i c_i^{hcc} - p_c c_c^{hcc} = (c_i^{hcc} - c_i^{beg}) - (c_c^{hcc} - c_c^{beg}) > 0$<br>The above inequality holds, because:<br>• differences between total costs do not depend on the death rate (as it was explained earlier)<br>• annual costs of health states for intervention are higher than annual costs of health states for comparator (assumption 3), so the difference between total costs for intervention is also higher than respective difference for comparator |

*Table 4. Percentage difference between ICERs obtained from HCC and 'beginning' method*
*The same results may be obtained for comparison between HCC and 'end' method.*





| Category | Method | Intervention | Comparator | Intervention vs Comparator |
|---|---|---|---|---|
| Annual costs | - | 530,000 | 800,000 | - |
| | | Results | | |
| Total costs (per 1 patient) | Beginning | 692,490 | 640,490 | 52,000 |
| | End | 736,657 | 707,157 | 29,500 |
| | HCC | 714,574 | 673,823 | 40,750 |
| | Percentage difference | 3.1% | 5.0% | 27.6% |
| QALY (per 1 patient) | Beginning | 1.133 | 0.689 | 0.444 |
| | End | 1.204 | 0.760 | 0.444 |
| | HCC | 1.169 | 0.725 | 0.444 |
| | Percentage difference | 3.0% | 4.9% | 0.0% |
| ICER | Beginning | - | - | 117,126 |
| | End | - | - | 66,447 |
| | HCC | - | - | 91,787 |
| | Percentage difference | - | - | 27.6% |

*Table 5. Large difference between ICERs for specific costs data*
*Assumptions: 1 month cycle, probability of transition – 0.5 for intervention, 0.68 for comparator, discount rates – 5% for costs, 3.5% for utilities, utility of 'alive' state – 0.85*

Generally, the smaller the difference between total costs of intervention and comparator, the higher the difference between ICERs, namely when

$$c_i^{hcc} - c_c^{hcc} \to 0$$

then the percentage difference between ICERs increases rapidly:

$$\frac{ICER^{hcc} - ICER^{beg}}{ICER^{hcc}} = \frac{p_i c_i^{hcc} - p_c c_c^{hcc}}{c_i^{hcc} - c_c^{hcc}} \to \infty.$$

The results obtained for incremental results for HCC cannot be easily generalized for LT method, as the assumption of the same initial cohort distribution among health states and the same utilities for each health state for both options does not imply that incremental QALY will be the same for LT and 'beginning' / 'end' method.

## DISCUSSION

There is no general rule concerning the necessity of using half-cycle correction depending on cycle length. The ISPOR Good Research Practice recommend applying HCC in all cost-effectiveness analyses[15]. The guidelines provided by HTA agencies which mention this method do not precisely state when HCC should be used[6–9]. Therefore various approaches are adopted in economic analyses [16–19].

For a simple, 2-state Markov model it seems that in case of 2-week cycles or shorter half-cycle correction is unnecessary. The cycles shorter than thresholds result in differences between methods of less than 5%, which seems not to have significant impact on final results.

However the results were obtained under few assumptions:

- costs/utilities constant in time,
- progression probabilities constant in time,
- 2-state Markov model.

It is more difficult to calculate the threshold cycle lengths if some of the assumptions are not satisfied. However, it is possible to determine roughly the behavior of thresholds in cases where there are some variations in assumptions.

Costs/utilities are often not constant in time, e.g. utilities may depend on age. In case of relationships between HCC and 'beginning' / 'end' methods: if the costs/utilities decrease/increase, the total outcomes also decrease/increase and as a result the percentage differences increase/decrease which makes the thresholds lower/higher. If the changes are irregular, no general rule may be concluded. The highest variations, comparing with results for constant cots/utilities values, were observed for lower death probabilities. Furthermore, in practice progression probabilities are almost never constant. In case of relationships between HCC and 'beginning' / 'end' methods: if a probability of transition to state which is cheaper (or has lower utility) increases in time, the total results decrease and as a result the percentage differences increase which makes the thresholds lower. Similar conclusions can be made for opposite situations and LT method. Usually models consist of more than two states and some probabilities increase and other decrease. In such situations no general rule may be concluded.

If the model consists of more than two states it is difficult to make general conclusions about threshold cycle lengths. In order to make general rules, all possibilities of transitions between states should be analyzed and it would be complicated for multi-state models. When economic evaluations of health technologies are conducted, the key outcomes are usually ICERs and budget impact. Calculating the threshold cycle lengths for ICERs is a challenging problem. We made an attempt to analyze the relationship between threshold cycle lengths obtained for single interventions and the percentage differences between ICERs obtained using different methods. We showed that under a few assumptions, the percentage difference between ICERs obtained using different methods is not higher than the respective percentage differences between total costs for two compared interventions. However, there are situations when, despite low differences between total costs, the differences between ICERs are considerably high.

All the calculations and conclusions were made for lifetime horizon. However, if all the assumptions made at the beginning are satisfied, the results may be generalized for finite horizon models.

We did not identify other researches concerning the problem of conditions under which half-cycle should always be applied. Naimark et. al.[20] provided an explanation of half-cycle correction method. However, the authors did not make any specific recommendation when the correction should be used. Barendregt[4] outlined a few limitations of the method and suggested 'life-table' as alternative approach to be used in economic modeling. Another solution was suggested by Taylor et. al.[5], namely choosing as a time of transition the moment when half of the events occurs in each cycle. The authors indicated also the situations when the half-cycle correction use would not be justified, e.g. when patients use drugs which are bought at the beginning of cycles.

The main limitation of the study is a set of assumptions adopted in order to determine threshold cycle lengths. The set is very rarely satisfied in practice. However, skipping any of the assumptions significantly complicates the calculations and an appreciable number of possibilities need to be analyzed. An attempt was made to provide some general effects associated with relaxing some of assumptions as a pragmatic way forward.

Another limitation is applying the half-cycle correction to all costs/utilities in model. It is not always justified, e.g. there exists some costs that are incurred at the beginning of each period[5].

ALL THE CALCULATIONS AND CONCLUSIONS WERE MADE FOR LIFETIME HORIZON. HOWEVER, IF ALL THE ASSUMPTIONS MADE AT THE BEGINNING ARE SATISFIED, THE RESULTS MAY BE GENERALIZED FOR FINITE HORIZON MODELS.

## CONCLUSIONS

Choice of the time of transitions in the model may have a significant impact on results. For cycles shorter than 2 weeks HCC/LT method does not seem to be necessary. However, HCC/LT method should always be applied for cycles longer than 1 year. For cycles between 2 weeks and 1 year, we were unable to make a general recommendation. ■

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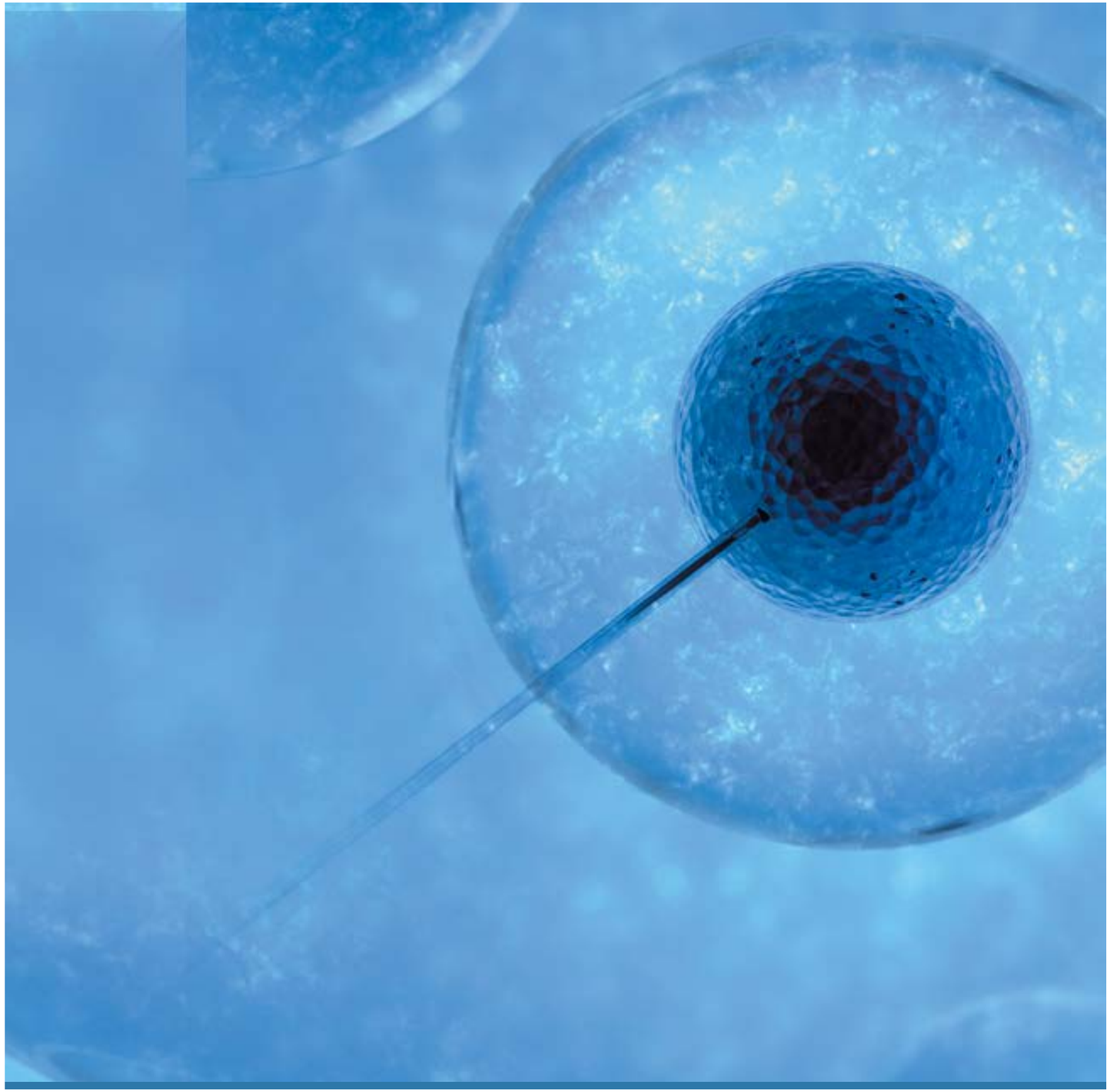

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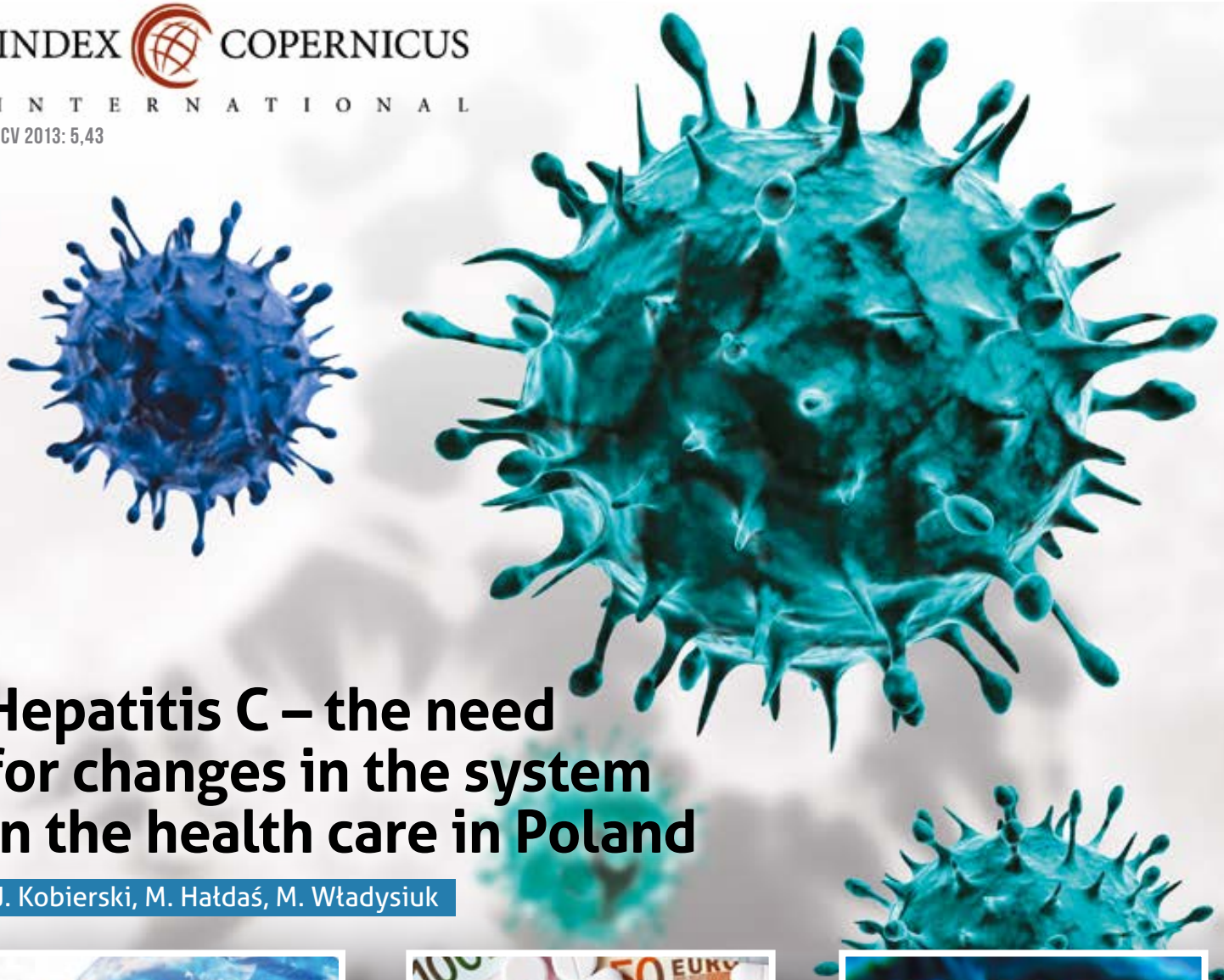

# Hepatitis C – the need for changes in the system in the health care in Poland

J. Kobierski, M. Hałdaś, M. Władysiuk

**Patients Registries - the role of the health system, new trends and hopes for Polish patients - 2nd JHPOR conference, Warsaw March 19th 2015**

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**Polish Experience in Financial Management of Medicines Market by Public Payer**

T.Płusa

**Ebola viral hemorrhagic fever**

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# Risk of severe hypoglycaemia for various treatment regimens – a systematic review and meta-analysis of observational studies

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diabetes mellitus, antidiabetic medications, insulin regimens, observational studies, severe hypoglycaemia

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## ABSTRACT

***Background:*** **Previous publications show that diabetes mellitus (DM) is a grave medical and economic problem, largely due to complications. The objective is to evaluate real-life risk of severe hypoglycaemic events (SHEs) among diabetic patients (type 1 and 2, T1&2) for various therapies.**

***Methods:*** **We conducted a systematic review of observational studies in MEDLINE, Embase, and The Cochrane Library databases. Observational, retrospective or prospective, studies (with at least 100 participants) in children and adults were included, with focus on: time horizon, number of patients, number of SHEs, and number of patients experiencing SHEs.**

**In T1 DM we distinguished basal-bolus/pre-mix insulin and insulin pump, and in T2 DM we singled out basal-bolus/pre-mix insulin, basal supported oral therapy with insulin as the basal component, sulfonylurea, and other antidiabetic medications.**

**We used a Poisson model implemented in Bayesian framework in WinBugs to estimate the SHE.**

***Results:*** **We identified 55 relevant studies encompassing 245,028 patients (103,741.81 patient-years). Annual SHE rates varied in T1DM from 0.18 (95%CI: 0.13–0.25) for insulin pump up to 1.1 (0.57–2.71) for basal-bolus with human basal insulin, and in T2DM from 0.006 (0.001–0.008) for oral antidiabetic drugs (excl. SU) up to 0.56 (0.16–9.65) for basal-bolus with human insulin as the basal component.**

***Conclusions:*** **Our results confirm that available treatment regimens differ in SHEs risk in real-life setting. Still SHEs are also driven by other factors, e.g. lifestyle, which may impact treatment selection.**

## BACKGROUND

Not only is diabetes mellitus (DM) an expensive medical condition, but it is also a multidimensional one, leading to wide range of complications that themselves may be clinically important or associated with high resource consumption. One of these is hypoglycaemia, that is often related to antidiabetic drugs and might affect patients compliance, quality of life and treatment outcomes. Most of hypoglycaemic events are not documented, however severe hypoglycaemic events (SHEs) require assistance of another person, and can be even fatal, although rarely. Antidiabetic drugs are associated with various rates of hypoglycaemia, and the burden of hypoglycaemia is determined mainly by drug use patterns and patients' adherence, but also diet and exercise. A review of the importance of hypoglycaemia from the perspective of the clinical process (clinical inertia, patient's adherence) and the list of possible causes and risk factors can be found e.g. in Ahrén[1].

**IN POLAND, AMONG THE MOST FREQUENTLY PRESCRIBED DRUGS ARE THE ONES FOR THE TREATMENT OF CARDIOVASCULAR RELATED DISEASES, INCLUDING ANTIHYPERTENSIVE DRUGS.**

Hypoglycaemia is now being frequently used in cost-effectiveness modelling in DM[e.g. 2,3] and often constitutes an important part either strongly influencing the resulting incremental cost-effectiveness ratios[e.g. 4,5] or being an outcome measure [e.g. 6]. Hypoglycaemia has also been subject to cost-of-illness studies, e.g. Jönsson et al.[7] for T2 DM in Sweden. The body of evidence in such studies is limited as–to the best of our knowledge–no systematic review and meta-analysis of severe hypoglycaemia risk has been performed. E.g. in their study Jönsson et al. assumed the rates of SHE based on five studies only[8-12]. The above observations motivate our research to try to estimate real-life risk of SHE based on best available evidence. The aim of the present study is to collect real-life data on absolute number of hypoglycaemic events in order to evaluate risk of SHE among patients with DM using various treatment regimens. These estimates can then be used e.g. in cost studies or to populate economic models on DM and its complications.

In order to make the estimates as close to real-life settings as possible, we decided to use observational studies only and not randomized controlled trials (RCTs). Importantly our goal was to assess the absolute risk of SHE in an observational, rather than interventional, context, i.e. we want to assess what the risk of hypoglycaemia is when we observe a patient to use a given therapy, and not when we prescribe a given therapy to patient. In real-life clinical practice many factors influence the treatment selection in DM, baseline risk of SHE being probably one of them. That is why a problem of confounding would appear when trying to interpret our results (obtained from observational studies) in interventional manner. Thus, for our purpose observational studies are more relevant than RCTs. It is also important to stress that our results ought not to be used to compare treatments between each other to see what the results of replacing one treatment by another would be. Therefore we did not present relative rates.

As there are numerous drugs that can be used in DM, some grouping is necessary, as otherwise the body of evidence for each individual treatment would be too small to make credible inferences, and random errors would drive the results. That is why we decided to group all possible treatment regimens in a dozen of categories (4 in T1, 8 in T2) based on clinical guidelines and consultation with clinical experts.

The paper is structured as follows. In the next section we present the methodology of our systematic review. We present the search strategy and criteria used, as well as assumptions made in meta-analysis of the data. We then present results in section 3. These encompass the results of our systematic review of observational studies and of a review of secondary studies that was used to fill in the gap when primary studies were unavailable for some regimens. We also present the resulting estimates of SHE rates for analysed regimens. We discuss the findings and limitations in section 4 and briefly conclude in the last section.

## METHODS

We analysed SHEs in type 1 and type 2 (T1&T2) DM patients. We used SHE definition proposed by Jönsson et al.[7] i.e. an event of low plasma glucose level when a patient requires help from another person to manage, as this definition directly relates to resource usage.

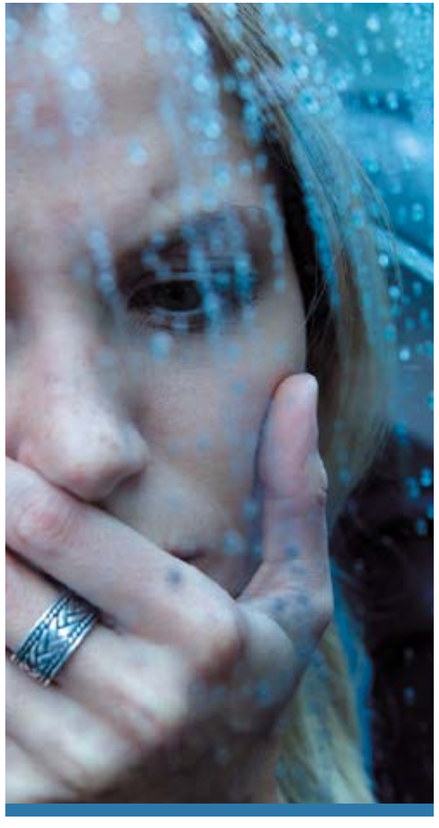
Based on the anticipated different drug related SHEs risk we defined the following treatment groups. In T1 DM: insulin pumps, basal-bolus insulin therapy with long-acting insulin analogue as the basal component (BBA), basal-bolus insulin therapy with human insulin as the basal component (BBH), biphasic insulin analogue, biphasic human insulin. In T2 DM: sulfonylurea (SU) with or without other oral drugs but excluding insulin, other antidiabetic medications especially oral antidiabetic medications different than SU (OADs excl. SU), basal long-acting insulin analogue (BOTA), basal human insulin (BOTH), basal-bolus with long-acting insulin analogue as the basal component (BBA), basal-bolus with human insulin as the basal component (BBH), biphasic insulin analogue, biphasic human insulin (all insulin regimens could be in combination with OADs). We defined basal bolus insulin therapy as long acting insulin analogue once or twice daily and short/ultrashort insulin at mealtime (BBA).

Although SR did not have a registered protocol, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[13]. As we wanted to assess SHEs rates in real-life rather than in experimental settings we looked for observational studies in: MEDLINE, Embase and The Cochrane Library databases (search strategies are given in Online Resource ESM_1). To account for changes in clinical practice in recent years and possible impact on treatment related risks, only recent studies were included (newer than 10 years).

We limited our search strategies to insulins or SU (i.e. we used no specific keywords for other-than-SU oral antidiabetic medications). We took this approach as NICE, IDF, ADA and EASD guidelines[7,14-17] firmly indicate that among oral antidiabetic medications used for treatment of T2 diabetes sulfonylureas are associated with an increased risk of hypoglycaemia as compared to other drug groups. The risk of hypoglycaemia associated with GLP-1 agonists and DPP-4 inhibitors is similar and very low[18,19]. Hence we treated GLP-1 agonists and OADs other than SU as one group, associated with a similar and most likely negligible SHEs risk. We assumed that the estimate of the risk of hypoglycaemia will use the best data found for one of these drugs. We decided to narrow the primary search then and to asses SHE rate in this group by applying a relative rate found in the literature as compared to SU, as described in more details below.

Precisely, specific inclusion criteria for observational studies encompassed: i) population of children and adults with T1 or T2 diabetes; ii) study design, i.e. observational, retrospective or prospective; iii) at least 100 participants (in total in a study, possibly split into smaller subgroups); iv) assessment of SHEs defined as an episode when the patient required an assistance from another person; v) publication date from 1st January 2002 until the search date, i.e. 1st October 2012.

Two authors independently conducted the selection process of relevant trials. Protocol assumed that in case of discrepancies between the authors discussion would be held until consensus was reached.



To estimate SHEs rates various types of data had to be extracted: time horizon in which hypoglycaemia was assessed, number of patients in a study group, number of hypoglycaemic episodes (absolute or mean per patient in a specified period of time, if available), number of patients experiencing at least one SHE (if available). If one study was described in many manuscripts, then the ones with the most appropriate and complete results were selected for extraction (e.g. data for a total study cohort instead of subpopulation, results presented separately for patients with T1 and T2 diabetes or results split by insulin regimens of interest). Data from included studies were extracted by one of the reviewer and checked by the other one.

As mentioned above, we planned to assess the risk related to other antidiabetic medications – GLP-1 or OADs (excluding SU) for T2 DM, calculating the relative rates as compared to SU based on secondary studies and then imposing them on the background SU-related SHE rate. We looked for the relative rates in secondary studies (SRs, meta-analyses) searched in a systematic way (see Online Resource ESM_1 for a search strategy) in MEDLINE, Embase, The Cochrane Library and Centre for Reviews and Dissemination (CRD). Inclusion criteria for this additional search encompassed: i) search performed at least in two databases (including at least one of the above databases), ii) at least two authors, iii) description of search strategy, iv) inclusion of randomized controlled trials (RCTs) conducted on T2 DM with at least one of the following: dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 agonist, other oral antidiabetic drugs i.e. metformin, TZD, v) with hypoglycaemia defined as an episode when a patient required help form another person. We decided to use RCTs as they are more common to provide data on relative rates (than observational studies).

Our systematic review of primary studies yielded no studies in T1 DM patients treated with biphasic insulins. We thus had to update our methods and we conducted a supplementary literature search for secondary studies. We applied a similar methodology as with OADs, i.e. we looked for systematic reviews of RCTs in T1 DM patients treated with premixed insulins. We then applied relative rates to assess absolute rates.

We wanted eventually to asses annual SHEs rates per one person, i.e. average number of SHEs per one patient-year of staying on therapy. We assumed a random effects model, i.e. assumed that mean rates per treatment regimen in individual studies are drawn from some distribution, whose average we aim to estimate. We assumed that number of SHEs in individual patient follows a Poisson distribution, which allowed to use the information on both the average number of SHEs in a study and the fraction of patients with at least one SHE in a given horizon. Our model was expressed in Bayesian framework and implemented in WinBugs (see Online Resource ESM_2). Random effects model and non-informative priors were used. Median from a posterior distribution was used as a point estimator, and 2.5% and 97.5% percentile defined a 95% Bayesian confidence interval.

Risks related with other ADs were assessed in a two-step procedure. First a relative rate between other ADs and SU was assessed based on RCTs using fixed effect model in WinBugs. It was then applied to the baseline rate estimated for SU from observational studies.

We assessed the quality of included studies using the Newcastle-Ottawa Scale[20] – for case-control and cohort studies. According to systematic review by Deeks et al.[21], this scale is one of the two best identified for evaluating non-randomised interventional studies and is suitable for use in a systematic review (either as a scale or a checklist). Moreover, this tool is mentioned in the Cochrane Handbook as a tool for assessing methodological quality or risk of bias in non-randomized studies[22]. Non-interventional studies of other types were assessed by focusing in methods of patients selection, methods of outcome recording, study size and study representativeness.

## RESULTS

### *Systematic review of observational studies*

Literature search (for primary studies) yielded 6214 records, from which 994 duplicates were removed. The remaining 5220 articles were screened by title and abstract, and then 526 full texts were reviewed. Finally, 101 manuscripts [23-123] describing 55 individual trials were assessed as eligible for the analysis. Fig. 1. shows the studies selection process. Characteristics of included studies and references to the excluded studies with justifications are given in Online Resources ESM_3 and ESM_4, respectively.

For T2 DM 76 articles describing 35 studies were included: 11 (11 278.88 patient-years in total) provided data on BOT with insulin analogue; 7 (2142.13 patient-years in total) – BOT with basal human insulin; 6 (3022.27 patient-years in total) – BB with basal insulin analogue; 3 (227.46 patient-years in total) – BB with basal human insulin; 12 (63 776.85 patient-years in total)

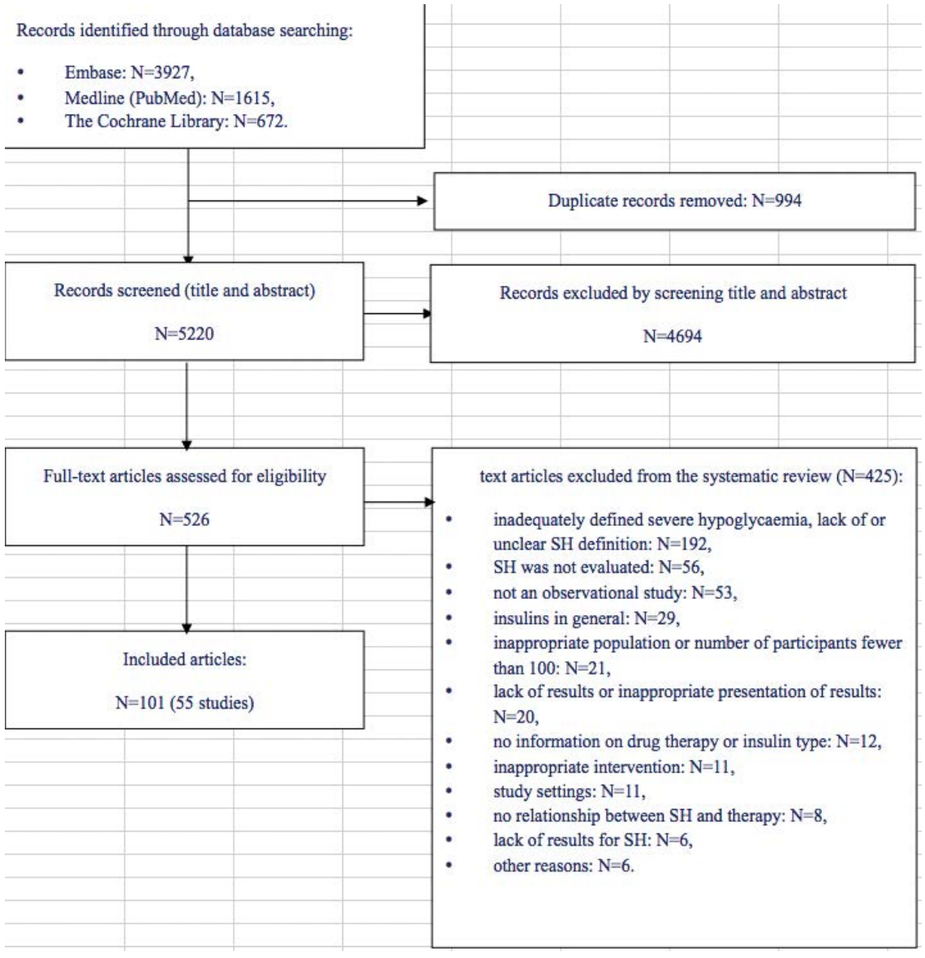



*Figure 1. Systematic review of observational studies selection process*



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.



– pre-mixed insulin analogues; 6 (2265.87 patient-years in total) – pre-mixed human insulin ; 6 (1776.00 patient-years in total) – sulfonylureas.For T1 DM 33 articles describing 21 studies were included: 14 (6714.61 patient-years in total) provided data on SHEs in patients on insulin pumps, 7 (9656.18 patient-years in total) – BB with insulin analogue as the basal component, and 6 (2881.57 patient-years in total) – BB with human insulin as the basal component. As mentioned above, no studies on the treatment with biphasic insulins in T1 diabetes were found. A supplementary search for studies on pre-mixed insulins in T1 was carried out using the following key words: "biphasic", "pre-mix", "insulin", "type 1" and "diabetes" and resulted in six systematic reviews[124-129] describing five relevant RCTs[130-135] (as no observational studies were found by our SR, we decided to use RCTs). These were then used to assess relative risk in this group of drugs relative to risks estimated based on primary, observational studies.

We used New Castle Ottawa Scale[20] for case-control and cohort studies to assess the quality of included studies. Observational studies of other types were assessed with focusing in methods of patients selection, methods of outcome recording (regarding only severe hypoglycaemia), study size and study representativeness. Overall studies' quality varied. Among 9 case-control studies three scored 2 out of 9 possible points, three – 3 points, two – 4 points, and one – 5 points. Among 13 cohort studies one study scored 5 out of 9 possible points, six – 6 points, and six – 7 points. The residual studies, assessed by description with no scoring, were of medium quality. Details on quality of included studies is given in Online Resources ESM_5.

### *Systematic review of secondary studies*

Literature search for other antidiabetic drugs yielded 12 systematic reviews (see fig. 2 in ESM_6), from which a study conducted by Karagiannis et al.[136] was assessed to provide the most appropriate data on severe hypoglycaemia associated with various antidiabetic medications in type 2 diabetes (for reference list of included studies and excluded studies with justification see ESM_7).

Data from the RCTs included in the study Karagiannis[136] indicated that in insulin-naïve patients with T2 DM treatment with sulfonylureas resulted in higher SHEs rate than treatment with other OADs (0.009 vs 0.0008 events per person-year, respectively, in patients treated with SU and patients treated with OADs other than SU – the estimated relative rate was 14.14, 95% CI: 5.53; 47.18, for the comparison of SU to DPP-4, while there was no statistical proof to differentiate the risk rate between these other OADs. The fact that SUs are related with greatest risk among all the OADs supports the approach to concentrate on SU risk in the systematic review of primary studies.

### *SHEs rates for various treatments*

Systematic review carried out for SHEs risk in assumed drug groups provided data on absolute annual number of SHEs per one treated patient with diabetes. Results available in each of the studies split by diabetes type are presented in Tables 1 and 2. The quantitative analysis of these data resulted in the following mean annual SHEs rates per person are presented in Table 3.

Our results show that SHEs rates differ among drug regimens. In T1 DM basal-bolus insulin therapy with human insulin as the basal component was associated with the highest risk of SHEs (1.1 events per person-year) while the insulin pumps led to the lowest risk of SHEs (0.18 events per person-year). In type 2 diabetes basal-bolus insulin therapy with basal human insulin was also associated with the highest risk of SHEs (0.56 events per person-year) and patients may be at the lowest rate of SHEs when treated with OADs other than SU (0.006 events per patient-year). This pattern in type 2 diabetes may reflect the disease progression, from oral antidiabetic medications to insulin in monotherapy or combined with OADs.

*Table 1. Diabetes type I results of the included studies*

| Study | Time horizon (years) | Number of participants | Patients with ≥1 SHE | Number of events | Mean events no per patient-year | SD |
|---|---|---|---|---|---|---|
| Insulin pump therapy | | | | | | |
| Bruttomesso 2002 | 7.4 | 138 | | 92 | 0.09 | 0.02 |
| de Bock 2012 | 3 | 75 | | 11 | 5 | |
| Garg 2004c | 0.97 | 216 | 45 | 84 | 0.4 | Not clear |
| Jakisch 2008 | 1 | 412/300/199 | | 74/60/34 | 17.87/20.04/17.33 | 2.85/3.91/4.47 |
| Kapellen 2007 | 1/1/2.75/2.75 | 248/544/76/177 | | | 0.25/0.14/0.27/0.27 | |
| Katz 2012 | 1.69 | 93 | | 50 | 31.8 | |
| Leinung 2010 | 1 | 117 | 37 | 68 | 58.9 | |
| Muller-Godeffroy 2009 | 0.5 | 88 | 6 | | | |
| Nimri 2006 | 1/1/1 | 127/129/23 | | | 11.1/23.3/0 | |
| Reda 2007 | 2.6 | 105 | | 15 | 0.05 | |
| Rudolph 2002 | 3.01 | 107 | | | 19.2 | |
| Scaramuzza 2011 | 1.7/1.4 | 493/493 | | | 6.6/3.9 | |
| Scheidegger 2007 | 0.46 | 19 | 1 | 1 | | |
| Wood 2006 | 1 | 132 | | | 7.4 | |
| Basal bolus with long-acting insulin analogue | | | | | | |
| DAFNE, Keen 2012 | 1/1 | 124/124 | 15/6 | 37/22 | | |
| Garg 2004 a | 1.09 | 292 (98, 299) | 81 (28, 81) | 167 (n.a., n.a.) | 0.57 (0.5, 0.6) | |
| Herwig 2007 | 1.68 | 74 | | 11 | 0.14 | 0.4 |
| Kapellen 2009 | 1 | 6558 | | | 32.2/100 | 3 |
| Katz 2012 | 1.8 | 50 | | 31 | 34.4 | |
| Kristensen 2012 | 1 | 1052 | | | 1.47 | SE=0.18 |
| PREDICTIVE, Marre 2009 | 1 | 647 | | 11 | 0.02 | |
| PREDICTIVE, Preumont 2009 | 0.5 | 232 | | | 0.1 | 0.7 |
| PREDICTIVE, Sreenan 2008 | 0.23 | 1500 | | | 0.52 | |
| PREDICTIVE, Yenigun 2009 | 0.08/0.23 | 506/506 | | 94/28 | | |
| Basal bolus with human basal insulin | | | | | | |
| Garg 2004b | 1.06 | 98 | 30 | | 1.2 | SEM=0.40 |
| Hartemann--Heurtier 2003 | 1/1 | 110/110 | 14/26 | | 0.2/0.83 | 0.62/3/34 |
| Herwig 2007 | 1.68 | 68 | | 62 | 0.73 | 1.68 |
| Kristensen 2012 | 1 | 2085 | | | 1.09 | SE=0.11 |
| Leckie 2005 | 1 | 243 | 83 | | 0.98 | |
| PREDICTIVE, Sreenan 2008 | 0.077 | 1500 | | | 3.51 | |

*Table 2. Diabetes type II results of the included studies*

| Study | Time horizon (years) | Number of participants | Patients with ≥1 SHE | No of events – absolute or mean per patient-year |
|---|---|---|---|---|
| Basal long-acting insulin analogue ± OADs | | | | |
| A1chieve, Home 2011 | 0.46 | 12 078 and 3467 | | 0 and 0.01 |
| EARLY, Hanefeld 2012 | 0.46 | 1389 | 1 | 1 |
| FINE, Tsai 2011 | 0.50 | 2016 and 16 | | 0.003 and 0 |
| IMPROVE, Gumprecht 2009 | 0.25 | 245 | | 0.197 |
| Kawamori 2008 | 0.46 | 97 | 0 | 0 |
| LIGHT, Verges 2012 | 0.25 | 1863 | 18 | 0.12 |
| PREDICTIVE, Dornhorst 2008 b | 0.08 | 118 | | 0.26 |
| PREDICTIVE, Meneghini 2009 | 0.23 | 1652 | | 0.00 |
| PRESENT, Jang 2008 | 0.23 | 348 | | 1.1 |
| Sudhakaran 2010 | 0.46 | 54 | 0 | 0 |
| Sudhakaran 2011 | 0.46 | 2743 | 0 | 0 |
| Yang 2012 | 0.31 | 297 | 2 | 2 |
| Basal human insulin ± OADs | | | | |
| FINE, Tsai 2011 | 0.50 | 589 | | 0.031 |
| Furlong 2002 | 2.42 (median) | 133 and 67 | 6 and 1 | |
| Honkasalo 2010, Honkasalo 2011 | 1 | 431 | 53 (12.3%) | 116 |
| IMPROVE, Gumprecht 2009 | 0.25 | 497 | | 0.153 |
| PREDICTIVE, Dornhorst 2008 b | 0.08 | 175 | | 0.78 |
| PRESENT, Jang 2008 | 0.23 | 3414 | | 0.39 |
| Sudhakaran 2010 | 0.46 | 23 | 0 | 0 |
| Basal bolus with long-acting insulin analogue ± OADs | | | | |
| A1chieve, Home 2011 | 0.46 | 1593 and 2512 | | 0 and 0.001 |
| JDDM23, Oishi 2012 | 0.50 | 126 | 1 | 1 |
| PREDICTIVE, Sreenan 2008 | 0.23 | 2137 | | 0 |
| SAFIR, Zick 2007 | 0.15 | 455 | 0.7% of patients | 0.05 |
| Suzuki 2012 | 1 | 400 | 1 | 1 |
| Zjačić-Rotkvić 2012 | 0.5 | 203 | 0 | 0 |
| Basal bolus with human insulin ± OADs | | | | |
| Biesenbach 2006 | 1 | 34 | | 0.05 |
| JDDM23, Oishi 2012 | 0.23 | 126 | 1 | 1 |
| PREDICTIVE, Sreenan 2008 | 0.23 | 126 | | 0.78 per patient year |
| Pre-mix insulin analogues | | | | |
| A1chieve, Home 2011 | 0.46 | 27 591 and 13 318 | | 0 and 0.20 per patient-year |
| BIAsp Start, Berntorp 2011 | 0.52 | 1154 | 2 | 2 |
| Danish BIAsp Study Group, Breum 2008 | 0.5 | 392 | 4 | |
| IMPROVE, Khader 2010 | 0.5 | 1613 | | 0.05 |
| IMPROVE, Valensi 2009 | 0.5 | 52 419 | | 0.008 |
| INITIATE plus, Oyer 2011 | 0.46 | 4812 | 87 | 127 |
| Levit 2011 | 2.9 | 115 | 0 | 0 |
| Ligthelm 2009 | 1.5 | 149 | 0 | 0 |
| Makela 2012 | 0.5 | 496 | | 19 |
| Nobels 2012 | 0.5 | 498 | 6 | |
| PRESENT, Gao 2009 | 0.23 | 3697; 4754; 2392; 817 | | 0.04; 0.13; 0.3; NA |
| PRESENT, Khutsoane 2008 | 0.50 | 21 977 | | 0.1 |
| Temizel 2010 | 1 | 71 | | 0.06 per patient- month |
| The 1-2-3 study, Garber 2006 | 0.31 | 100 and 68 and 25 | 3 and 3 and 1 | |
| Pre-mix human insulin | | | | |
| Gu 2012 | 0.31 and 0.31 | 409 and 235 | | 2 and 0 |
| IMPROVE, Shah 2009 a | 0.25 | 3856 | | 0.355 |
| Nobels 2012 | 0.08 | 592 | 4 | |
| PRESENT, Shestakova 2007 | 0.23 | 3241 | 162 | 0.7 |
| Progens-first-step, Strojek 2008 | 0.25 and 0.25 | 482 and 483 | 1 and 2 patients during first 13-week observation and during second 13 weeks, respectively | 2 and 2 episodes, respectively |
| Temizel 2010 | 1 | 69 | | 0.04 per patient-month |
| SU | | | | |
| Andayani 2010 | 0.5 | 49 | 1 | 1 |
| Aung 2012 | 1 | 10.43 | 24 | |
| Exhype, Pettersson 2011 | 0.5 | 430 | 5 (1.2%) | |
| Iványi 2012 | 2.54 | 86 | 2 | 2 |
| UK Hypoglycaemia Study Group | 0.73 | 103 | | 0.1 |
| Vexiau 2008 | 0.5 | 400 | 16 | |

*Table 3. Annual mean (95% CI) number of SHEs in patients with type 1 and type 2 DM*

| Therapy | Average number of SHEs per patient per year | 95% CI | Remarks |
|---|---|---|---|
| Type 1 DM | | | |
| basal-bolus (basal insulin analogue) | 0.53 | 0.29–1.18 | |
| basal-bolus (basal human insulin) | 1.10 | 0.57–2.71 | |
| insulin pump | 0.18 | 0.13–0.25 | |
| pre-mix insulin analogue and pre-mix human insulin | 1.10 | | due to lack of statistically significant differences between pre-mix human insulin and pre-mix insulin analogues, the same SHEs rate as for pre-mixed insulin analogues (so BBH) |
| Type 2 DM | | | |
| BOT analogue | 0.13 | 0.04–1.17 | |
| BOT human | 0.21 | 0.08–0.88 | |
| basal-bolus (basal insulin analogue) | 0.01 | 0.003–0.25 | |
| basal-bolus (basal human insulin) | 0.56 | 0.16–9.65 | |
| pre-mix insulin analogue | 0.10 | 0.05–0.26 | |
| pre-mix human insulin | 0.20 | 0.07–0.93 | |
| sulfonylureas | 0.05 | 0.02–0.14 | |
| OADs (excl. SU) | 0.006 | 0.001–0.008 S | |

## DISCUSSION

We conducted a systematic review and meta-analysis in order to estimate average annual rates of severe hypoglycaemia events associated with various insulin regimens and other antidiabetic medications. For insulin therapy and sulphonylureas we included observational studies that met the predefined criteria to directly assess rates of SHEs. For residual antidiabetic medications in type 2 diabetes we used data from another systematic review to assess the relative SHE frequency and apply it to a baseline rate estimated for SU. Due to lack of observational data for premix therapies for type 1 we had to refer to secondary studies as well in order to assess the relative risks in comparison to other therapies and indirectly calculate associated SHEs rates. That is why this part of results should be treated with greater caution.

The inclusion criteria for observational studies were defined so as to obtain as high quality of identified studies as possible. Thus, we decided to use newer publications only to account in possible changes of diabetes management over time (only studies published from 2002 on were used). Further we took into account only studies with at least 100 participants (we did not want to include small studies of a poor quality as the number of participants is also assessed in The Newcastle-Ottawa Scale). Most importantly the definition of SHE used in the identified studies was carefully checked so as to guarantee consistency among them, but at the same time we had to reject numerous studies due to lack of information in the definition used therein. That reduces the body of evidence but provides greater consistency of results. The overall quality of the studies, as measured by the New Castle Ottawa scale, is nonetheless rather medium. The most frequent shortcomings of the included case control studies were no definition of controls and using self reports or medical records only for the ascertainment of exposure. Major shortcoming of the included cohort studies was that it was not demonstrated that the outcome of interest was not presented at the start of the study. The heterogeneity of the studies is quite substantial, that is why a random effects model was used, and the resulting confidence intervals for mean rates are rather wide. We still have to notice that best available evidence was used, and so these limitations simply suggest the direction for further research when more observational studies have been published. With more data a better assessment of overall means should be possible, and perhaps a meta-regression approach could explain some sources of heterogeneity.

The applied methodology allowed to use two types of results reported in the studies, either number of SHEs or fraction of patients with at least one episode. As can be seen in tables 1 and 2, various reporting was used in identified observational studies. Focusing on number of SHEs only would substantially reduce the amount of data available, and that is why we decided to assume the Poisson distribution. Obviously, this assumption comes at a price, as potential biases may emerge. Poisson distribution forces the mean being equal to the variance, while hypoglycaemia events may concentrate in single patients more than this distribution would suggest (e.g. patient lifestyle either diminishes or augments chances of an event), but may also spread out more evenly (e.g. a patient having experience SHE will adapt her lifestyle to reduce future risk). We considered using another distribution (e.g. negative binomial) to allow for difference between mean and variance, but additional parameters made the estimation process and results very unstable. Secondly, it was mostly in T2 that substantial amount of data came in the form of number of patients with at least one SHE, where the overall risk was quite small and so the discrepancy between Poisson and some other distribution would be much smaller.

Eventually, annual rates varied from 0.18 for insulin pump up to 1.1 for basal-bolus with human basal insulin and from 0.006 for oral antidiabetic drugs up to 0.21 for basal human insulin with oral antidiabetic medications for type 1 and type 2 DM, respectively. Spread of results between individual studies is large, which means that several other factors may affect the outcome (e.g. life style). More data would probably make it possible to identify these factors, e.g. by meta-regression. However, the mean value may be still estimated and our calculations are based on the best (available at the time of the review) data.

It is worth to mention that our analysis of observational studies yielded results different from those based on RCTs. And so the risk of SHE associated with sulfonylureas estimated from observational studies amounted to 0.05 event per patient per year, and was higher than 0.01 coming from RCTs included in the systematic review by Karagiannis et al.136. This can lead to the conclusion that a real SHEs risks are higher than those in RCTs due to factors other than therapy associated with hypoglycaemia occurrence, however obviously both numbers are estimated with an error, and both are actually small in absolute terms.

It's important to notice that our purpose was not to compare given drugs between themselves – that is we defined our approach so as to get the best possible estimate of SHE rate for each treatment separately, rather than the best possible estimate of relative SHE rate between pairs of treatment regimes. The latter would require e.g. looking for studies with several arms encompassing more than one treatment regimen, so as to get relative effects and then meta-analyse them (while we meta-analysed individual treatment rates for each regimen separately). Another important decision would then also be whether to use interventional or observational studies, and that depends largely on a question we are asking. If we wanted to know – "what is the risk if I give this treatment to my patient?" – we should rather go for interventional studies. In our case our question rather is – "what is the risk if I observe this patient using this treatment" – and then observational studies seem to be more appropriate, as they account for the fact that some patients may be using drugs that address their life-style and moderates their baseline SHE risk. Additionally, observational studies do not impose very strict protocol that may bias complication rates downwards in RCTs when compared to real-life situations. Thus, our results should not be used to quantify consequences of switching patients between drug regimens, but rather to assess the actual overall burden of SHE when drug usage patterns are known.

We did not find other systematic review or meta-analysis that evaluate real-life risk of severe hypoglycaemia among diabetic patients (type 1 and type 2) for various therapies. A review closest to ours was the one conducted by Bolen et al.[137] that summarized the English-language literature on the benefits and harms of oral agents in adult patients with T2 DM. In their review, Bolen et al. included 216 controlled trials and cohort studies and 2 systematic reviews in total of which 169 articles evaluated adverse events. In comparison to our review they estimated weighted absolute risk differences between individual drugs, drug groups or therapies, while our aim was to estimate average annual rates of SHEs associated with various insulin regimens and other antidiabetic medications. Moreover, they presented combined results for minor and major hypoglycaemia and did not provide the definition of major hypoglycaemia. Results of their meta-analysis indicated that in patients receiving second generation sulfonylureas hypoglycaemic episodes (minor and major) were more frequent than in patients receiving metformin or TZD. They obtained concordant conclusion as can be seen in NICE, IDF, ADA and EASD guidelines[14-17] in the treatment of type 2 DM which indicate that sulfonylureas are associated with higher risk of hypoglycaemia than other antidiabetic oral drugs.

Other meta-analysis of observational studies conducted in patients with T2 DM by Goto et al. [138] evaluated association between severe hypoglycaemia and risk of cardiovascular disease. Cohort studies and randomised controlled trials were included as long as an observational analysis of the analysed association was available. Goto et al. included six studies in their meta-analysis (two were secondary analyses of RCT and four were based on administrative databases) of which none fulfilled inclusion criteria of our systematic review due to inappropriate definition of severe hypoglycaemia. The association between SHE and cardiovascular disease was estimated with the use of relative risk as a measure of effect. Results suggest that severe hypoglycaemia is associated with approximately twice the risk of cardiovascular disease. These results indicate the need for evaluation and quantification of the risk of severe hypoglycaemia.

## CONCLUSIONS

Various drug regimens differ in terms of severe hypoglycaemia risk, as also pointed out in published guidelines. Our results indicate that basal-bolus therapy with basal human insulin is associated with the highest average number of SHEs per patient per year, both in type 1 and type 2 DM, while insulin pump and OADs (excl. SU) seems to be the safest therapies in T1 and T2 diabetes, respectively. These differences can be quantified based on results of published observational studies. Results of the current analysis can be used to provide parameters for cost-of-illness studies estimating the overall burden of hypoglycaemia.

## LIST OF ABBREVIATIONS

- AD – antidiabetic medication
- BB – basal-bolus
- BBA – basal-bolus insulin therapy with long-acting insulin analogue as the basal component
- BBH – basal-bolus insulin therapy with human insulin as the basal component,
- BOTA – basal supported oral therapy with long-acting insulin analogue as the basal component
- BOTH – basal supported oral therapy with human insulin as the basal component
- CI – confidence interval
- DM – diabetes mellitus
- OAD – oral antidiabetic medication
- RCT – randomized controlled trial
- SHE – severe hypoglycaemia event
- SU – sulfonylurea
- T1, T2 DM – type 1, type 2 diabetes mellitus
- TZD – thiazolidinediones

## COMPETING INTERESTS

The project was funded by Novo Nordisk. The author(s) declare that they have no competing interests. There is no specific organization that may in any way gain or lose financially from the publication of this manuscript.

## AUTHORS' CONTRIBUTIONS

MJ, JP, MN and MC are the authors of general analytic framework. MJ, JP, ER and MN have participated in the systematic review. All authors participated in preparing, read and approved the final manuscript.

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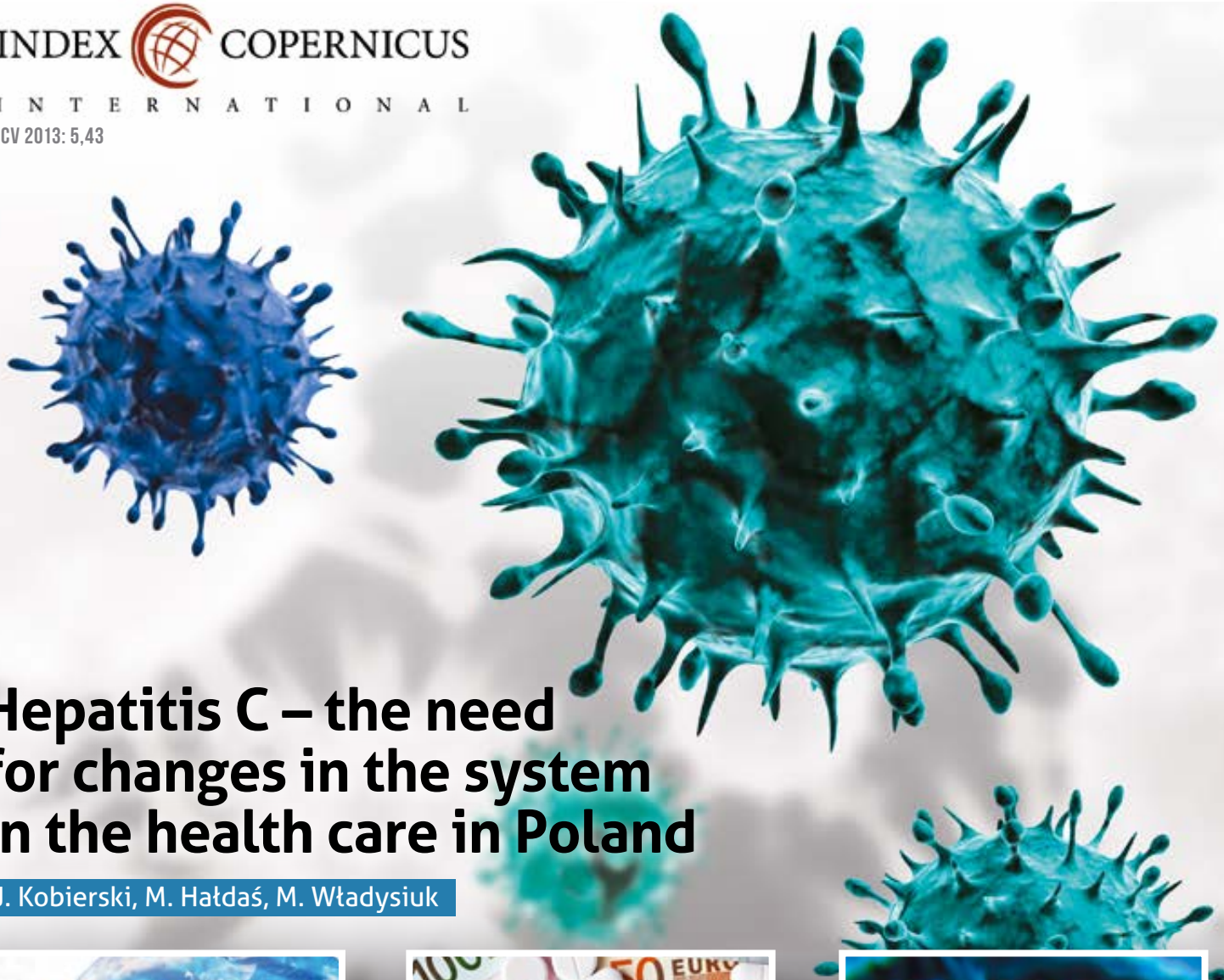

# Hepatitis C – the need for changes in the system in the health care in Poland

J. Kobierski, M. Hałdaś, M. Władysiuk

**Patients Registries - the role of the health system, new trends and hopes for Polish patients - 2nd JHPOR conference, Warsaw March 19th 2015**

A. Fałek et al

**Polish Experience in Financial Management of Medicines Market by Public Payer**

T.Płusa

**Ebola viral hemorrhagic fever**

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# Do we need real world data Polish ISPOR Chapter Therapeutic Programs, Pharmaceutical Care and Pharmaceutical Law Section (TPPCPL) initial discussion

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real world data, registries, RWD

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## ABSTRACT

***Objective:*** **to discuss potential areas for use and sources of real world data in relation to medical treatment.**

***Methods:*** **we performed Pub-Med and an internet based search in literature for definitions, sources and examples of real world data use.**

***Results:*** **we identified 13 publications fitting our search criteria and we found that there are not many full publications related to real world data even if they can provide significant additional information regarding patient related outcomes, resources use, costs and the effect of therapies in a non-controlled environment and on broader populations than those from randomized clinical trials.**

***Conclusion:*** **Real world data can provide additional information in relation to medical treatments however there is a need to focus attention on methodology of data collection, data quality, potential sources of data and ensure proper legal environment for data collection. Unfortunately, despite large number of publications identified in PubMed database, there are only few available in a form of full text papers, the majority of publications are only abstracts from scientific conferences. In the future in order to share RWD experience it will be of benefit to encourage authors to work on full publications and not to limit their work only to abstracts.**

## INTRODUCTION

Nowadays it is not enough to obtain information related to new treatment option only from the randomized clinical trials. We can observe that the RCTs considered till now as the golden standard of evidence are not able to provide us with all the information we would like to have. Information about what the effectiveness of the new therapeutic treatment is, how it works on daily basis, if it is safe, what the real resources are used when treating patients with the new option. That and much more questions are related to real life data.

***Objective:*** Our aim at the Therapeutic Programs, Pharmaceutical Care and Pharmaceutical Law Section (TPPCPL) task force was to investigate what is understood as real world data and what are the potential areas for use of real world data in relation to introduction of new therapeutic options to the market. This is only an initial approach to potential further discussion to be continued by the task force.





DURING THEIR WORK THE TASK FORCE MEMBERS LOOKED AT RWD SOURCES AND TYPE OF OUTCOMES (ECONOMIC, PROS AND CLINICAL OUTCOMES).

***Methods:*** The analysis we performed was based on a literature search using the Internet. The Medline-PubMed databases have been reviewed. The initial search was focused on "real world data" term. Second search was restricted to real world data and the use of definition in the performed studies. Search strategy was based on terms: "real world data" [All Fields] AND "definition"[All Fields]. Reviewing all obtained publications from the performed search we analyzed in detail the publications from the period between years 2011-2014 and species – humans.

***Results:*** We identified 7208 publications, however only 13 were meeting our search criteria (diagram 1). After analysis of the full texts we found 1 publication was the ISPOR Task Force report[1], 4 publications related to outcomes, disease or therapies[2,3,4,5], 1 was a quality of life study[6], and 1 was a methodology discussion paper in relation to statistical testing for clinical effectiveness studies[7]. Additionally, we realized that there are many abstract publications available. Based on those publications we found that real world data can provide additional valuable information to clinicians, payers, industry, patients and society on how the product or technology works in real life setting, in a non-controlled environment, outside randomized clinical trials; what the health related outcomes are, resources used for a disease treatment or the costs.

An important initiative identified was the one by ISPOR organization who has created a task force to discuss using RWD for coverage and payment decisions[1]. The task force defined RWD as data that is collected outside conventional Randomized Controlled Trials (RCTs). The real world data are raw data, non-informative while real world evidence is information that is organized to inform a conclusion or a judgment, it is typically undertaken according to a research plan and it is shaped to be informative, i.e. to clinical or payer decisions.

During their work the task force members looked at RWD sources and type of outcomes (economic, PROs and clinical outcomes).

They concluded that "Real world data are essential for sound coverage, payment, and reimbursement decisions. The types and applications of such are varied, and context matters greatly in determining the value of a particular type of evidence in any circumstance. Different study designs can provide useful information in different situations. Randomized controlled trials remain the gold standard for demonstrating clinical efficacy in restricted trial setting, but other designs—such as observational registries, claims databases, and practical clinical trials—can contribute to the evidence base needed for coverage and payment decisions."[1].

E.T. Masters in her publication about outcomes assessment and RWD related to pain mentions the different sources of real world data we have such as supplements to RCTs, large simple trials, patient registries, administrative claim databases, surveys, electronic health records[2].

Depending on the further data use and the sources for data which are available in each of the countries in the literature we can find examples of different approach to real world research and analysis. Some countries have disease registries in place and due to ongoing collection of real world information they are able to analyze the data about the disease and its treatment.

An interesting finding in our search was that despite a large number of records identified there are not that many real world data full text publications related to pharmaceutical products, registries or methodologies. Based on the final number of 13 full publications only 3 were related to collection of real world data using data from registries or electronic databases either in a prospective or retrospective way[3,4,5].

Based on the few identified publications and the large number of abstracts we can see cases when the real data can provide additional information on the effect of treatment, also on real length of the treatment[8] or how utilizing real world data can provide input into medical costs or health care cost reduction[9,10,11,12], and also examples showing how RWD can be useful to provide more understanding about disease burden, epidemiology or resources used in relation to the disease treatment[13]. RWD are not only valuable to learn more about treatment but can also provide significant input into prevention, information about the management of diseases like e.g. management of cardiovascular risk in primary prevention[14].

Important are the discussions about methodology for data collection, quality of the data and usage for decision-making. A discussion about methods how to enable implementation of RWD into network meta-analyses supporting regulatory or reimbursement decisions was published by D. Jenkins, M. Czachorowski, S. Bujkiewicz et al.[15]. Related to methods and quality of data is the issue of representative sample. E. Gemmen, L. Parmenter and A.B. Mendelsohn look at the most effective approaches to achieve data from real world being representative of the target population[16].

In Brazil there was a research on potential usage of the existing database in health economic analyses with a study focused on acute myocardial infarction[17]. Another use of RWD from databases information can be budget impact calculations[18].

Long-term data collection within a large database can be basis for benefit and patient reported outcomes assessment. Such example is the German registry for psoriasis showing burden of the disease at the time when patient enter into the registry and the quality of care with assessment of the impact on health outcomes[19].

S.J. Rizvi with co-workers indicated that real-world data can confirm the high prevalence of treatment-resistant depression (TRD) and impact the burden of illness associated with TRD in primary care settings in Canada[20].

E. Katodritou with co-workers published their study concluding that RWD are not comparable with the results of the RCTs. However, they may be used to confirm the data of the RCTs and, thus, facilitate the incorporation of certain therapies in standard clinical management[21].

Research in the real world is necessary because of the variety of factors that may play an important role influencing the effectiveness in real life. Factors such as comorbidities, concomitant treatments, adherence, access to care, the strength of the physician-caregiver communication and socio-economic factors among others can modulate the treatment results. Observational studies databases can provide a sufficient level of evidence to support the creation of guidelines i.e., clinical or provide significant information for the decision-making process [22].

***Conclusion:*** Real world data can provide additional information in relation to medical treatments however there is a need to focus attention on methodology of data collection, data quality, potential sources of data and ensure proper legal environment for data collection. Unfortunately, despite large number of publications identified in PubMed database, there are only few available in a form of full text papers, the majority of publications are only abstracts from scientific conferences. In the future in order to share RWD experience it will be of benefit to encourage authors to work on full publications and not to limit their work only to abstracts.■

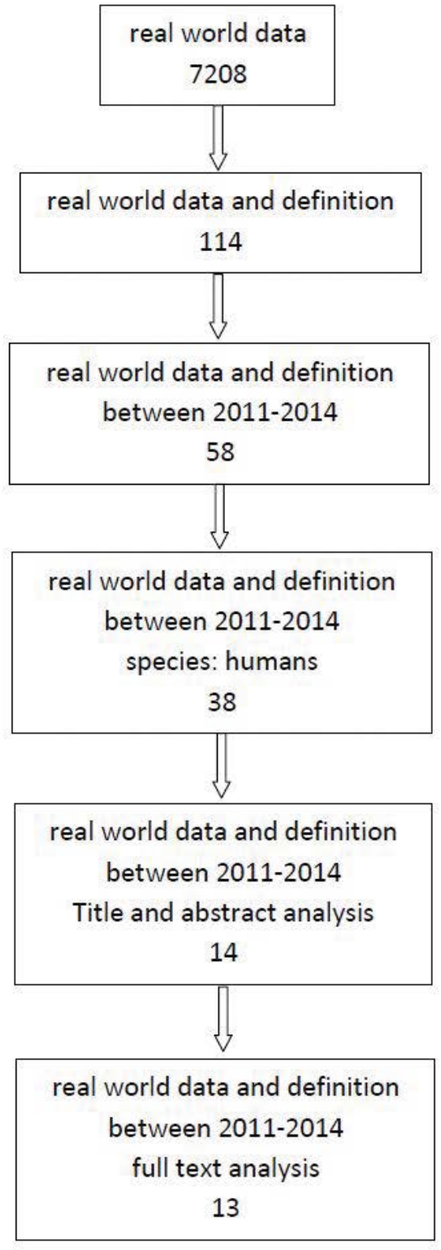


*Diagram 1. Search strategies in the library database – PubMed*

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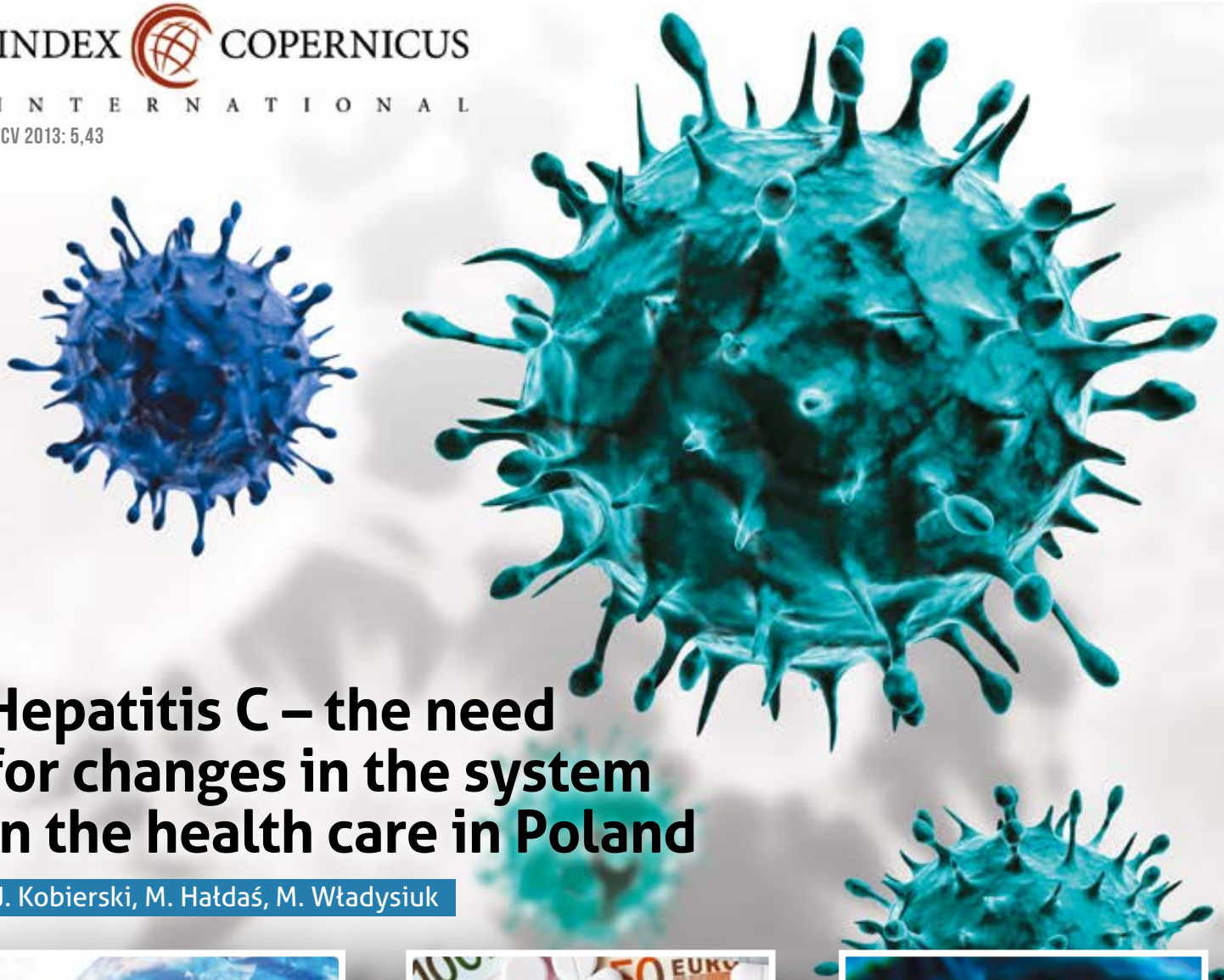

# Hepatitis C – the need for changes in the system in the health care in Poland

J. Kobierski, M. Hałdaś, M. Władysiuk

**Patients Registries - the role of the health system, new trends and hopes for Polish patients - 2nd JHPOR conference, Warsaw March 19th 2015**

A. Fałek et al

**Polish Experience in Financial Management of Medicines Market by Public Payer**

T.Płusa

**Ebola viral hemorrhagic fever**

# Polish Pharmacoeconomic Society activities' review 2/2014

M. Szkultecka-Dębek, Roche Polska Sp z o.o.

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Pharmacoeconomic Society
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JHPOR, 2014, 2, 100-101

## ABSTRACT

**Polish Pharmacoeconomic Society activities' review 2/2014**

Polish Pharmacoeconomic Society sections continue working on already initiated projects and have started discussions about next year focus.

The most recent news is that the Polish ISPOR Chapter finalized the translation of the ISPOR book on Therapeutic and Diagnostic Device Outcomes Research and the Health Related Quality of Life Section (HRQoL) finalized working on the Quality of Life Dictionary. Both books were published and made available at the Polish ISPOR Chapter Conference in December 2014.

The Therapeutic Programs, Pharmaceutical Care and Pharmaceutical Law Section (TPPCPL) continue to analyze adverse events costs based on therapeutic programs examples and started discussions on initiating different projects in 2015. Among other proposals Section there is a suggestion inspired by the HRQoL to work on pricing related terms in Polish language.

The Polish Pharmacoeconomic Society also continues to support the Journal of Health Policy and Outcomes Research (JHPOR) and after the successful Scientific Conference in 2014, JHPOR already started preparations to organize the 2nd Scientific Conference dedicated to "Registries". The conference will take place in Warsaw on 19 th March 2015 and will be a forum to discuss real world data needs in Poland. An interdisciplinary input into the discussion is expected.

In December 2014 the Polish Society for Pharmacoeconomics organized the 12th International Conference dedicated to "Effective health care, how to make it profitable?".

The conference was focused on important issues related to healthcare in Poland and in Europe. There were sessions about risk sharing instruments, about a new approach to decision-making process based on Multi-Criteria Decision Analysis, exploring the possibilities of their practical implementation in the health care system. Another topic at the conference was dedicated to the functioning of the drug programs in Poland, from both the clinical perspective on basis of concrete examples and the National Health Fund's perspective.

There were sessions dedicated to health outcomes in oncology with particular emphasis on the analysis of survival and sessions about indirect costs in health care and methodology for measuring indirect costs.

Special guest invited to the conference was professor Michael Drummond, who gave a plenary lecture during which he summarized the most significant financial challenges European countries are facing. He also shared some experiences of other European countries in relation to Risk Sharing Agreements and Value-based Pricing. ■

IN DECEMBER 2014 THE POLISH SOCIETY FOR PHARMACOECONOMICS ORGANIZED THE 12TH INTERNATIONAL CONFERENCE DEDICATED TO "EFFECTIVE HEALTH CARE, HOW TO MAKE IT PROFITABLE?".

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