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SEASONAL INFLUENZA VACCINE
ECONOMIC MODELING THROUGH ECONOMIC AND
SOCIAL BENEFIT ANALYSIS OF VACCINATION

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**SEASONAL INFLUENZA VACCINE
ECONOMIC MODELING THROUGH ECONOMIC AND SOCIAL BENEFIT
ANALYSIS OF VACCINATION**

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Business sciences

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Declarations

I, undersigned (name: Peter VAJÓ, date of birth: 21/10/1990) declare under penalty of perjury and certify with my signature that the dissertation I submitted in order to obtain doctoral (PhD) degree is entirely my own work.

Furthermore I declare the following:

- I have examined the Code of the Károly Ihrig Doctoral School and I acknowledge the points laid down in the Code as mandatory;
- I handled the technical literature sources used in my dissertation fairly and accordingly and I have followed the provisions and stipulations related to the dissertation;
- I have indicated the original source of other authors' data in the reference section in a complete and correct way taking into consideration the prevailing copyright protection rules;
- No dissertation which fully or partially identical to the present dissertation has been submitted to any other university or doctoral school in order to obtain a PhD degree.

Debrecen, 5 January, 2022

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Peter VAJÓ

CONTENTS

DECLARATIONS	3
INTRODUCTION.....	5
1. SUBJECT MATTER AND OBJECTIVES	9
1.1. HYPOTHESIS	9
2. LITERATURE REVIEW.....	11
2.1. HEALTH ECONOMICS ANALYSIS AND TYPES.....	11
2.1.1. <i>Cost-minimization analysis</i>	11
2.1.2. <i>Cost-effectiveness analysis</i>	13
2.1.3. <i>Cost-benefit analysis</i>	15
a) <i>The human capital approaches</i>	16
b) <i>Past decisions of the public sector</i>	16
c) <i>Implicit preferences</i>	16
d) <i>Hedonistic pricing</i>	17
e) <i>Contingency assessment</i>	17
2.1.4. <i>Cost-utility analysis</i>	17
2.2. RELATED ANALYSES STUDIES IN FOREIGN LITERATURE	18
2.2.1. <i>A UK data-based study</i>	18
2.2.2. <i>A Netherlands data-based stud</i>	20
2.3. SUMMARY OF MY ARTICLE PUBLISHED IN <i>ECONOMICA</i>	21
2.4. OTHER PUBLICATIONS WITH MY PARTICIPATION	23
2.5. CHARACTERISTICS OF THE PATIENT GROUP INVOLVED IN THE ANALYSIS AND THE CURATIVE- PREVENTIVE PROCEDURE; DETAILED DESCRIPTION OF THE NEED FOR HEALTHCARE SERVICES	23
2.5.1. <i>Description of the demographic and socio-economic situation of the patient group exposed to infection with influenza A/H1N1, A/H3N2 and B viruses</i>	23
2.5.2. <i>The course of the disease</i>	26
2.6. DESCRIBING TRENDS OVER THE PAST 5 TO 10 YEARS IN HUNGARY	27
2.7. DESCRIPTION OF THE COURSE, OUTCOME AND EPIDEMIOLOGICAL DATA OF THE DISEASE, PRESENTATION OF THE CURRENTLY USED TREATMENTS.....	35
2.8. FACTORS INFLUENCING THE NUMBER OF NON-OCCURRING DISEASES AND ITS ESTIMATION	36
2.8.1. <i>Protection by vaccination</i>	37
2.8.2. <i>Influenza vaccine</i>	37
2.8.3. <i>Cross-immunity</i>	38
2.8.4. <i>Vaccination for the elderly and pregnant women</i>	38
2.9. CONSEQUENCES	39
2.10. CRITICAL OPINIONS	41
2.11. ASSESSMENT OF NON-OCCURRING ILLNESSES	41

2.12. ADVANTAGES OF VACCINATION IN GIVEN PATIENT GROUPS	41
3. MATERIAL AND METHOD	48
4. STUDY RESULTS AND THEIR ASSESSMENT	51
4.1. NUMBER OF NON-OCCURRED DISEASES BASED ON FACTS	51
4.1.1. <i>Basic data</i>	51
4.1.2. <i>Influenza season data, 2018/2019</i>	53
4.2. IMPACT ON THE NATIONAL ECONOMY	71
4.2.1. <i>Avoided cases in the active and passive groups</i>	71
4.2.2. <i>Presentation of US data and comparison of US and Hungarian data</i>	73
4.2.3. <i>Cost of hospital care per day</i>	77
4.3. ECONOMIC IMPACT	77
4.3.1. <i>Economic impact on the active population group</i>	77
4.3.2. <i>Economic impact on the passive population group</i>	79
4.4. SUMMARY OF THE IMPACT ON THE NATIONAL ECONOMY	86
4.5. QALY CALCULATION	87
4.5.1. <i>Calculating QALY based on the current vaccination strategy</i>	87
4.5.2. <i>Calculating QALY based on the recommended vaccination strategy</i>	89
4.6. ICER CALCULATION	90
5. CONCLUSIONS, RECOMMENDATIONS	93
6. MAIN FINDINGS OF THE DISSERTATION AND THE NEW AND NOVEL RESULTS THEREOF	98
SUMMARY	101
LITERATURE	103
ACKNOWLEDGEMENTS.....	107
LIST OF OWN PUBLICATIONS.....	109
LIST OF FIGURES	110
LIST OF TABLES	112
ANNEX	113
REFERENCES.....	119
DECLARATION.....	120

Introduction

The influenza disease

Influenza is a worldwide epidemic viral disease that poses a serious threat to health. Epidemics are caused by the different influenza virus strains.

Seasonal influenza is a seasonal disease lasting from October to March on the Northern Hemisphere, and from April to September on the Southern Hemisphere. Since it is spread by droplet infection and direct contact, or through the transmission of contaminated objects, the virulence of the virus is extremely high.

Major symptoms include headache, sudden high fever, cough, muscle, and joint pain. Infected patients are bedbound, and healing usually takes over two weeks. Serious cases might end in viral pneumonia, infection of other organs (nervous system), or bacterial superinfection, which sometimes might be fatal.

A common mistake about influenza is to underestimate it; when a patient thinks and communicates that they are infected by some rhinitis viruses that cause many upper respiratory infections that are easy to get through, and that they do not really need to get protected against. This is a hazardous and faulty strategy about the influenza virus.

Influenza is a hazardous viral disease with severe adverse effects (MayoClinic, 2019)

Influenza epidemics and types

Due to its extremely effective infection strategy and its subsequently rapid spread, the influenza virus strains annually infect several ten million people on a global scale (Bernstein et al., 2020)

According to above publication in Lancet, seasonal influenza infections were to blame for 291,000-646,000 deaths between 1999 and 2015 (the annual average mortality was 409,000). The mortality rate per 100,000 people infected by influenza ranges from 4.0 to 8.8. During seasonal influenza epidemics in Europe, the number of fatal infections is 15,000 – 70,000.

In view of the above data, the WHO (World Health Organization) is prepared to treat influenza infections in the long term and has elaborated its global influenza strategy, entitled “*Global Influenza Strategy 2019-2030*” (WHO, 2019a).

The paper highlights the following major goals:

- reduce the load caused by seasonal influenza
- minimize zoonotic influenza infections

- ease the effects of pandemic influenza.

Influenza virus

The hazards of a virus depend on the severity of the disease it causes as well as on the frequency of the infection. From this respect, the influenza virus is considered hazardous since it can cause disease of varying severity each year due to its different serotypes.

Mode of infection

The high pathogenicity of the virus is due to its **mode of infection**. The influenza virus is spread by **droplet infection** that is highly effective and fast. However, high virulence and fast spread merely would not make the influenza virus so dangerous. Apart from being able to spread fast and effectively, the influenza virus is also characterized by a special feature that increases its hazard, namely its variability.

Variability

One of the most typical characteristics of the influenza virus is its high degree of **variability**, which is primarily due to its **biological structure**. As for the influenza virus, apart from tiny changes (mutations) in its genome, larger sections can be replaced in one step thus forming a completely new type of virus in one extremely fast step. The structural basis for this rapid, one-step virus change is the segmentation of the virus genome. The virus typically contains eight independent pieces of segmented RNA. Each segment codes for any of the 10 viral protein molecules. Due to the independence of the segments, it is possible that if two different types of viruses simultaneously infect a given cell, complete nucleic acid segments are replaced while the newly synthesized “virus components” are “assembled” thus resulting in viruses with fundamentally new biological structures and properties. This gives the main biological basis for the extreme variability of the influenza virus. This mechanism causes a high degree of variability and therefore a vaccine developed against a particular serotype virus can become ineffective very quickly (usually within a year) due to newly emerging virus variations and this is also the reason why vaccine producing companies have to develop an influenza vaccine with different composition every year (Tanyi, 1998).

To sum it up, the influenza virus is characterized by several properties that can lead to extremely dangerous epidemics with severe symptoms that must be controlled.

As a conclusion: the most effective prevention against influenza virus infection currently is vaccination (*Figure 1*).

Fortunately, such vaccines are now widely available and can be used effectively to prevent infection.

The paramount importance of vaccination is supported and justified by the theoretical consideration arising from the data listed above.

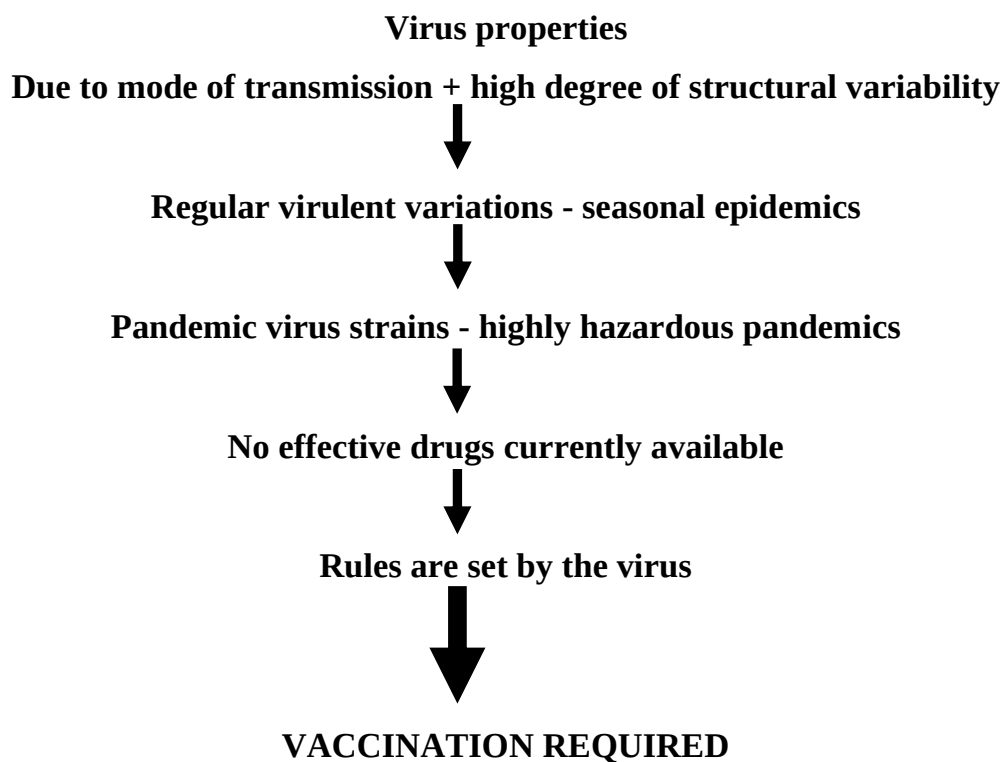


**Figure 1.: Influenza virus properties, challenges
and addressing them**

Source: OWN EDIT VAJO, 2020

1. Subject matter and objectives

1.1. Hypothesis

My hypothesis is that greater emphasis should be placed on vaccinating the active (19-60 years of age), as well as the children and adolescent (3-18 years of age) population groups, while maintaining the supply of free vaccines to the age group of 60 and older that current Hungarian regulations define as one of the most vulnerable groups. I suppose that the same level of vaccination coverage amongst children and adolescents and active population groups would lead to much greater economic benefits compared to the current vaccination strategy surplus.

The primary aim of my dissertation is to present the economic impact of the actual vaccination strategy which is focusing on the vaccination of 60 and older population group. After identifying the outcomes of the primary aim the next goal of my dissertation is to present the economic impact in case of a new suggested vaccination strategy, assuming that the same vaccination coverage would be applied in population groups of active (19-60 years of age) and children and adolescents (3-18 years of age) as in the elderly age group. I intend to justify this hypothesis with figures and facts.

My study is focused on seasonal influenza and its impacts on the national (domestic) healthcare and social security system; I do not aim at exploring the effects and economic correlations of pandemics (including the current Covid-19 pandemic). Thus, I will not quantify the economic consequences of the collapse of tourism and aviation, the closure of factories and shops, the lack of construction investments, or the unemployment resulting from the pandemic. These impacts are so severe and complex that they affect all areas and actors of the economy. In such a situation, general interest in tourism, hospitality, event organization or transport services decreases due to people's cautiousness and the lockdowns or limitation of movements. These steps might lead to further factory closures, service outages, and in some cases supply difficulties. These economic problems already pose real challenges to industries other than tourism and hospitality reaching far beyond the direct economic impacts. Prolonged uncertainty and deteriorating business confidence will reduce consumer spending and investments, which could lead to a further and wider-scale decline in economic performance. Production disruptions and weak economic activity threaten the stability of

corporate management, productivity growth is stopped, and lost revenues can push indebted companies to insolvency. A global economic crisis is unfolding. (Behraves, 2020)

I will describe the different aspects of the impact of seasonal influenza on the national economy (employees, employers, social security expenditure aspects, variables within individuals and social groups, variables within age groups) based on international and national data, my own and previously published research results, and publications.

With the help of the conclusions drawn from the international and national comparison of influenza vaccination data, I intend to prove that the only available effective “antidote” to this infectious disease and the negative healthcare, economic and market impacts it generates is regular and increasing degree of vaccination.

The currently available most effective method to fight influenza is prevention, that is, **annual vaccination**.

There are several types of influenza vaccines currently in use that are grouped as follows:

1. Live (reproducible), weakened (attenuated) virus vaccines,
2. Inactivated virus or virus component vaccines (CDC, 2020b).

My dissertation processes data available regarding the nationally produced, inactivated, whole virion, adjuvanted (the adjuvant has potency-enhancing properties) 3Fluart seasonal influenza vaccine (Fluart, 2019).

In addition to simple individual, communal and general social health improving aspects, increasing vaccination assumes other economically important correlations, reducing disadvantages and expanding available benefits.

The following parts of my dissertation intend to present an analysis of these correlations.

2. Literature review

2.1. Health economics analysis and types

Health economics analyses support the optimal use of any given budget. Consequently, health economics analyses can be prepared from the aspects of

- the financers (service users), or
- the service buyers (e.g. hospital), or
- the society.

The results calculated from different points of view should be presented separately.

The analysis must be prepared from the point of view of the financer if the analysis is aimed at influencing the public funding of the studied curative-preventive procedure.

Analyses made from the point of view of service buyers should indicate the results calculated from the social point separately. This is because achieving an optimal allocation of resources at society level is a more desirable “superior” goal. It means that all the health benefits and costs associated with the said therapies, which emerge in society as a whole, i.e. inside and outside healthcare, need to be taken into account.

The cost-effectiveness of any healthcare technology can only be studied through a full-scale economic analysis. A necessary prerequisite is on the one hand that the assessment compares at least two healthcare technologies and on the other hand that it examines changes in both costs and health benefits.

Health economics analyses are basically differentiated according to the way health improvement is measured. The following chapters will describe three internationally accepted basic types of health economics analyses.

2.1.1. Cost-minimization analysis

The cost-minimization analysis is the right choice provided that the clinical results of the compared processes (e.g. number of saved years or improvement in life quality) are equal in controlled or routine curative activities based on the available and reliable scientific results (e.g. randomized clinical trials with an appropriate number of subjects, or systematic literature reviews). In other words, the benefits (health improvement) and costs (e.g. adverse effects)

they generate are corresponding. In such case the analysis should focus on comparing the costs.

Cost minimization analysis is required in case the effectiveness of the comparative interventions is equal or they result in equivalent health gains under routine circumstances (clinical efficiency).

Cost minimization analysis is one of the fastest and cheapest studies to perform, yet this method **can be used only in an extremely small percentage of cases**. This analysis can only be performed in case the health gains associated with the healthcare technologies to be compared are identical and this condition is rarely met.

While all other full-scale economic analysis methods give high importance to the unit which measures health gains, cost minimization analysis **does not give any relevance to the unit that measures changes in health status**. Therefore, health improvement can be measured by a natural unit, that is *Quality-adjusted Life Year (QALY)*, or even in Forint (the Hungarian national currency); the most important aspect is equality. Decision-makers can easily interpret the result of the cost minimization analysis since they have to choose the less expensive process out of the alternative possibilities after they have compared the expenses. It is important to stress that **inexpensiveness alone is not a sufficient reason to apply a given healthcare technology**. A common mistake in economic analyses or analysis-based decision-making is to compare the costs only but to not provide sufficient evidence of equal health improvement. This is an incorrect method as in most cases the “no-intervention” alternative is the less expensive. Accordingly, **cost minimization analyses would constantly suggest downsizing healthcare services and products and terminating their support**.

The cost minimization analysis can be applied with one extended condition. If a new healthcare technology produces demonstrably higher healthcare gains than the comparator procedure, but at the same time the costs associated with its application are lower, it is sufficient for the cost minimization analysis to justify the cost-effectiveness of the new technology. However, this is only a coincidence for innovative technologies, since if a new healthcare technology has proven health benefit surplus, manufacturers would rarely make the mistake to offer their product cheaper than the widely used technology that is the basis for the comparison. This pricing decision would inevitably result in a loss of profit for them plus a reducing rate of return on research and development.

Cost minimization analyses are **most commonly applied for decision-making related to the funding of generic drugs**. In case of undoubted bioequivalence study results of drugs with identical active substance, therapeutic equivalence - i.e. the equality of health benefits – is assumed, thus the cheaper product is considered cost-effective.

Outpatient surgery and conventional surgery can also be compared by cost-minimization analysis. However, the cost-efficiency of outpatient surgery can only be assessed with this method if evidence proves that the cost-savings from reduced nosocomial infections due to shorter hospital stays outweigh the extra costs caused by complications observed only later due to the shorter post-operative monitoring period. **Outpatient surgery is a good example of how the methodology of cost-minimization analysis seems simple only at first sight** (Kaló, 2010).

2.1.2. Cost-effectiveness analysis

Cost-effectiveness analysis measures clinical efficiency in so-called natural units (e.g. physiological parameters, adverse effects, number of asymptomatic days, number of lives saved, number of years saved, patient satisfaction indices, etc.). Cost-effectiveness analyses include studies that measure health improvement by means of patient-specific or generic (general) quality of life questionnaires that are based on scores independent of utility values and measurements of the occurrence of clinically minimal changes. There are a number of life quality questionnaires that are perfectly suitable for cost-effectiveness analyses, for example, the SF-36 questionnaire, which also has a validated Hungarian version (Fábián, 2014).

If the efficacy of the interventions to be compared is different or produces different health benefits under routine circumstances, a cost-effectiveness analysis is required.

Using cost-effectiveness analysis, we compare the extra cost generated by a new healthcare technology (D-cost) to the extra health benefits generated by the same technology (D-effectiveness). The analysis measures costs and savings in monetary units, and health benefits in natural biological or medical units (e.g. mmol / l cholesterol reduction, Hgmm blood pressure reduction, life years saved, number of healthy days). The evaluation is based on a quotient, the incremental cost-effectiveness ratio (ICER), where the increase in costs and effectiveness is compared to a benchmark, such as the cost-effectiveness rate of an already funded healthcare technology. $ICER = D\text{-cost} / D\text{-effectiveness}$.

The cost-effectiveness indicator shows the extra costs required to achieve one unit of efficiency change; that is, the specific costs of achieving one effect unit. Depending on the point of view of the analysis, the costs can involve healthcare or total social expenditure. The perspective of financiers (*in Hungary the NEAK - National Health Insurance Fund Management*) is most commonly applied to study decisions on introducing new healthcare technologies.

Basically, there are two limits to cost-effectiveness analyses, which define their application scope as well. Since cost-effectiveness analysis can only measure changes in health benefits in a specific dimension, it does not allow for the comparison of technologies that generate changes in health status in different dimensions (hip replacement vs. lung transplantation vs. new antihypertensive). Thus, this method of analysis can only compare the cost-effectiveness of healthcare technologies that result in a change in health status in identical medical or biological parameters. These can be ranked depending on which procedure can generate one unit of health gain at lower costs. Consequently, the application of cost-effectiveness analyses is limited for preparing decisions on acceptance policy, since they are not suitable, for example, for defining the full scope of publicly funded benefits or for redefining the basic plan for the insured. However, the method may be appropriate for preparing individual acceptance decisions that, for example, assess funds for a new antihypertensive taking into account the cost-effectiveness analyses of previous antihypertensive drugs.

Another limitation of cost-effectiveness analysis is that it can measure changes in health status in only one dimension; even if a given healthcare procedure causes obvious changes in health status in other dimensions. For example, chemotherapeutic drugs that prolong survival or progression-free survival also have serious adverse effects, yet these cannot be included in a single natural health dimension. However, it is also possible to include adverse events in the costs (i.e. in the numerator) and not in the health status changes (i.e. in the denominator of the cost-effectiveness rate). The effect of nausea associated with chemotherapeutic treatments can be considered, for example, by including the cost of antiemetic drugs administered for the symptomatic treatment of the adverse effect. Other effects are thus indicated in the change in costs, i.e. the numerator: positive effects are accompanied by a cost-decreasing sign and negative effects are indicated by a cost-increasing sign. Although this method can extend the scope of cost-effectiveness analyses, the outcome will be results that are more difficult to interpret in case of several common adverse effects and less reliable conclusions.

As for cost-effectiveness analyses, it is best to measure health gains at hard endpoints (e.g., years of life gained, number of lethal heart attacks, etc.). In the case of an intermediate endpoint (e.g. Hgmm decreased blood pressure or mmol/l decreased cholesterol), the model will only provide a reliable result if the intermediate endpoint has been validated by means of a reliable test for the given drugs class, i.e. the improvement at the intermediate endpoint will certainly increase the expected survival and/or patients' overall life quality. Due to the detailed limitations, standard cost-effectiveness analysis is neglected as a method of assessment used in decision-making. At the same time, the concept of cost-effectiveness analysis is increasingly applied in a broader sense, as a synonym for comprehensive economic analysis. (MedicalOnline, 2010c)

2.1.3. Cost-benefit analysis

The cost-benefit analysis (CBA) is a type of comprehensive economic analysis that can be applied to any investment decision.

When used for funding decisions in healthcare technologies or programs, it compares the net cost of interventions with the change in health status and other consequences resulting from the intervention.

For this type of full-scale economic analysis, both costs and health gains should be expressed in monetary terms. The evaluation is based on the difference between the yield and cost of the processes to be compared: $(B1 - C1) - (B2 - C2) > 0$, where B is the benefit from the alternatives and C is the cost. The formula helps compare the net benefits from the alternatives, which eases the choice between two procedures with positive net benefits.

If the effect of the technology or program to be assessed extends over several years, a present value calculation should be used to aggregate net costs and benefits. Costs include healthcare costs and, in the case of social analyzes, the direct and indirect costs outside the healthcare system. In addition to health gains, benefits include avoided expenses. The difficulty of the analysis lies in how express the health gains generated by healthcare technologies in monetary terms.

The main advantage to cost-benefit analysis is that enables the comparison of any program or intervention on a purely financial basis, regardless of their nature or purpose. From an economic perspective, the investment with the highest net return should be selected. Another

advantage is that this method not only enables the comparison of two or more options, but also makes it possible to decide if a given investment is worth realizing, i.e. whether it has a positive net return. Thus, the cost-benefit analysis may be relevant to all social investment related decisions. The practical application of cost-benefit analyzes can make allocation decisions for “publicly available” resources more impartial and well-founded. It can also help with funding policy decisions related to new technologies and the development of social care packages.

Cost-benefit analyses express the value of health improvement in money. The most common method for this is contingency assessment, which examines how much society would be willing to pay for a certain degree of health improvement associated with a particular healthcare service.

Measuring the extent of health improvement in monetary terms may seem unrealistic at first. Nevertheless, several methods have already emerged to quantify the value of life years. These include:

a) The human capital approaches

- net current value of future earnings over the years of life gained
- net current value of products consumed during the years of life gained
- gross domestic product (GDP)

b) Past decisions of the public sector

- court rulings in forensic assessment of health damage (e.g. legal proceedings due to medical malpractice, damages paid due to adverse effects)
- general court rulings on damages (e.g. compensation for unjustified imprisonment)
- insurance decisions (e.g. costs of general insurance payable for a specific risk)
- health insurance financing decisions (e.g. one year costs of persistent disease)

c) Implicit preferences

- how much we are willing to pay to reduce certain risks (e.g. safety helmet, airbag)
- related to the market assessment of a certain product (e.g. to what extent air pollution can reduce the value of a given plot)

d) Hedonistic pricing

- wages in high-risk workplaces (amount of hazard allowance compared to normal risk workplaces)

e) Contingency assessment

- willingness to pay – assessment by means of questionnaire of how much people are willing to pay to avoid certain health damage or to reduce the risk of the disease
- willingness to accept – how much people are willing to accept in exchange for a certain extent of health damage or for increased risk of the disease. (MedicalOnline, 2010a)

Certain international guidelines (Lisa A. Robinson, 2019) accept the use of cost-benefit analysis in making decisions on the use of public funds as a possible type of economic analysis, while other guidelines do not recommend its application in healthcare. Despite the increasing use of cost-benefit analyses within the healthcare sector, its methodology is not yet fully developed, and very little experience is available in Hungary.

2.1.4. Cost-utility analysis

Cost-utility analyses measure health gains in life years weighed by health status and expressed in terms of utility. Cost-utility analyses are recommended to be performed to supplement cost-effectiveness analyses (in parallel with them) provided that the required data are available or can be generated. For example, a life expectancy calculation can be supplemented with a QALY calculation (provided changes in utility values are also known from basic research or literature), and thus the cost / QALY ratio can also be defined.

When applying cost-utility analysis, health improvement is measured in QALY units. QALY is a unit of measure that combines health improvement with regard to life expectancy and quality of life (based on utility).

Quality of life adjustments can be obtained primarily through the use of utility-based health questionnaires in which individual values were defined using surveys of the general population. Such internationally accepted questionnaire is e.g. EQ-5D (EuroQol-5D) (Balestroni and Bertolotti, 2012); (iHealth, 2020).

If healthcare interventions relate to diseases for which the dimensions of quality-of-life questionnaires (e.g., pain, physical function) do not adequately monitor changes in the patients' health status, direct utility measurement methods (scale method, forced selection of time length, standard game) can be used to assess patient utility values.

There might be several reasons to introduce Quality-adjusted Life Year (QALY) calculations into the analysis as supplementary information:

- * It considers quality of life in addition to mere prolongation of life or avoided death, thus reflects both dimensions that are important to individuals.
- * The cost-effectiveness of supplies with different purposes (e.g. related to other diseases and patient groups) is comparable, which helps optimize the allocation of resources within healthcare.
- * A cost-threshold can be established that indicates how much society is able and willing to spend on a quality life year that can be gained through a given curative-preventive procedure in addition to the country's economic development. This cost threshold facilitates explicit decision-making (MedicalOnline, 2010b).

Despite the scarcity of experience with cost-utility analyses in Hungary, and due to the challenges, it raises, I consider this analysis type closest to my own methodology, therefore I use some methods from this type of analyses in my dissertation to present the use and economic effects of nationally produced influenza vaccines.

2.2. Related analyses studies in foreign literature

Some previous attempts are found in the foreign literature to set up economic models to calculate the costs and benefits of the seasonal influenza vaccination.

2.2.1. A UK data-based study

The **UK data-based study** has outlined the findings of an economic model of flu vaccination cost-benefit analysis. From the two major approaches (so-called static and dynamic) the authors have used the static, or conservative one to model the cost savings from flu vaccination in the UK. It is stated by the authors, that there are limitations in any, and so in their attempt to measure the cost savings from flu vaccination (I realized the same during my attempts to get as much close as possible to the correctness with my calculations). The

uncertainty of the vaccination efficacy amongst patients mostly influences the correctness of the calculation. I see a difference in my approach in this respect, as I have calculated the effectiveness of the flu vaccination based on statistical data, not on clinical ones. It turned out for the authors, as well as for me that any output calculated with any kind of different economic method should be handled with care regarding the flu vaccination economic benefits.

In my study I intend to demonstrate that not only the so-called endangered parts of the population (elderly of 65 and older, people with chronic diseases) but the children and adolescents, as well the “active” population groups’ vaccination should be given greater consideration. The referred article outlines the same conclusions – necessity to increase the vaccination coverage among the young generation (0-15 years of age), to combine the increase of efficacy of vaccines with keeping up the coverage amongst elderly, and to put greater emphasis on vaccination of the active population parts with encouraging the employers in offering vaccinations to their workforce.

The referred study was addressing the issues of related vaccine administration costs, as well (Hochlaf, 2018).

In my study approach during examination of the economic impacts of the flu vaccination I did not calculate with the vaccine administration costs, due to the following reasons.

According to the seasonal nature of the influenza vaccine product it takes several months to produce the necessary “new” vaccines for the forthcoming season. Thus, it is indifferent from the manufacturing perspective how severe the flu season will be after finishing the manufacturing process.

As far as my study calculations are based on Hungarian statistical data it is worth to emphasize the fact that the Hungarian Government and the national flu vaccine manufacturer have a long-term agreement on doses and costs of the supply of seasonal influenza vaccine products for the Hungarian internal market. These values are independent from the severity and the length of the actual influenza season; therefore, they can be considered as fix costs. In other words, the changes in the vaccination coverage does not affect these cost items.

On the other hand, the costs of the vaccine administration and storage also do not affect the overall vaccination costs, because the healthcare system and the supportive facilities in Hungary are continuously in place functioning. The human personnel of the system are

available constantly, therefore the vaccines' administration activity does not generate any extra costs within the system.

Based on the above in my study I did not calculate with vaccination costs, as varying costs, I have only calculated the economic effects of the influenza vaccination.

2.2.2. A Netherlands data-based study

A Netherlands data-based study's aim was to determine the costs associated with influenza and the cost effectiveness of influenza vaccination in The Netherlands. The evaluation of the above was performed from the healthcare perspective. The modelling framework for the economic evaluation linked epidemiological aspects of influenza to vaccination coverage ratio and resources of the healthcare system used.

In this study during their economic evaluation the authors combined both the cost-of-illness assessment and cost-effectiveness analysis associated to two different scenarios – 1995/96 season when flu vaccination have covered only elderly (65 years and older) with increased risk of infection due to their chronic illnesses status and a season after the extension of vaccination program for all individuals 65 years and older (season of 1997/98). In this latter case, the approach became similar to the Hungarian practice for decades – the general practitioners have received vaccines directly, avoiding the pharmacy costs. In addition to that, in Hungary the eligible parts of the population receive influenza vaccines and vaccination free of charge.

In the study, both epidemiological aspects, as well as economic aspects of flu vaccination were considered.

The statistical data referring to the Dutch population in terms of influenza, as a direct illness, as well as related illnesses, like pneumonia; plus hospitalization costs, general practitioners costs, excess hospitalization costs; different categorization of elderly due to their health status (High Risk, Low Risk); the vaccine coverage ratio amongst elderly (65 years and older); the flu vaccine efficacy estimation at 56%; incidence, mortality, years of life lost were used to undertake a cost-effectiveness analysis of the influenza vaccination.

As a result, the cost-effectiveness ratio (CER) is more favorable in case of vaccination of elderly population with high risk, while CER is less favorable in low-risk group of elderly (Postma et al., 1999).

2.3. Summary of my article published in *Economica*

“Effect of influenza vaccination on certain other health factors” –Economica XII, 1-2 (Vajó, 2021)

My article, published in May 2021, was aimed at demonstrating the correlation between influenza vaccination, certain healthcare aspects and life quality. To this end, I generated regional comparisons and used databases from independent, objective sources that could be readily justified. The data used in the publication were taken from the Health Statistics Yearbook published by the Central Statistics Office (CSO) in 2018.

The regional comparisons were based on national and regional data. Apart from its capital, Hungary has 19 counties and seven regions. Whenever county-level data were available, I made county-level comparisons in my study. However, if county-level data were not available, I opted for regional-level relationship analysis. My analysis separated Budapest from the Central Hungarian region since the capital acts as a focus point in terms of healthcare and epidemiology

I examined the effect of influenza vaccination in three aspects.

I. The correlation of influenza vaccine and pulmonary medicine

This section of my study indirectly justifies the relationship between influenza and pneumonia. The methodology was based on comparing the influenza vaccination of the population and the pulmonary medicine data available in healthcare statistics broken down by region.

I performed correlation calculations for the connection between influenza vaccination rates for each county and the typical indicators of pulmonary medicine. I found that the higher the vaccination rate in a county, the lower the incidence per 100 inhabitants in outpatient care, the number of interventions per 100 inhabitants, and the average duration of hospitalization. Although the degree of correlation did not show a strong relationship, it was not the extent but the direction that really mattered.

CSO data on mortality are also available. Such data shed light on the total mortality on an annual basis and as per county, as well as morbidity due to the major causes of death. In my study, I focused on mortality due to the diseases of the respiratory system. I divided the number of deaths due to respiratory disease in a given county by the total county mortality

data thus I got the rate of respiratory causes of death within total morbidity. I studied this mortality rate in relation to the frequency of influenza vaccination. The result was surprising: examining the causes of death showed a negative correlation between the rate of respiratory deaths and the rate of vaccination withing total mortality. That is, the higher the vaccination rate, the lower the number of respiratory deaths relative to all deaths.

Overall, I could justify that the beneficial effects of influenza vaccine not only significantly reduce the likelihood (and severity) of influenza and influenza-like illnesses, but also the fact that influenza vaccination has a demonstrable impact on the frequency and severity of respiratory disease in general, and finally on mortality.

II. The correlation of influenza vaccine and infectious disease

I examined the relationship between influenza vaccination and other infectious diseases. I used the same methodology as for studying pulmonary medicine and respiratory diseases. I studied the correlation between health statistics data and vaccination rate.

I found that the higher the vaccination rate in a region, the lower the number of infectious diseases per thousand inhabitants. The correlation was evident, though its medical-professional background could not be revealed.

III. Influenza vaccine and life-expectancy

I wondered if there was any correlation between vaccination and life expectancy. Life expectancy is general data used in statistics to determine the health status of a given population. The correlation between influenza vaccine and life expectancy cannot obviously be established within a couple of years; the impact of immunization on life expectancy, if any, cannot be influenced in the short term. However, it is worth looking at the possible relationship in the long run. I aggregated the vaccination data for a decade as ten years is long enough to establish some correlation. I presented vaccination data for the years 2009-2018.

I calculated the correlation between the ten-year average vaccination rate as per region and the average life-expectancy at birth, at age 40 and at age 60, broken down by males and females.

The correlation coefficients revealed a positive relationship. In regions where influenza vaccination rate as for the total population was high, life-expectancy at birth, at age 40 as well

as at age 60 was surprisingly longer. Trends show a strengthening correlation with ageing for both sexes, though strengthening is consistently lower for females than for males.

There are several circumstances that can be associated with longevity. As an outcome of my research, it was possible to justify by means of mathematical methods that influenza vaccine has an impact even on life-expectancy. Consequently, apart from professional arguments for vaccination, there is yet another very important and practical aspect of immunization, which is increased life-expectancy.

2.4. Other publications with my participation

My contribution to the articles of “*Licensing the first reduced, 6 µg dose whole virion, aluminum adjuvanted seasonal influenza vaccine – A randomized-controlled multicenter trial VACCINE 37*” (Vajo et al., 2019) and “*Dose sparing and lack of dose response relationship with an influenza vaccine in adult and elderly patients - a randomized, double-blind clinical trial, BRITISH JOURNAL OF CLINICAL PHARMACOLOGY 83*” (Vajo et al., 2017b) included the statistical analyses preparation and controlling, while to the article “*Az új, csökkentett dózisú, hazai gyártású influenzavakcina (FluArt) forgalomba hozatalát követő első szezonjának biztonságossági vizsgálata [Safety data of the new, reduced-dose influenza vaccine FluArt after its first season on the market] ORVOSI HETILAP 158*” (Vajo et al., 2017a) included preparation of the related charts and graphs based on the study statistics’ analyses.

2.5. Characteristics of the patient group involved in the analysis and the curative-preventive procedure; detailed description of the need for healthcare services

2.5.1. Description of the demographic and socio-economic situation of the patient group exposed to infection with influenza A/H1N1, A/H3N2 and B viruses

Typical risk age-groups: The risk groups at high risk in order to reduce the severity of illnesses caused by the influenza virus and the number of deaths are as follows:

A) People 60 and older regardless of their health status; only this group is currently entitled to free vaccination (according to the “Methodological letter issued by the National Public Health Center about vaccinations in 2019”) (NNK, 2019c).

B) People over six months of age who are at risk of serious illness, especially the following:

- patients with chronic respiratory disease, asthmatic patients;
- patients with impaired respiratory function due to severe obesity or neuromuscular disease;
- patients with cardiovascular disease (excluding treated hypertension);
- patients with congenital or acquired immunodeficiency (including HIV-positive patients, cancer patients);
- patients with chronic liver and kidney disease;
- patients with metabolic diseases, e.g. diabetes;
- persons who have been cared for a long time in institutions providing nursing, care, rehabilitation, temporary accommodation, residential homes or healthcare institutions;
- pregnant women;
- women who plan to have children during the seasonal flu season;
- children and adolescents receiving long-term salicylate treatment (due to the risk of Reye's syndrome).

C) Persons posing risk to the above risk groups through transmission:

- healthcare professionals, in particular those in transplantation, oncology, hematology, dialysis, obstetrics and gynecology, intensive care for adults and children, and those who come into direct contact with patients in chronic internal medicine departments,
- healthcare workers (including nurses) caring for pregnant women, newborn babies and infants,
- employees of social institutions.

D) Due to the risk of mixing zoonotic and human influenza viruses and the possibility of gene exchange, those working in livestock farms where pigs, poultry and horses are kept and transported. In addition, those working in poultry processors, slaughterhouses and all those

who may be involved in the destruction of animals infected or suspected of being infected with zoonotic influenza virus.

Annual influenza vaccination is recommended for all high-risk groups through occupational healthcare services. Unfortunately, only truly responsible management approves annual vaccination, although this method could significantly reduce the time burden of vaccinating the active population which is not entitled to free vaccination (*making out a prescription, buying the vaccine, administering the vaccine – in normal cases this requires two doctor-patient meetings and an additional pharmacist-patient meeting, which only a few people venture to undertake mainly due to lack of time*).

Typical social and economic situation of the risk group: People belonging to the highest risk groups from all walks of life.

Incidence: In epidemiology, an incidence is a measure of the frequency of new cases (e.g., illness) that occur in a given population over a given period of time. Incidence data for the past 7 influenza seasons can be found under “**2.6. Describing trends over the past 5 to 10 years in Hungary**” (*Table 1, page 34*).

Prevalence: In epidemiology, prevalence means the frequency of occurrence (e.g. illness) of a population in a given period or at a given time. Prevalence calculated from data from the past 7 influenza seasons is 538 (number of confirmed influenza cases / 7 seasons). For more information, see “**2.6. Describing trends over the past 5 to 10 years in Hungary**” (*Table 1, page 34*).

Gender differences in incidence and/or prevalence: No data are available.

Number of patients to be treated: On average a minimum of 538 persons/influenza season (prevalence calculated from data from the past seven seasons). Several hundreds of thousands of people visit their doctor with influenza-like illness per year in Hungary. Given that the majority of patients do not consult their physician when affected by an influenza-like illness, the number of patients actually that would require treatment is much higher than the number of known cases.

No data are available for currently treated (cared for) patients and therapy-resistant patients.

Rate of patients with mild, moderate, and severe symptoms: Complications occur in the high-risk, usually multi-morbid, patient groups. As influenza vaccine is highly recommended

for these groups and is available free of charge in Hungary, the number of severe patients is low. No published data are available for mild, moderate and severe patients.

2.5.2. *The course of the disease*

The body gives an immune reaction to the virus infection. The immune system recognizes the surface proteins of the virus and produces antibodies against them that can react with that protein. By binding to the surface proteins, the antibodies inhibit the virus from infecting new cells, thereby slowing the development of the disease. In the case of influenza, the production of a sufficient amount of antibody takes approximately 7 days after infection.

Symptoms improve usually within 3-4 days. If there are no complications, **recovery is expected within a week**, but weakness and malaise may persist especially in old age or in the case of other chronic disease.

Influenza is only an unpleasant disease for most people, but it causes serious conditions for some of them.

More serious complications of influenza include bronchitis and pneumonia due to bacterial superinfection, and less commonly encephalitis and sepsis. People with the above complications often require hospitalization, as they can even develop a life-threatening condition, especially among the young and the old as well as in patients with deteriorating health conditions.

The most common complications and their characteristics are summarized below:

- Secondary bacterial pneumonia: it is the leading cause of death associated with seasonal influenza. The influenza virus damages the respiratory mucosa, opening the door to bacteria. In a body weakened by viral infection, the bacteria cause severe pneumonia. At particular risk are infants, the elderly (80% of deaths over the age of 60!), patients with chronic lung, heart, liver or kidney disease, diabetics, and patients with immune deficiency. Pneumonia usually occurs 1 to 3 days after the fever has subsided, with rising fever, cough, heavy breathing, and chest pain.
- Primary viral pneumonia: it is a rare complication, but it is characterized by very high mortality. Immune-impaired patients are at increased risk, but in some cases, it affects young adults who do not belong to any high-risk group. It occurs in the acute phase of

influenza (days 2-5) with increased dyspnea and bloody sputum. It is barely recognizable by physical examination; the chest x-ray shows characteristic changes. Its course is usually severe and requires intensive ward care. Antibiotics are ineffective.

- Otitis media, sinusitis: it is a relatively common complication in infancy. It can be treated well with antibiotics.
- Reye-syndrome: it is a very rare but highly fatal complication that occurs almost exclusively in childhood (under 16 years of age). It is characterized by confusion suggestive of central nervous system involvement and signs of severe hepatic impairment. It mainly occurs in children who receive salicylic drugs (e.g. aspirin, kalmopyrin) during influenza infection. Such drugs should not be administered in childhood influenza.

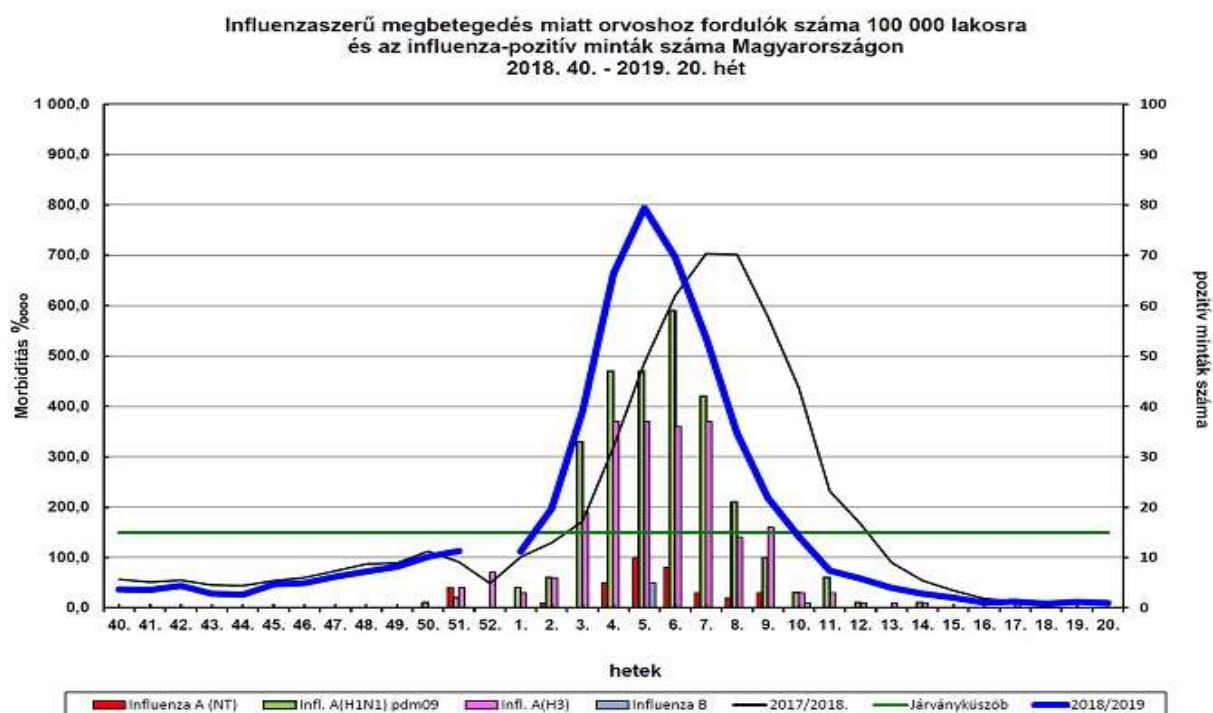
Mortality in seasonal epidemics is 1-4 / 1,000 patients, but this figure is rather uncertain: the number of deaths is close to real facts, but the total number of influenza cases is based on estimates only.

In order to assess the costs of hospital care, I need data on how many i.e., what proportion of all patients ultimately require hospital care due to the severity or complications of their illness. Unfortunately, there are no reliable data on how many of the patients are hospitalized; therefore, I can only make estimations on the basis of international comparison.

2.6. Describing trends over the Past 5 to 10 Years in Hungary

The Epidemiology and Infection Control Department of the National Public Health Center runs an influenza surveillance system in each influenza season, between the 40th week of the given year and the 20th week of the following year. The program is published on the agency's website.

During the influenza season of 2018/2019, the Respiratory Virus Department of the National Public Health Center processed test materials from 1,306 patients showing typical influenza symptoms and confirmed 545 cases of influenza A infection [283 influenza A (H1N1) pdm09, 226 influenza A (H3N2), 36 influenza A (NT)] and 6 cases of influenza B infection (a total of 551 confirmed cases caused by the influenza virus). *Figure 2* shows the morbidity data for the influenza season of 2018/2019.

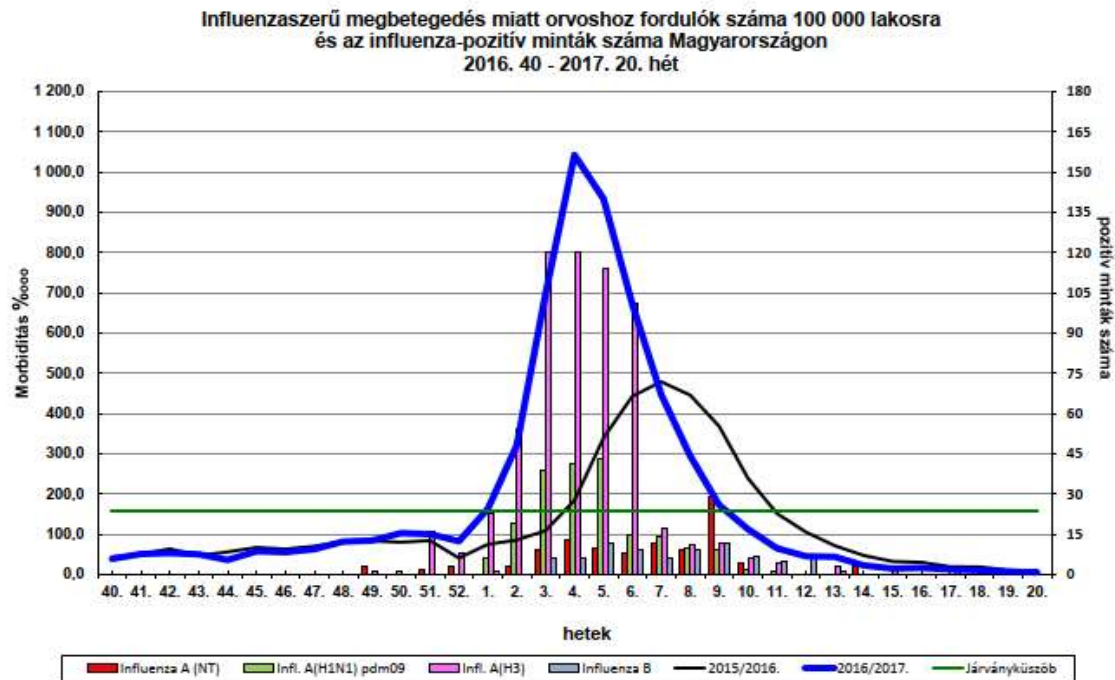


Forrás: Nemzeti Népegészségügyi Központ

Figure 2.: Number of patients out of 100,000 people visiting medical doctors with influenza-like illnesses and number of influenza-positive samples in Hungary between week 40 of 2018 and week 20 of 2019

Source: (NNK, 2019b)

During the influenza season of 2016/2017, the National Influenza Laboratory processed test materials from 2,288 patients and confirmed 921 cases of influenza A infection [613 A(H3), 200 A(H1pdm09), 108 A(NT)] and 81 cases of influenza B infection (a total of 1,002 confirmed cases caused by the influenza virus). *Figure 3* shows the morbidity data for the influenza season of 2016/2017.

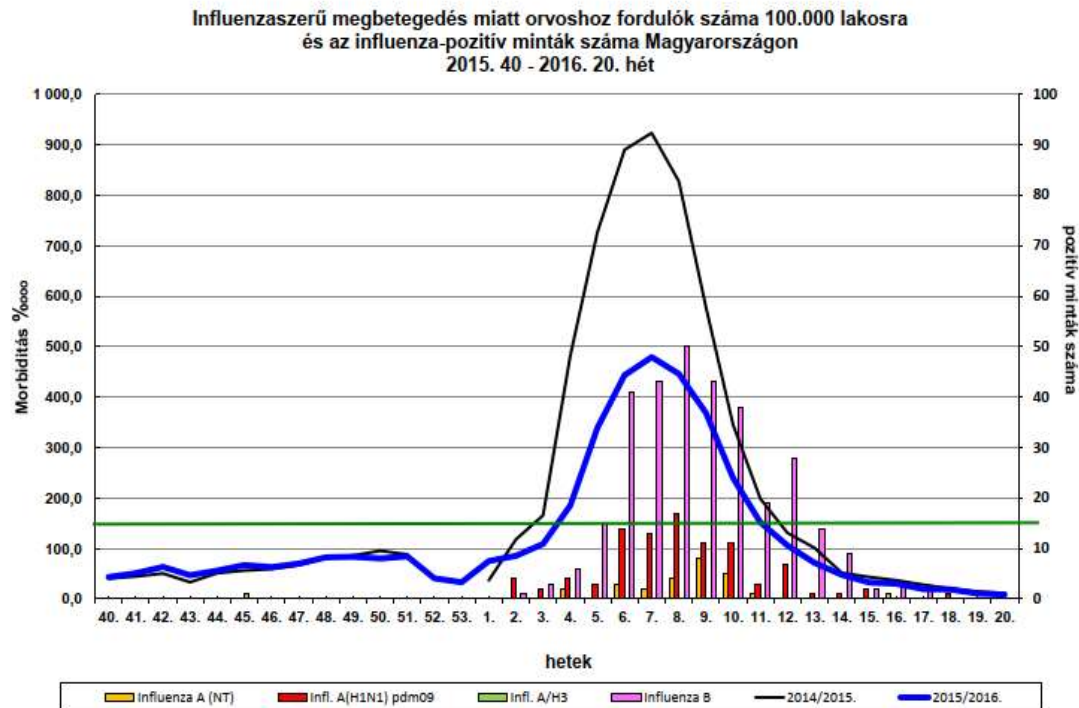


Forrás: EMMI Kórházhigiénés és Járványügyi Felügyeleti Főosztály

Figure 3.: Number of patients out of 100,000 people visiting medical doctors with influenza-like illnesses and number of influenza-positive samples in Hungary between week 40 of 2016 and week 20 of 2017

Source: (EMMI, 2017)

During the influenza season of 2015/2016, the Respiratory Virus Department of the National Center for Epidemiology processed test materials from 1,713 patients and confirmed 121 cases of influenza A infection [1 influenza A(H3), 94 influenza A(H1N1)pdm09, 26 influenza A(NT), and 317 cases of influenza B infection (a total of 438 confirmed cases caused by the influenza virus). *Figure 4* shows the morbidity data for the influenza season of 2015/2016.

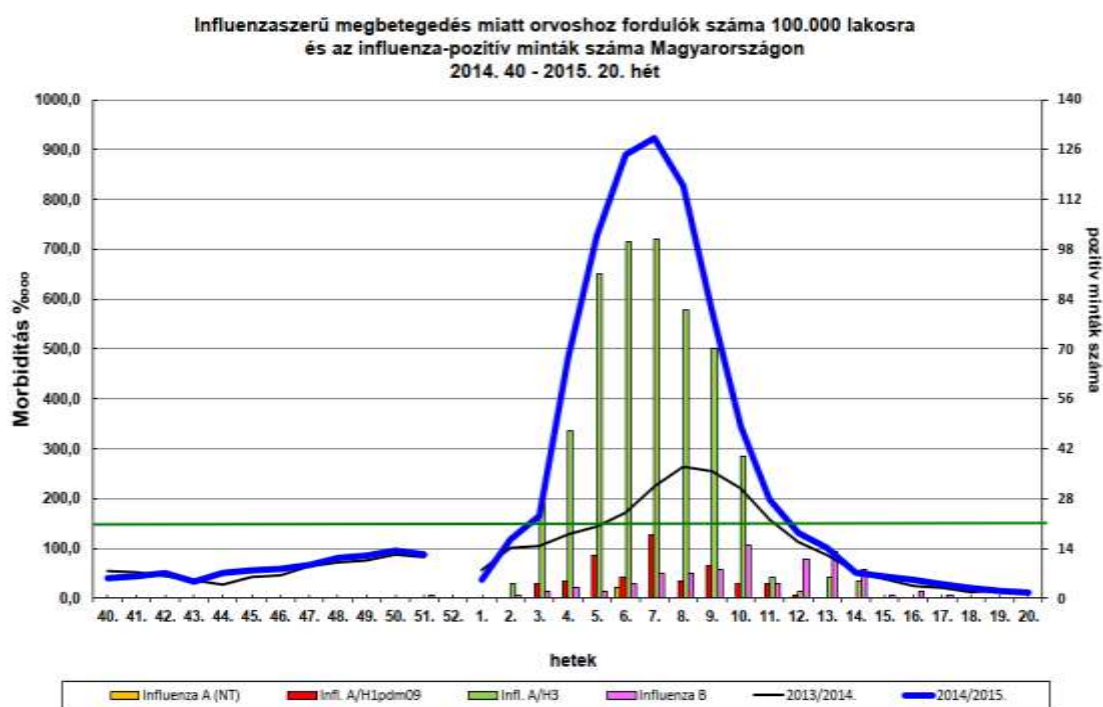


Forrás: OEK Járványügyi osztály

Figure 4.: Number of patients out of 100,000 people visiting medical doctors with influenza-like illnesses and number of influenza-positive samples in Hungary between week 40 of 2015 and week 20 of 2016

Source: (OEK, 2016)

During the influenza season of 2014/2015, the Respiratory Virus Department of the National Center for Epidemiology processed test materials from 1,982 patients and confirmed 654 cases of influenza A infection [581 influenza A(H3), 68 influenza A(H1N1)pdm09, 5 influenza A (NT)], 94 cases of influenza B infection, and **99 cases of RS virus** infection (a total of 748 confirmed cases caused by the influenza virus). *Figure 5* shows the morbidity data for the influenza season of 2014/2015.

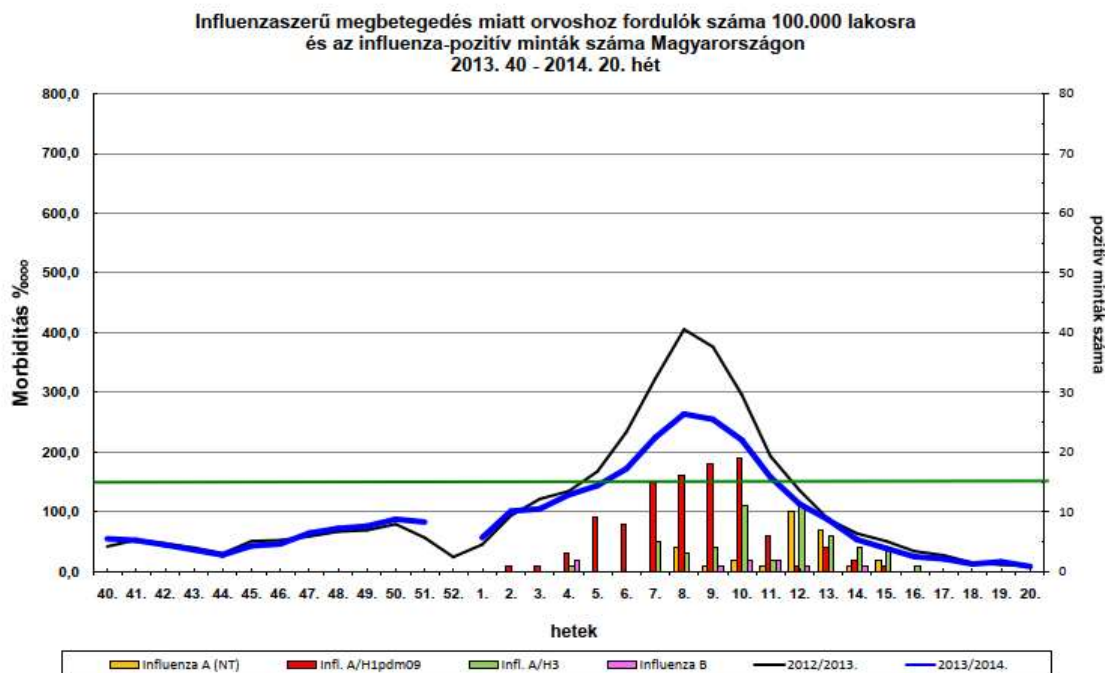


Forrás: OEK Járványügyi osztály

Figure 5.: Number of patients out of 100,000 people visiting medical doctors with influenza-like illnesses and number of influenza-positive samples in Hungary between week 40 of 2014 and week 20 of 2015

Source: (OEK, 2015)

During the influenza season of 2013/2014, the National Influenza Reference Laboratory of the National Center for Epidemiology processed test materials from 1,114 patients and confirmed 190 cases of influenza A infection [107 influenza A(H1N1)pdm09, 53 influenza A(H3), and 30 influenza A(NT)], and 9 cases of influenza B infection (a total of 199 confirmed cases caused by the influenza virus). *Figure 6* shows the morbidity data for the influenza season of 2013/2014.

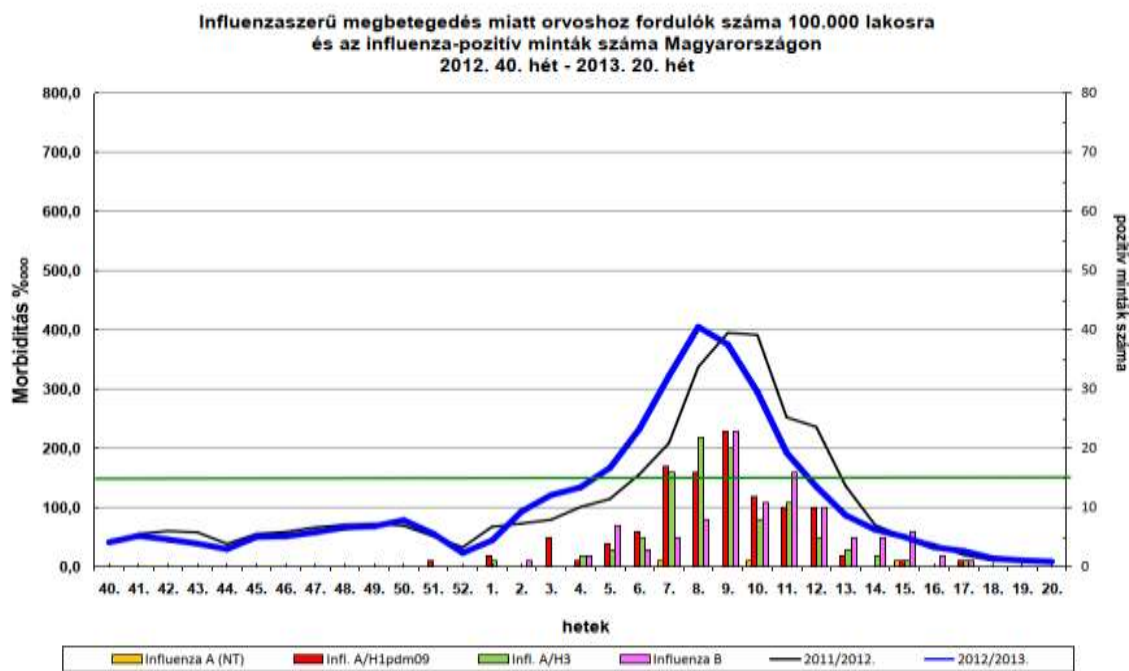


Forrás: OEK Járványügyi osztály

Figure 6.: Number of patients out of 100,000 people visiting medical doctors with influenza-like illnesses and number of influenza-positive samples in Hungary between week 40 of 2013 and week 20 of 2014

Source: (OEK, 2014)

During the influenza season of 2012/2013, the National Influenza Reference Laboratory of the National Center for Epidemiology processed test materials from 1,155 patients and confirmed 212 cases of influenza A infection [111 influenza A(H1N1)pdm09, 100 influenza A(H3), and 1 influenza A(NT)], and 105 cases of influenza B infection (a total of 317 confirmed cases caused by the influenza virus). *Figure 7* shows the morbidity data for the influenza season of 2012/2013.

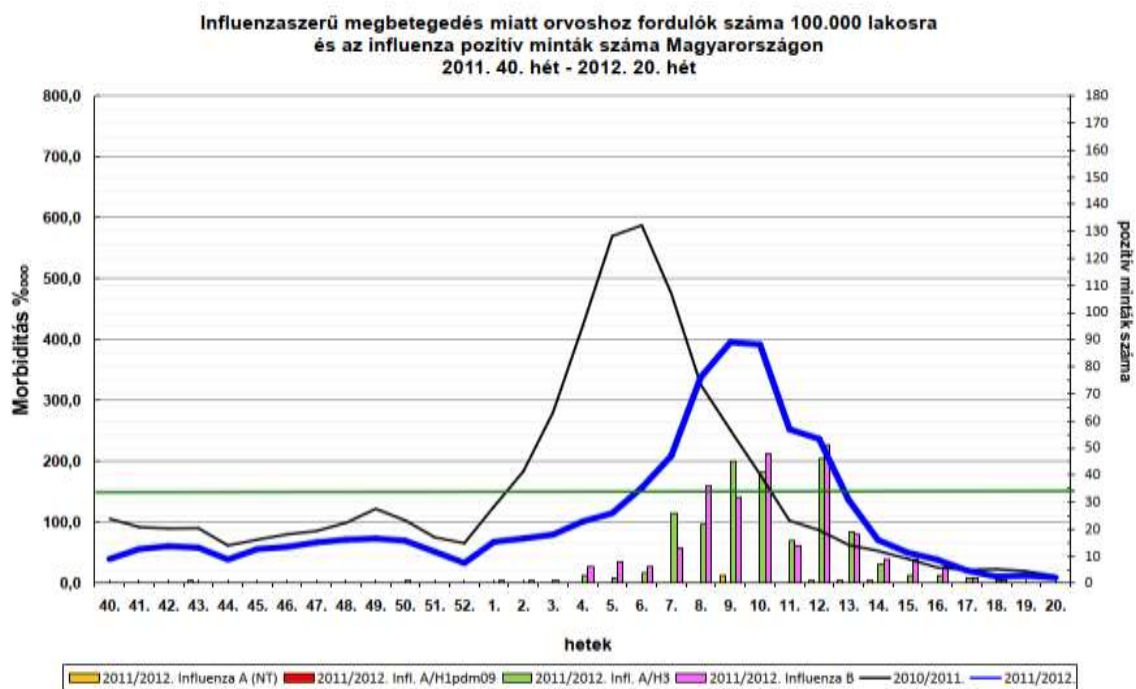


Forrás: OEK Járványügyi osztály

Figure 7.: Number of patients out of 100,000 people visiting medical doctors with influenza-like illnesses and number of influenza-positive samples in Hungary between week 40 of 2012 and week 20 of 2013

Source: (OEK, 2013)

During the influenza season of 2011/2012, the Respiratory Virus Department of the National Center for Epidemiology processed test materials from 2,006 patients and confirmed 261 cases of influenza B infection and 249 cases of influenza A infection (a total of 510 confirmed cases caused by the influenza virus). *Figure 8* shows the morbidity data for the influenza season of 2011/2012.



Forrás: OEK Járványügyi osztály

Figure 8.: Number of patients out of 100,000 people visiting medical doctors with influenza-like illnesses and number of influenza-positive samples in Hungary between week 40 of 2011 and week 20 of 2012

Source: (OEK, 2012)

Table 1.: Influenza incidence and prevalence data in Hungary, 2011-2019

Influenza season	Incidence
2018/2019	551
2016/2017	1002
2015/2016	438
2014/2015	748
2013/2014	199
2012/2013	317
2011/2012	510
Prevalence (average)	538

Source: NATIONAL PUBLIC HEALTH CENTER, 2011-2019

2.7. Description of the course, outcome and epidemiological data of the disease, presentation of the currently used treatments

Data on the course and outcome of the disease:

Influenza has the following symptoms.

Mild to medium symptoms: rapid/immediate onset of symptoms AND at least one of the following systemic symptoms: fever/high temperature, malaise, headache, muscle pain AND at least one of the following respiratory symptoms: cough, sore throat, heavy breathing (ECDC, 2018).

Severe symptoms, complications: High fever poses a hazard for infants, the elderly and people suffering from chronic disease: it burdens the heart and lungs, upsets metabolism (diabetes), but can also worsen the condition of patients with kidney, liver, and hematopoietic diseases. Complications are more common in people with bronchitis, pneumonia, immune insufficiency (cancer patients), the elderly and smokers.

Time of the onset of the disease (age): Influenza infection is not age dependent.

Gender differences: Influenza infection is not gender dependent.

Average length: Influenza usually **heals in 1-2 weeks** but requires longer time with complications.

Frequency of relapse: It cannot be interpreted due to the seasonal changes in the virus strains causing influenza infection.

Prognosis of the disease by subgroup: No data are available.

Spontaneous recovery rate: Influenza usually heals in 1-2 weeks but requires longer time with complications.

Mortality and average survival time: Complications occur in high-risk patient groups and typically multi-morbid patients' groups. Since influenza vaccination is highly recommended and available free of charge in Hungary for these groups, the number of severe patients is low. No published data are available on mortality and average survival time.

Common diseases to accompany influenza: Bronchitis, pneumonia that can be lethal.

Co-morbidity:

- chronic respiratory disease, asthma;
- limited respiratory function due to severe obesity or neuromuscular disease;
- cardiovascular disease (excluding treated hypertension);
- congenital or acquired immunodeficiency (including HIV positivity, cancer);
- chronic liver and kidney disease;
- metabolic disease, e.g. diabetes;
- long-term salicylate treatment in children and adolescents (due to the risk of Reye's syndrome).

Current therapy for the disease:

Prevention: influenza vaccination (protection against influenza A and B virus strains): inactivated-attenuated; whole virion split virus-subunit vaccine; trivalent-quadrivalent 3Fluart suspension for injection contains a whole virus, inactivated, adjuvanted, trivalent, i.e. 3 influenza virus strains (A/H1N1, A/H3N2, and B) (Fluart, 2019).

Treatment:

- symptomatic treatment (treating the symptoms of the disease such as fever, pain, cough): analgesic, antipyretic, antitussive, etc.
- antiviral substance (substance against influenza A and B virus strains in case of disease): neuraminidase inhibitor such as oseltamivir (Tamiflu®) (MayoClinic, 2019),
- Tamiflu - the main disadvantage is that administration should start no later than 2 days after infection otherwise there is no positive effect on the disease. The incubation period for influenza is 3-4 days, so it is virtually impossible to start treatment in time. Consequently, it is rarely applied (Roche, 2019).

2.8. Factors influencing the number of non-occurring diseases and its estimation

Influenza is the mostly debated vaccine-preventable disease of all both in professional and lay groups. It causes problems not only in Hungary but also almost all over the world.

The higher the rate of vaccination, the higher the so-called epidemiological protection, the lower the risk of infection as well as the intensity of the epidemic.

2.8.1. Protection by vaccination

In the case of compulsory vaccination, the so-called epidemiological protection is established approx. at 80% vaccination rate; however, ideal vaccination rate would be over 90%. It means if over 90% of the population is vaccinated, transmission of the disease is almost impossible and no epidemic can develop (Kim et al., 2011).

Childhood infectious diseases that can be prevented by vaccination show a relatively uniform clinical picture, and vaccination helps effectively prevent the development of the said disease. Consistent vaccination programs, especially vaccination rates above 98% in Hungary, resulted in immunity or sporadic reduction of certain communicable diseases in the age-related compulsory vaccination schedule. Physicians and laymen who rely on vaccinations as the most important means of preventing infectious diseases generally have such expectations for all vaccinations. It works in most cases since infectious diseases to be prevented are caused by pathogens that have remained unchanged for years or even centuries, and there is massive experience with vaccines developed to prevent them (NNK, 2019a).

2.8.2. Influenza vaccine

Unfortunately, the more or less positive facts outlined above regarding the obligatory vaccination situation do not apply to influenza. The core problem is that influenza is impossible to clinically distinguish from influenza-like illness. Laboratory testing is essential to establish an accurate diagnosis, which is time-consuming and not readily available. Given the fact that the outcome is received only a week after sampling, the accurate diagnosis does not affect therapy. Therefore, the establishment of etiological diagnosis is not supported. Another difficulty in prevention is that influenza virus is one of the most variable of the human viruses; therefore producing an effective vaccine is rather problematic.

Influenza viruses are constantly changing, and the number of incidents depends on the dominant strains circulating in a given season. The protective effect of a seasonal influenza vaccine is largely influenced by the extent to which the strains contained within and those circulating coincide. In order to produce the most effective vaccine possible, WHO reviews its recommendation on the composition of the seasonal influenza vaccine twice a year (WHO, 2018a).

As the most contagious virus in the world is the influenza virus, vaccination rates much lower than that of compulsory vaccines can produce results.

It is generally agreed that major influenza epidemics can be prevented by at least 75% vaccination. According to the WHO, at least 75% vaccination is ideal, which is achieved in quite a few countries, e.g. the United States, France, and Germany (Jorgensen et al., 2018) (CDC, 2019b); (ECDC, 2018).

Citizens in increased risk groups are people who, for some reason, are more likely to become infected with the influenza virus (e.g., healthcare workers, those suffering from chronic illnesses, the elderly, children, and those with impaired immune system). The virus is spread much faster in these groups, they are more susceptible to infection, and are more prone to transmit the disease. An important aspect of curbing the epidemic is the so-called herd immunity, which means that there are so many members of the population who are resistant to a disease that the disease stops spreading. Immunity can be developed in two ways: naturally, when the immune system produces antibodies (transfections) or by means of vaccination. The more people are vaccinated in the risk groups, the more effectively they can contribute to developing herd immunity since they are less prone to infection due to the higher vaccination rates, thus the spread of the virus is slowed down.

2.8.3. Cross-immunity

You must not forget about the indirect impacts of influenza vaccination, which reduce the probability of developing other diseases, or the effects and complications of already developed diseases (Hancock et al., 2009).

2.8.4. Vaccination for the elderly and pregnant women

Vaccination of the elderly as well as the usefulness thereof should not be overlooked either. The ever-weakening immune system of elderly people should be supported in all possible means. Providing protection against influenza can also be such means. Vaccination:

- reduces the risk of laboratory justified influenza infections by 24–56%;
- in case of infection following vaccination, preliminary immunization reduces lethal and non-lethal complications by 30%;
- reduces the risk of hospitalization due to influenza infection or pneumonia by 27–48%;

- reduces mortality due to any reason by 47–68% (Ócsai, 2018).

Vaccinating pregnant women was in the focus of heated debates for years. According to the Methodological Letter of the National Center for Public Health, Hungary, the pregnant women, as well as women who plan to have pregnancy during an influenza season in Hungary are eligible for the free-of-charge vaccination against influenza, due to their endangered status. Thus, influenza vaccination provides inevitable protection for pregnant women as well as the fetus. (NNK, 2020)

2.9. Consequences

Apart from foreign literature, mortality data published by the Central Statistics Office (CSO/KSH) are worth considering since they justify the fact that mortality increases depending on the severity of the influenza epidemic. The influenza epidemics of 2015 and 2017 were more severe than usual in Hungary. These epidemics are responsible for 5,000 extra deaths in given seasons. (Házipatika, 2017)

Influenza-related morbidity and total mortality data for the influenza seasons between 2013 and 2017 are presented in the following graphs (*Figure 9, Figure 10*)

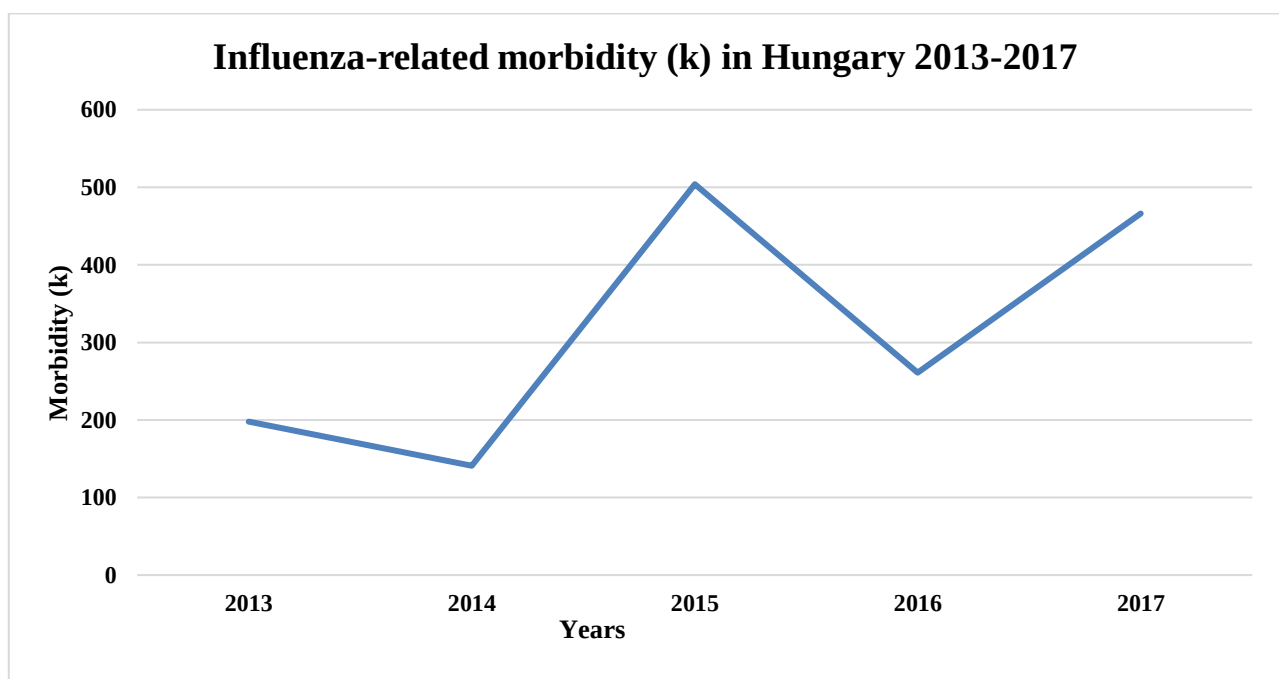


Figure 9.: Influenza-related morbidity in Hungary between 2013-2017

Source: OWN EDIT VAJO RESULTS, 2020

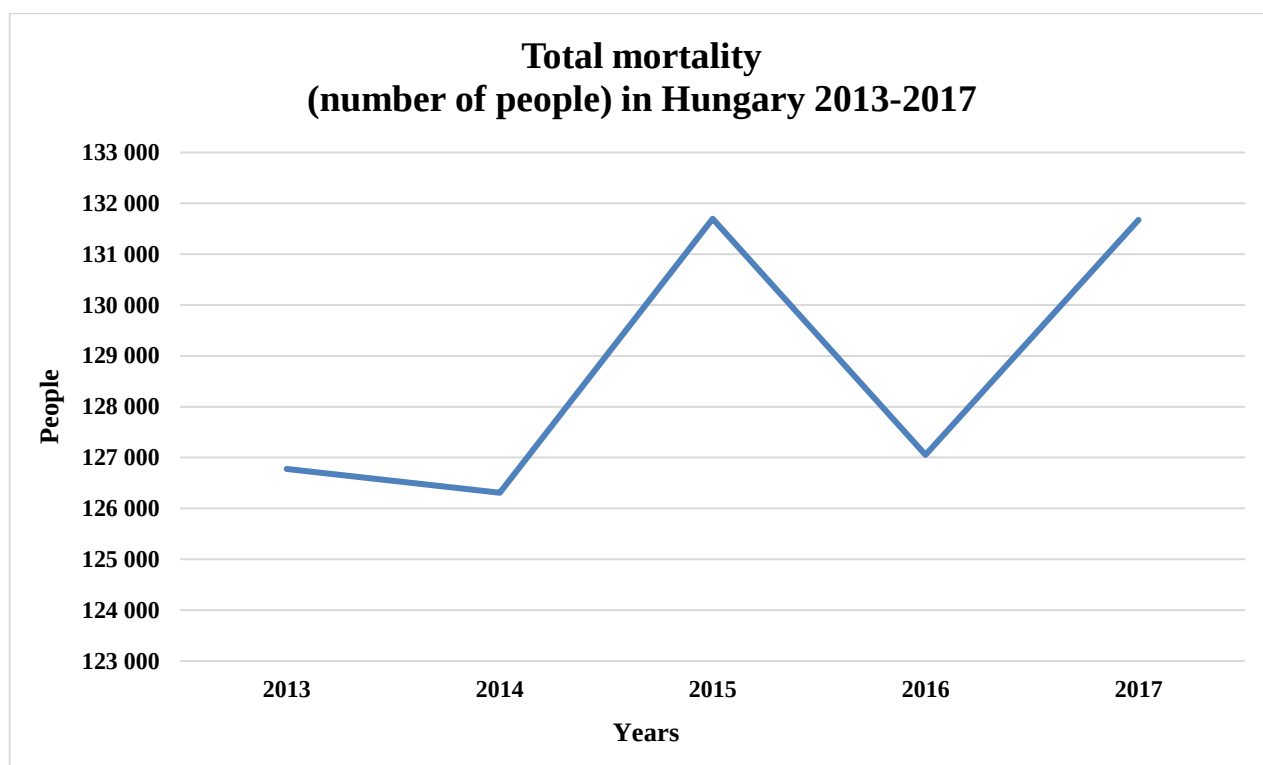


Figure 10.: Total mortality (number of people) in Hungary 2013-2017

Source: OWN EDIT VAJO RESULTS, 2020

It is remarkable that the graphs representing influenza-related morbidity and total mortality are almost identical.

All these supports the fact that even though we cannot demonstrate that the efficiency of influenza vaccination is as high as that of compulsory vaccines, yet the benefits are obvious and tangible.

Vaccination is still inevitably the most effective way currently known to prevent influenza, although no single vaccine can guarantee 100% protection against the given disease. According to data from recent years, influenza vaccines have provided approximately **40-60% protection** against laboratory-confirmed influenza diseases (Budai, 2019).

2.10. Critical opinions

It must be noted that certain studies discuss the decreasing effectiveness of influenza vaccination. These, of course, do not question the legitimacy of vaccination, but state mere facts and call the attention to a medical-professional problem (Wu et al., 2017).

They claim that the effectiveness of seasonal influenza vaccination has been deteriorating for the past years, especially for H3N2, which poses the biggest challenge for public healthcare worldwide. Whereas prior to 2009 the effectiveness of seasonal influenza vaccination was around 67% against the H1N1 type, 73% against H1N1pdm09, and 54% against B type, its effectiveness was as low as 33% against H3N2.

These research statements are inevitable and irrefutable. However, in my opinion worsening effectiveness is by all means of regional and transition nature, since the development of medicine in the field of vaccination is faster than average. With the increasingly precise definition of vaccine components and the continuous modernization of manufacturing processes, effectiveness can only increase in the long run.

2.11. Assessment of non-occurring illnesses

No data are available on the exact morbidity rate in case of no vaccination since typically vaccination is applied throughout the world. My study is based on data from countries (USA, Hungary) where the number of influenza and influenza-like illnesses is well documented and such data are reliable.

Hungary has been running an influenza surveillance service for decades. It currently is supervised by the Epidemiology and Infection Control Department of the National Public Health Center. The Influenza Surveillance Service publishes information on the number of people with influenza-like illnesses in the given week, their age distribution, the number of respiratory samples taken, and the results of the virological tests performed as of week 41, each year to week 20 of the following year (i.e. over a period of 32-33 weeks). All these data form an appropriate, accessible database accessible to everyone, which ensures that the conclusions drawn from it are statistically well-founded.

2.12. Advantages of vaccination in given patient groups

Cardiovascular diseases

- all-cause mortality rate is reduced by 78% in high-risk adult groups (including cardiovascular diseases),
- risk of death is reduced by 80% in patients with myocardial infarction after a cardiac event,
- risk of hospitalization is reduced by 87% in patients with cardiovascular disease or acute pneumonia,
- risk of myocardial infarction is reduced by 67% in patients who have had myocardial infarction, and
- risk of ischemic stroke is reduced by 54% in patients who have had stroke.

The effectiveness of influenza vaccination in this patient group is estimated at 15-45%. It means that the effectiveness of this measure in preventing coronary heart disease is considered equivalent with that of giving up smoking (32-43%), statin treatment (19 -30%) or antihypertensive therapy (17-25%).

As for chronic respiratory diseases, influenza vaccination administered to elderly patients with pulmonary disease treated between 1993 and 1996 (n = 1366, USA):

- reduced hospitalization by 52%, and
- reduced mortality by 70%.

Regarding diabetes, as part of the PRISMA study, data of 9,238 patients with diabetes type 2 were compared to data of a control group during the influenza A-dominant epidemic of 1999-2000, and the effects of influenza vaccination were also evaluated. Influenza vaccination of patients with diabetes during winter time

- reduced the influenza morbidity by 59%,
- reduced hospitalization by 54%, and
- reduced mortality by 58% (Ócsai, 2018).

2.13. International review – general vaccine-acceptance in certain parts of the world

An important question for my study is how vaccines are generally perceived in different parts of the world. This issue can be assessed based on how leading occupational health institutions

in the region communicate with the population, how much vaccines are accepted and what is the vaccination rate (especially with regard to pediatric vaccines). Also, the presences of multinational pharma companies in the region should also be considered, which obviously look for a market for their products, thus indirectly indicate the level of vaccine acceptance in the given area.

I will describe herein the vaccine market of the countries in the four major regions of the world, which provides a picture of the potential for the current and future influenza vaccination coverage in the world, thus the potential of increasing vaccination rate.

North America

The United States of America

- Vaccination of children attending public schools is mandatory in all 50 states of the United States, although different exemptions are available in each state. Each state provides an exemption for those who are hypersensitive to certain vaccine substances. All states except California, West Virginia, and Mississippi grant exemption for religious reasons, while eighteen states allow parents to refuse vaccination based on personal, conscientious, philosophical, or other reasons.
- In the US, Centers for Disease Control and Prevention (CDC) are responsible for pediatric immunization. Vaccination schedules are based on age: from birth to 6 years, 7 to 18 years, and over 19 years.
- An estimated 20 million illnesses and over 40,000 deaths were prevented in the age groups that received the recommended childhood immunizations. It means USD 70 billion in savings.
- Vaccination is often mandatory in the United States for military enlistment.
- The United States has one of the most advanced vaccine safety tracking systems in the world. The U.S. Department of Defense (DoD) and Department of Veterinary Affairs (VA) also have systems in place to monitor and research vaccine safety (CDC, 2020a), (NCSL, 2019).

Canada

- Vaccination is not mandatory in Canada, but children and adolescents must prove that they have been vaccinated in order to go to school in Ontario.
- The Canadian Public Health Agency supports immunization as an effective way to provide protection against infectious diseases and encourages citizens to ask for regular vaccination (PHAC, 2019).
- Virtually all major vaccine manufacturers of the world (GlaxoSmithKline, Merck, Novartis, Pfizer, and Sanofi) are present on the Canadian vaccine market. BIOTECCanada Vaccine Industry Committee (VIC), Canada's leading industry association, brings together the country's leading vaccine developers and suppliers. The VIC is aimed to raise awareness of the benefits of vaccines, and to help create a more effective and conducive environment that Canada will consistently and sustainably fund through its immunization programs (BIOTECCanada, 2021).

Eastern-Europe, Europe

The Czech Republic

- In the Czech Republic, the vaccination program is based on legislation by the Ministry of Health, which sets out the immunization schedule and the selection of vaccines for regular and mandatory vaccination.
- Mandatory vaccination is available free of charge for the population. The majority of vaccinations are administered by pediatricians, however, clinical doctors or epidemiologists can also administer special or mandatory vaccines.
- The two most common vaccines in the Czech Republic are meningococcal meningitis and tick-borne encephalitis (ECDC, 2020a).

Slovakia

- Vaccination against ten diseases is mandatory in Slovakia: diphtheria, hemophilic influenza B, hepatitis, measles, mumps, whooping cough, pneumococcus, polio, rubella and tetanus.

- In addition to children, Hepatitis B vaccination is mandatory for healthcare workers and students. Influenza vaccination is mandatory for residents in orphanages and care homes. A fine is imposed for those who do not follow the regulations.
- It is not allowed by law to refuse vaccination in Slovakia. Nevertheless, vaccination rate is steadily declining (ECDC, 2020c).

Poland

Poland has a mandatory vaccination program. Each child living in Poland for more than 3 months receive free vaccination. It is mandatory for parents to show up with the child for vaccination. Parents can receive a fine if they refuse vaccination.

- Every child is given a vaccination book after birth, which is held in the General Practitioner's office to keep track of vaccinations.
- Currently, there are eleven mandatory vaccinations: against tuberculosis, hepatitis B, diphtheria, tetanus, whooping cough, polio, Hemophilic influenza type B, pneumococcus, measles, mumps and rubella (ECDC, 2019).

Hungary

- The Hungarian vaccination rate is the highest in Europe in terms of mandatory vaccinations: it is around 98% (MTI, 2017).
- Being a part of the Hungarian government initiatives, mandatory vaccination is free of charge.
- Hungary offers mandatory vaccination against 11 diseases: diphtheria, hemophilic influenza type B, hepatitis B, measles, mumps, whooping cough, pneumococcus, polio, rubella, tetanus and tuberculosis (ECDC, 2020b).
- In March 2017, GlaxoSmithKline invested \$ 6.2 million in its Hungarian vaccine plant, where diphtheria and tetanus vaccines are produced (Elvidge, 2017).

Russia

- In August 2018, the WHO mentioned Russia for recording more than 1,000 measles cases. At the same time, the WHO is working with the government to improve immunization rates (WHO, 2018b).

- According to the Federal Center for Hygiene and Epidemiology, 48.7% of Russian children born in 2016 were not vaccinated according to the medically prescribed schedule.
- Russian mothers are skeptical about vaccinations and do not consider it necessary (Gershkovich, 2018).

Rest of Europe (the United Kingdom, France, Germany, Spain, Italy, the Netherlands, Finland, Denmark, Belgium, Greece)

- Vaccination is not mandatory in 15 of the 27 EU Member States (*2010 data*) (Finnegan, 2017b).
- France and Romania have elaborated new legislation to penalize parents of unvaccinated children (EFE, 2018); (Romania-Insider, 2017).
- In March 2018, Finland introduced legislation requiring healthcare and social care providers to ensure that their employees are immunized against measles, chickenpox, whooping cough and influenza (Finnegan, 2017a).

Some countries of the Commonwealth of Independent States

Kyrgyzstan

- In Kyrgyzstan, the number of people rejecting vaccination is increasing. Some refuse to have their children vaccinated for religious reasons, others for medical advice or because of the quality of the vaccine.
- Since 1995, vaccination rate of the three doses of diphtheria, tetanus and pertussis (DTP) has been at a minimum of 90% in Kyrgyzstan. In 2016, DTP3 vaccination rate was 95% in all Kyrgyz counties. The rate of infants who received the 3rd dose of the polio vaccine decreased from 97% in 2016 to 93% in 2017 (UNICEF, 2017).

Kazakhstan

- The number of non-vaccinated people has increased in recent years. Key reasons include personal beliefs like religious reasons.
- The number of infants who received the hepatitis B vaccine within 24 hours of birth fell from 95% in 2016 to 90% in 2017 (WHO, 2019b).

Some Gulf-countries

The United Arab Emirates

- The National Immunization Program launched by the Ministry of Health has generated significant demand for vaccines in the country.
- Vaccination awareness programs drew attention to the importance of vaccinations for children, schools, adults, and immigrants in the country (UAE, 2020).

Bahrain

- Bahrain is a growing market for vaccines due to recent epidemics. Between 2000 and 2010, as a result of measles, mumps, and rubella (MMR) immunization campaigns, the incidence of mumps and measles decreased and even almost disappeared in the country (Jawad et al., 2011).
- WHO and UNICEF jointly estimate that in 2017 vaccination rate for a number of vaccines including DTP1, Pol3 and MCV1 reached almost 100 percent in the country (UNICEF, 2020).

3. Material and method

My dissertation is aimed at describing the impact of influenza vaccination on the economy. To this end, I need to estimate how many incidents can be prevented by means of vaccination. Due to the novel approach of my methodology, no direct assessment is possible therefore I will apply indirect methods.

No such attempts have been made as was confirmed by all the professionals I have visited. In fact, I also felt significant skepticism on their part when I shared my intentions with them, as the obvious answer to the question of “how to predict what hasn’t happened” is “by no means”.

In the first approach, I will assess the magnitude of the “accepted efficacy” of vaccination based on the publications available in the literature.

After dividing the population into age groups, I will examine the vaccination coverage and number of illnesses in different age groups respectively. Analyzing these data, I will make assumptions on the vaccine efficacy based on statistical data. Afterwards on the basis of the vaccine efficacy data with the help of a mathematical method I will identify the number of non-occurred illness cases, as well. Further, I will identify the economic impact based on the above number of non-occurred cases in case of the current vaccination strategy.

Finally, in case of the newly suggested vaccination strategy, with the same methodology I will calculate the number of non-occurred cases and then I will compare these numbers to the numbers of the present vaccination strategy.

I believe that this method is a novel one, because I use justified and reliable statistical data instead of traditional clinical results for the identification of vaccine efficacy.

I neglect the drastic rates typical of pandemics in my assessment as they outline an extreme situation.

Unfortunately, this extreme situation has become very relevant right now, as the consequences of the current pandemic caused by the Covid-19 virus seemed unthinkable or even utopian when I chose the subject of my dissertation. The time that has passed since proves that mankind has not even been able to overcome nature. In addition to hostilities, new and new challenges have to be faced. Exploring the economic effects and correlations of the current coronavirus pandemic is likely to be the subject of numerous publications in the future.

Regarding the efficacy of the influenza vaccination, even the study referred to in sub-chapter **2.10.** (describing the decreasing effectiveness) applies an effectiveness of 33% as the worst-case scenario data. Other (national) professionals consider the effectiveness of vaccine to be between 40 and 60 percent (see sub-chapter **2.9.**). As for the elderly, the reduction in mortality rates is over sixty percent (see sub-chapter **2.8.4.**), and in certain (co-)occurring diseases the risk of cross-complications can be reduced by up to eighty percent (see sub-chapter **2.8.3.**).

Thus, my estimate for the effectiveness of vaccine is 50 percent based on scientific literature. This means that if one person out of those vaccinated falls ill, in lack of vaccination 2 people would become ill. I personally feel and believe that this is an underestimated value, yet with respect to the principle of precaution I do not assume a higher rate. However, I will not use this estimate in further calculations; I will use it only as a means of control for the final result of my own effectiveness calculations that I will base on available objective statistical data, so I can see how much it corresponds to the efficiency band defined in professional literature.

One of the aims of my dissertation is, as previously formulated, therefore, to quantify the number of cases that did not occur because the concerned person was vaccinated against influenza. My calculations are based on the public data of the Influenza Surveillance System of the Epidemiology and Infection Control Department of the National Public Health Center for the influenza season of 2018/2019 and the relevant data of the Central Statistical Office for the years from 2013 to 2017.

I divided the population into two parts: the so-called “active” and “passive” population groups. Currently, the retirement age in Hungary is 65, so I included the population between the age of 19 and 65 in the “active” population group, and the population under the age of 19 as well as the population over the age of 65 in the “passive” population group. Certain adjustment was required here as my previous calculations involved the age group of 60 and older. The distribution of non-occurring diseases between the active and passive population groups ended up being practically one-third to two-thirds (112k cases and 209k cases respectively).

In case future research results or ever sophisticated methodological effectiveness measurement further refine the value of non-occurring diseases, my calculations could become more specific as well. I believe my study can be considered a pioneer in studying the impact of vaccination on economic performance both in its approach and methodology.

It does not fully correspond to any types of health economics analysis (cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis), yet at the same time it is closest to cost-utility analysis. However, the methodology of the latter is not yet fully established, and we have little experience with it in Hungary. Even though my study is not a guideline, I hope it is a gap-filling analysis.

The future will definitely bring refinement to the methodology, but I am convinced that there will be no significant differences compared to my calculations.

4. Study results and their assessment

4.1. Number of non-occurred diseases based on facts

Before quantifying non-occurred diseases, let us first review the influencing data over a five-year period.

4.1.1. Basic data

a) Population

The total population in Hungary between 2013 and 2017 was as follows (*Figure 11*).

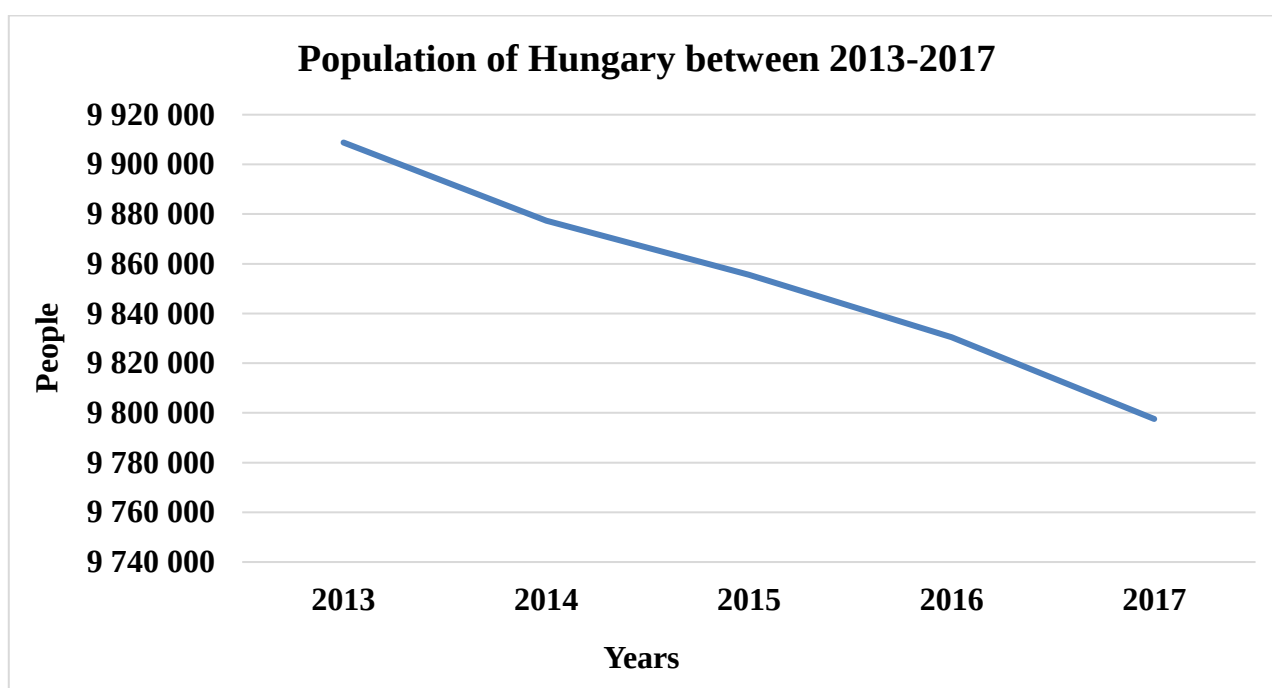


Figure 11.: Population of Hungary between 2013-2017

Source: CENTRAL STATISTICS OFFICE, 2017; OWN EDIT VAJO RESULTS, 2020

It can be clearly seen that the population is constantly and practically steadily declining. The decline was 1.1 percent in four years.

b) Vaccination

The number of people who received influenza vaccination developed as follows between 2013 and 2017 (*Figure 12*).

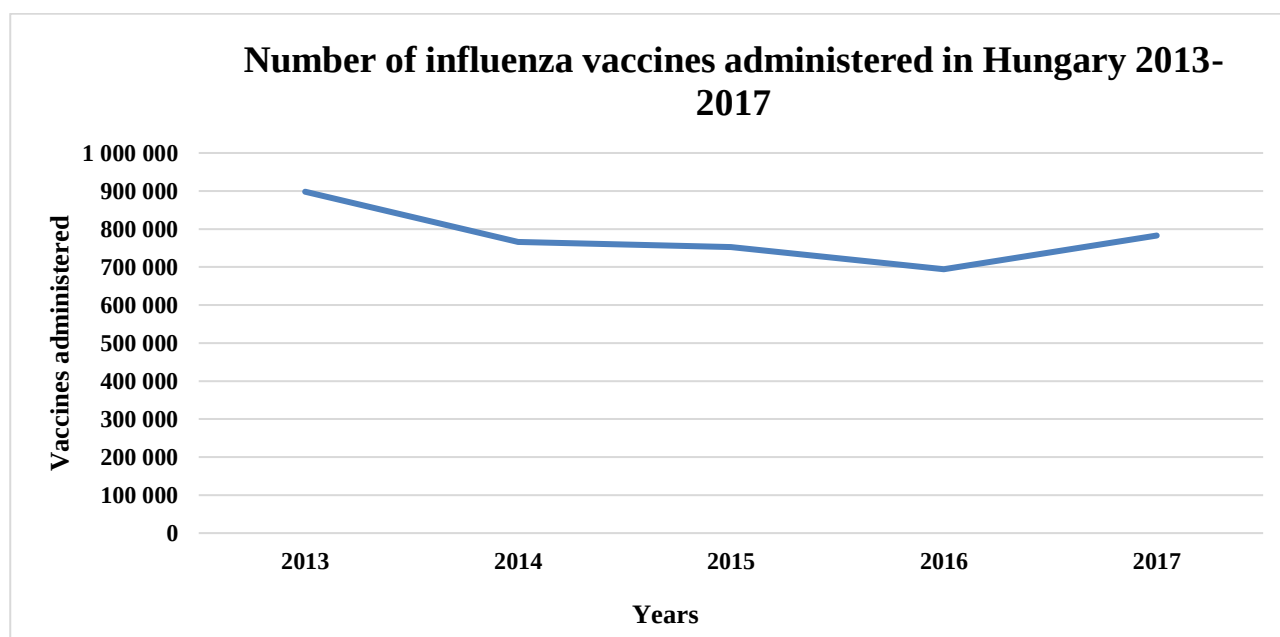


Figure 12.: Number of influenza vaccines administered in Hungary between 2013-2017

Source: NATIONAL PUBLIC HEALTH CENTER, 2013-2017; OWN EDIT VAJO RESULTS, 2020

The average number of people who received influenza vaccination during the period was 778,509 with a standard deviation of approx. ten percent. From the quotient of the previous figures, I can establish the vaccination rate, which was as follows during the reference period (*Table 2.*).

Table 2.: Influenza vaccination (%) /year in Hungary between 2013-2017

Year	2013	2014	2015	2016	2017
Vaccination (%)	9.1	7.7	7.6	7.1	8.0

Source: NATIONAL PUBLIC HEALTH CENTER, 2013-2017

The vaccination rate was 7.9 percent on average in the study period, and the deviation is adjusted to the number of people who received vaccination.

c) Influenza-related morbidity numbers (Figure 13)

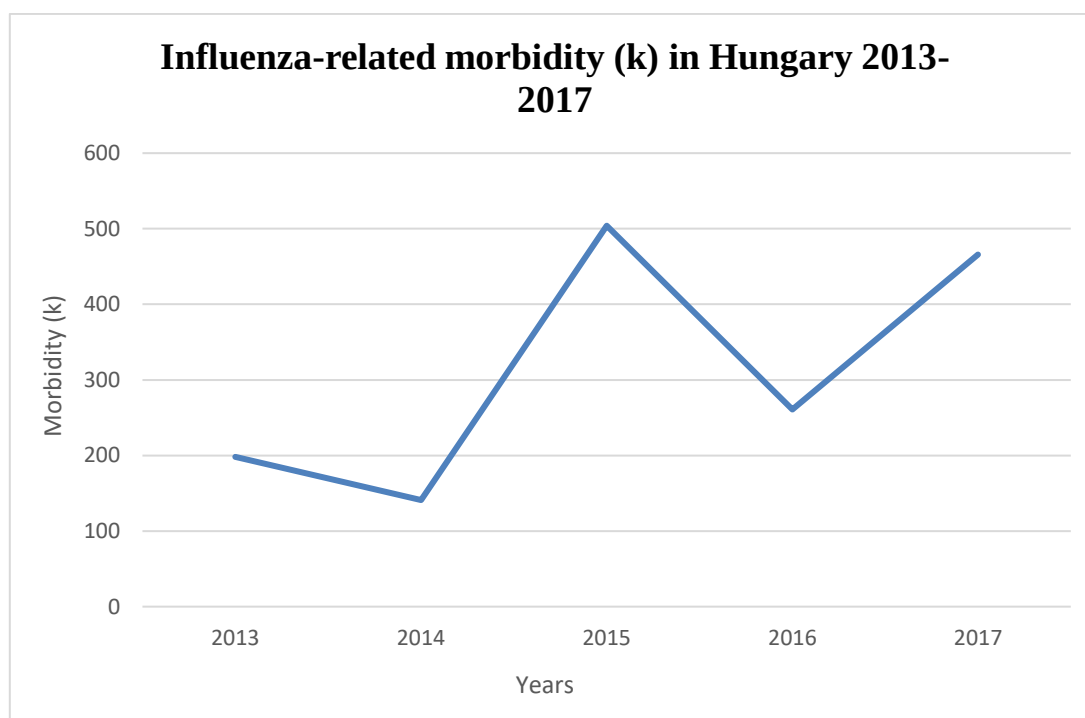


Figure 13.: Influenza-related morbidity (k) between 2013 and 2017 in Hungary

Source: CENTRAL STATISTICS OFFICE, 2017; OWN EDIT VAJO RESULTS, 2020

It is worth having a look at the ratio of morbidity and total population (*Table 3*).

Table 3: Influenza-related morbidity rate (%) /year in Hungary between 2013-2017

Year	2013	2014	2015	2016	2017
Morbidity rate (%)	2.0	1.4	5.1	2.7	4.8

Source: CENTRAL STATISTICS OFFICE, 2013-2017

4.1.2. Influenza season data, 2018/2019

I intend to quantify the number of illnesses that could be avoided based on the influenza season data in 2018/2019. I collected the required data from several sources.

Facts

The population was 9,778,371 on January 1, 2018. (KSH, 2017)

718,396 people were vaccinated in the influenza season of 2018/2019, which is 7.3 percent of the total population (Molnár, 2019). This resource categorized those that received influenza vaccine split into four age groups.

For the season of 2018/2019 the *Annex 1* includes the age group data combined with the patients' health status – I used figures and data for my calculations in my study (see in Annex 1). The *Annex 2* contains the same data sets for the reference period from 2010/2011 influenza season until 2017/2018 season. I decided to include these previous seasons' information for those who are interested in a possible comparison of my calculations with the above seasons' data sets (see in Annex 2).

Morbidity in the influenza season of 2018/2019 was 494,520, which is 5.1 percent of the total population (NNK, 2019b).

In other words, it can be stated that in the influenza season of 2018/2019, 7.3 percent of the Hungarian population received influenza vaccination, and 5.1 percent fell ill.

This value refers to the average of the total population. However, in terms of age distribution, vaccination is unlikely to be evenly distributed. It is necessary to analyze the available data in order to find out the distribution.

The distribution of vaccine recipients by age group is as follows (*Table 4, Figure 14*):

Table 4.: People/age group vaccinated in 2018/2019 season in Hungary

Age group	3-18	19-59	60-64	65 and older	Total
People	20 125	187 566	64 013	446 692	718 396
%	2.8	26.1	8.9	62.2	100.00

Source: NATIONAL PUBLIC HEALTH CENTER, 2019; ANNEX 1.

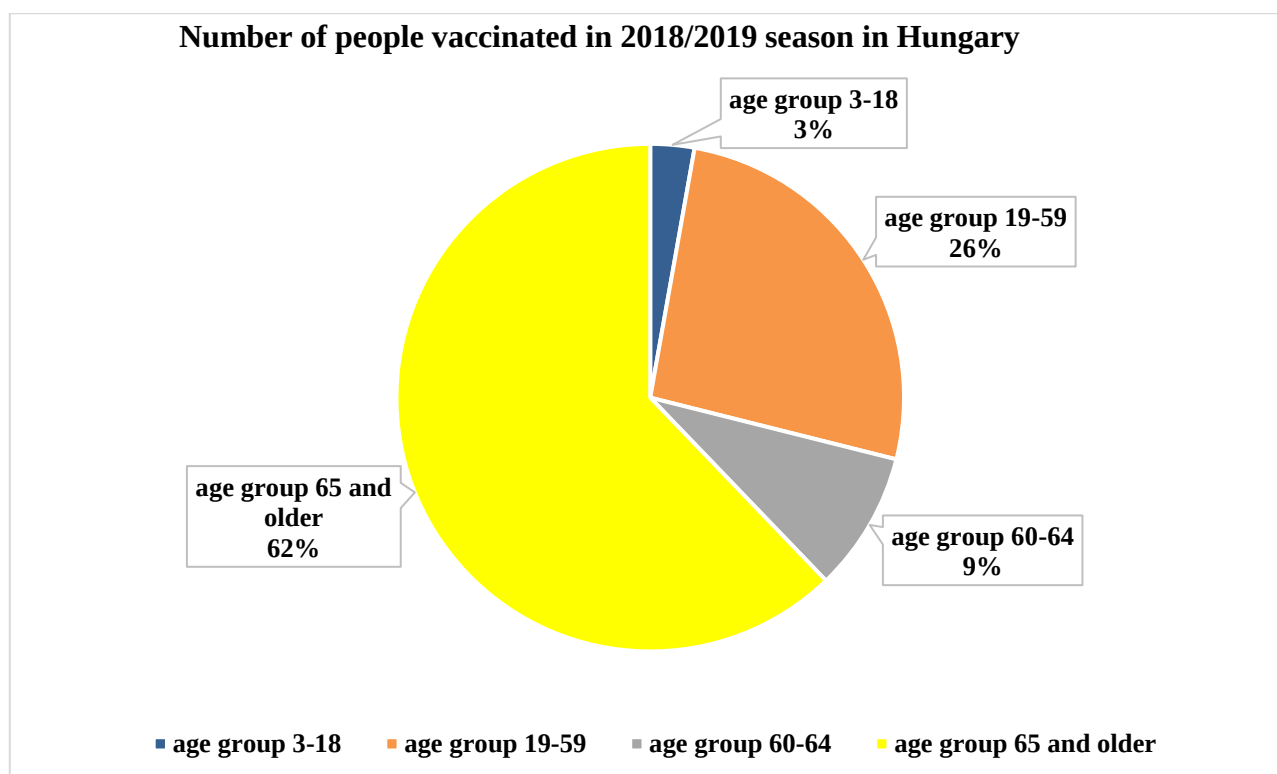


Figure 14.: Number of people/age group vaccinated in 2018/2019 season in Hungary
Source: OWN EDIT VAJO RESULTS, 2020

These data show – and the chart is also spectacular illustration – that people under 18 years of age received 2.8 percent of all vaccinations, and those over sixty received 62.2 percent of the vaccines. I need to know the distribution of these age groups in the total population in order to decide whether these values are too high or too low. The Central Statistics Office (CSO) categorizes the population by age group in the following breakdown: 0 - 14 years, 15-19 years, then ten-year groups (decades) afterwards (*Table 5, Figure 15*).

Table 5.: Number of people/age group in 2019, Hungary

Age group	0–14	15–19	20–29	30–39	40–49	50–59	60–69	70–79	over 80	Total
People	1 421 916	489 340	1 204 219	1 323 506	1 558 261	1 207 262	1 324 480	821 456	427 931	9 778 371
%	14.5	5.0	12.3	13.5	15.9	12.4	13.5	8.4	4.4	100.00

Source: CENTRAL STATISTICS OFFICE, 2019

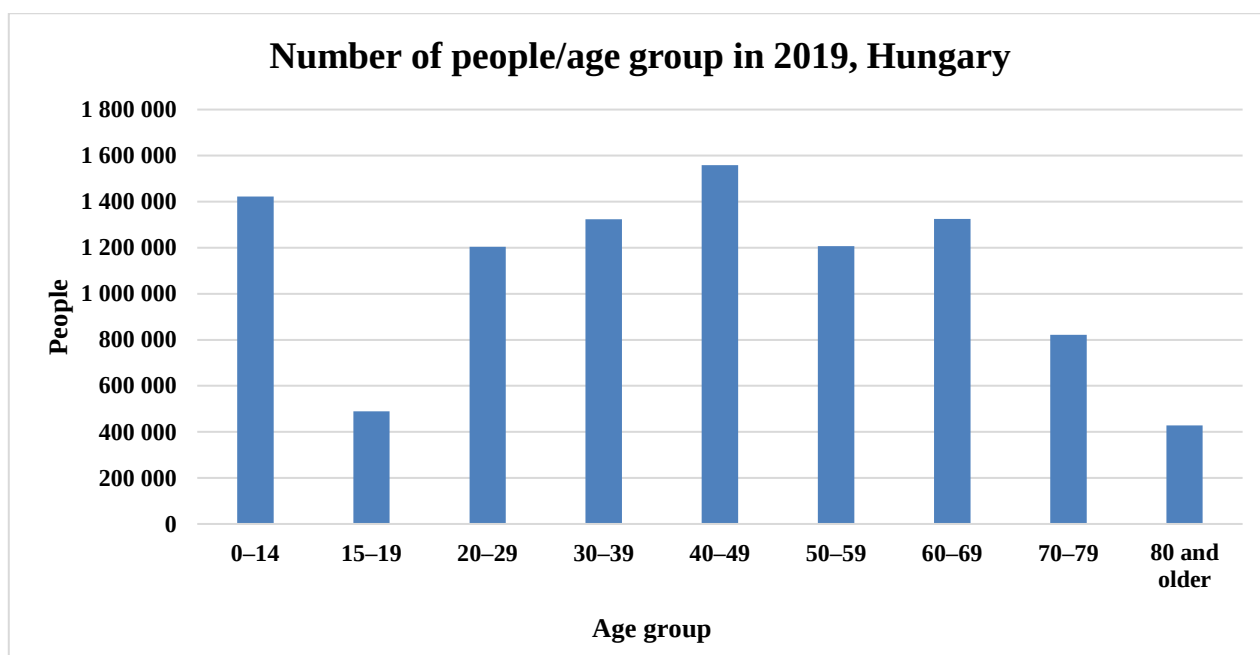


Figure 15. Number of people/age group in 2019, Hungary

Source: CENTRAL STATISTICS OFFICE, 2019; OWN EDIT VAJO RESULTS, 2020

Unfortunately, this age group distribution does not match the distribution of those age groups that received vaccination. Moreover, we have yet another data set: the number of people who visit their doctor with influenza-like illnesses.

The prevalence of influenza-like illnesses broken down by area and age group was monitored based on morbidity data of 1,349 general- and pediatric practitioners during the influenza season of 2018/2019. District offices asked 100 physicians that participated in the surveillance system to regularly send respiratory samples for virological testing from patients with influenza complaints in order to identify the pathogen of the disease. Based on the results of the received samples, the occurrence and spread of influenza viruses could be monitored weekly.

During the influenza season of 2018/2019, the number of influenza-like illnesses was as shown in the table below (*Table 6*) (NATIONAL PUBLIC HEALTH CENTER, 2019).

Table 6. Number of influenza-like illnesses in 2018/2019 season in Hungary

Period	Total number of people visiting a doctor with influenza-like symptoms	Percentage				People			
		age 0-14	age 15-34	age 35-59	age 60 and older	age 0-14	age 15-34	age 35-59	age 60 and older
Week 40, 2018	3 500	16.9	40	29.1	14	592	1 400	1 019	490
Week 41, 2018	3 500	11.3	42.6	33.8	12.3	396	1 491	1 183	431
Week 42, 2018	4 300	16.3	40.8	26.3	16.6	701	1 754	1 131	714
Week 43, 2018	2 700	16.9	41.3	27.1	14.7	456	1 115	732	397
Week 44, 2018	2 500	9.4	49.1	28.7	12.8	235	1 228	718	320
Week 45, 2018	4 500	15.1	43.4	28.3	13.2	680	1 953	1 274	594
Week 46, 2018	4 800	16	44.6	24.5	14.9	768	2 141	1 176	715
Week 47, 2018	6 000	18.4	44.3	25.7	11.6	1 104	2 658	1 542	696
Week 48, 2018	7 000	21.2	40.6	25.9	12.3	1 484	2 842	1 813	861
Week 49, 2018	8 000	18.4	42.3	27.4	11.9	1 472	3 384	2 192	952
Week 50, 2018	10 000	21.9	37.6	26.4	14.1	2 190	3 760	2 640	1 410
Week 51, 2018	11 000	22.9	38.4	26	12.7	2 519	4 224	2 860	1 397
Week 52, 2018	no data collected *								
Week 01, 2019	11 000	16.8	40.6	29.8	12.8	1 848	4 466	3 278	1 408
Week 02, 2019	19300	19.7	42.6	26.7	11	3 802	8 222	5 153	2 123
Week 03, 2019	38 200	32.5	34.9	24.3	8.3	12 415	13 332	9 283	3 171
Week 04, 2019	65 000	37.7	32.6	22.8	6.9	24 505	21 190	14 820	4 485
Week 05, 2019	77 500	35.5	34.5	23	7	27 513	26 738	17 825	5 425
Week 06, 2019	67 900	34.7	33.1	24.3	7.9	23 561	22 475	16 500	5 364
Week 07, 2019	52 200	31.6	34.1	25.8	8.5	16 495	17 800	13 468	4 437
Week 08, 2019	33 900	31.5	34.3	26.2	8	10 679	11 628	8 882	2 712

Table 6. Number of influenza-like illnesses in 2018/2019 season in Hungary (continuation)

Week 09, 2019	21 300	29.1	34.9	27.6	8.4	6 198	7 434	5 879	1 789
Week 10, 2019	13 900	25.3	37.2	26.6	10.9	3 517	5 171	3 697	1 515
Week 11, 2019	7 300	22.3	37.9	27.9	11.9	1 628	2 767	2 037	869
Week 12, 2019	5 600	20	39.2	28.8	12	1 120	2 195	1 613	672
Week 13, 2019	3 800	18.1	41.8	27.2	12.9	688	1 588	1 034	490
Week 14, 2019.	2 700	20.1	42.8	24.8	12.3	543	1 156	670	332
Week 15, 2019	1 970	10	47.4	33.1	9.5	197	934	652	187
Week 16, 2019	1 000	9.3	44.9	33.2	12.6	93	449	332	126
Week 17, 2019	1 200	8.3	54.4	25	12.3	100	653	300	148
Week 18, 2019	800	9.4	38.6	33.3	18.7	75	309	266	150
Week 19, 2019	1 200	6	55.9	23.9	14.2	72	671	287	170
Week 20, 2019	950	7.5	59.2	20.9	12.4	71	562	199	118
Total	494 520	N/A	N/A	N/A	N/A	147 715	177 688	124 451	44 667
Percentage	100.00	N/A	N/A	N/A	N/A	29.87	35.93	25.17	9.03

** Note: due to the year-end period (public holidays) there were no data collected by the physicians during the week of 52.*

Source: NATIONAL PUBLIC HEALTH CENTER, 2019

According to the assessment based on reports by the doctors participating in the surveillance system, 494,520 people visited their doctor with influenza-like symptoms between October 1, 2018 and May 19, 2019.

Table 7. Number and percentage of people visited doctor/age group in 2018/2019 season in Hungary

Age group	0-14	15-34	35-59	60 and older	Total
Number of people	147 715	177 688	124 451	44 667	494 520
%	29.9	35.9	25.1	9.1	100.00

Source: NATIONAL PUBLIC HEALTH CENTER, 2019

The **age group distribution of those that visited their doctor** (Table 7, Figure 16) is as follows: 29.9 percent of the patients was in the age group 0-14; 35.9 percent was in the age group 15-34; 25.1 percent was in the age group 35-59; and 9.1 percent was in the age group 60 and older.

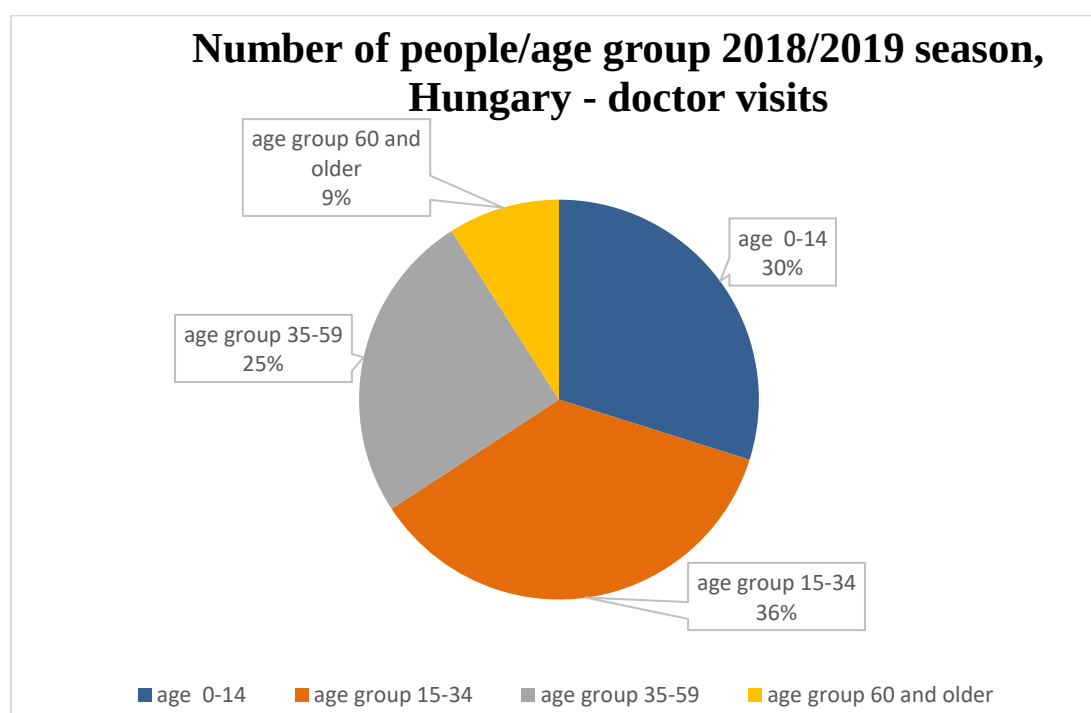


Figure 16. Number of people/age group visiting doctors with influenza-like symptoms in 2018/2019 season in Hungary

Source: NATIONAL PUBLIC HEALTH CENTER, 2019; OWN EDIT VAJO RESULTS, 2020

The figure above clearly shows how large an extent the age group under 14 became ill and how small an extent the age group 60 and older became ill. This is in sharp contrast with the figure showing distribution of vaccine recipients by age group.

Establishing comparative age groups

A serious disadvantage to the data presented in the previous figures is that although they can be interpreted on their own, they do not contain the values in identical age group distributions; therefore they cannot be compared with each other. In order to ensure comparability, identical age groups should be established on the basis of available data, which inevitably requires that data derived and calculated from the established age groups have to be shown.

Age groups established by the CSO: age group 0-14, age group 15-19, then ten-years groups (decades) afterwards.

Distribution of vaccination as per age group: age group 3-18, age group 19-59, age group 60-64, and 65 and older.

Morbidity data are available for age group 0-14, age group 15-34, age group 35-59, and age group 60 and older.

Comparable age groups from the above base age group data sources were selected (corresponding to all three data sources) so that the data for the given age group could be calculated as accurately as possible from the available data.

The exact data for the age group 60 and older can be determined from each data source without calculation, thus it was chosen to be one of the age groups.

The age group available for vaccination is between 19 and 59 years of age, the breakdown of which by calculations (establishing a new group) would have provided a great deal of uncertainty as to the end result. Consequently, this was selected as the second age group.

Hence, it follows that the next and smallest age group is the 0-18 age group. The vaccination data were factually available for all three age groups as established above, so no calculation or adjustment had to be performed in this respect.

However, it was required in terms of population per age group and morbidity per age group, in both cases by means of regrouping between the minors and the active. No adjustment was required for the age group 60 and older as the data were available in all three databases.

I resolved the age group adjustment with regard to the distribution of the population by considering the composition of the age group 15-19 (489,340 people) as equal then deducting

the portion for the age group 19 (one-fifth) from this value and taking it into account for the data of the age group 19-59. The value of this adjustment is 97,868 people.

In terms of morbidity, the age group to be broken down is the age group 15-34 (20 years). It means 177,688 illnesses. Assuming an evenly distributed morbidity, adjustment was required for four years (15-18 years of age). It makes up twenty percent of the total age group in this case as well, that is, 35,538 cases had to be withdrawn from the data of the age group 15-34, and adjusted the data of the age group 0-14 with this number.

As a result, three distinctive age groups were established: the group of minors (0-18 years of age), the economically active (19-59 years of age), and those 60 and older (mainly economically no longer active, inactive, or passive). These three age groups are clearly distinguishable by population, vaccination, and morbidity. At the same time, only a small amount of calculated data was generated, the error size of which can only be minimal.

Value data belonging to the established age groups and the correlations thereof.

Let us consider the adjusted values as for the established age groups (*Table 8*).

Table 8. Value data/age groups in Hungary, 2018

Age group	0-18	19-59	60 and older	Total
Population (people)	1 813 388	5 391 116	2 573 867	9 778 371
Vaccination (people)	20 125	187 566	510 705	718 396
Morbidity (people)	183 253	266 601	44 666	494 520
Distribution of population (%)	18.5	55.1	26.3	100.00
Distribution of vaccination (%)	2.8	26.1	71.1	100.00
Distribution of morbidity (%)	37.1	53.9	9.0	100.00

Source: OWN EDIT VAJO RESULTS, 2020

The age group of the minors makes up 18.5 percent of the population, those economically active mean 55.1 percent, and those 60 and older give 26.3 percent. (*Figure 17*)

These ratios are far from being matched by either the distribution of vaccination or the distribution of morbidity. 2.8 percent of all vaccination is made up by the minors, 26.1 percent are the economically active, and 71.1 percent are the retired. (*Figure 18*)

37.1 percent of the total morbidity occurred in the age group of minors, 53.9 percent in the economically active group, and 9.0 percent in the age group of 60 and older. (Figure 19)

The pie charts of the above ratios show strikingly different picture.

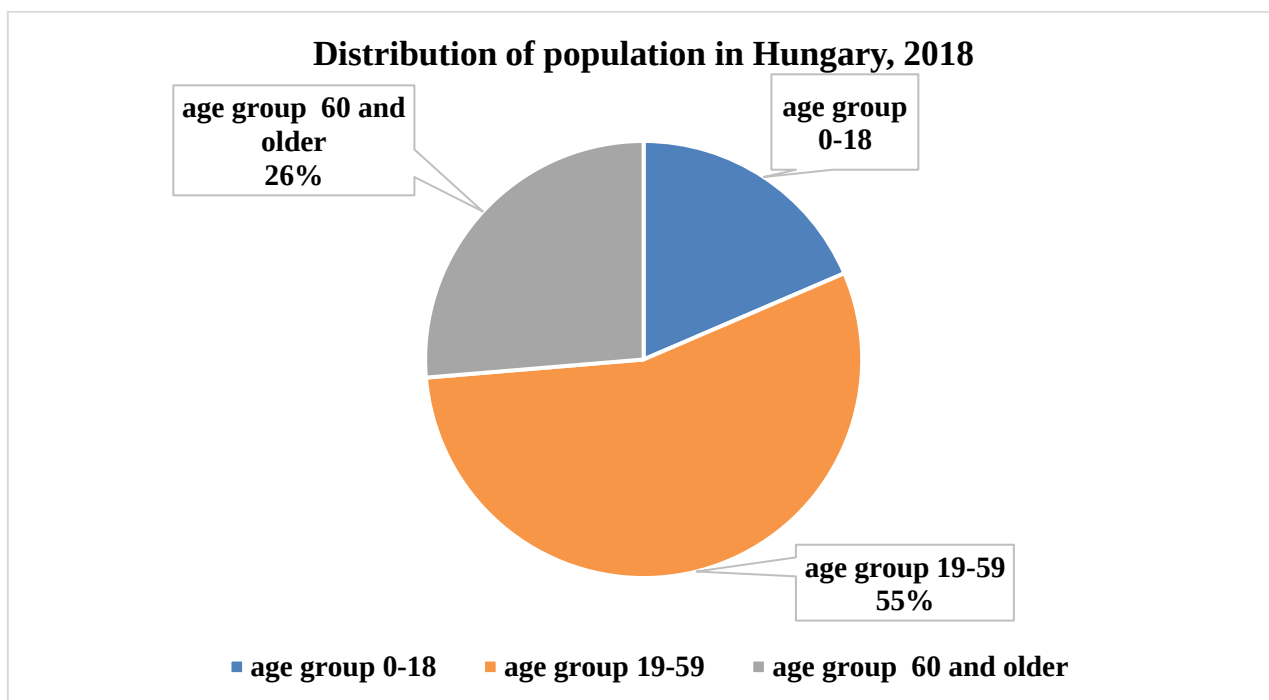


Figure 17. Distribution of population in Hungary, 2018

Source: OWN EDIT VAJO RESULTS, 2020

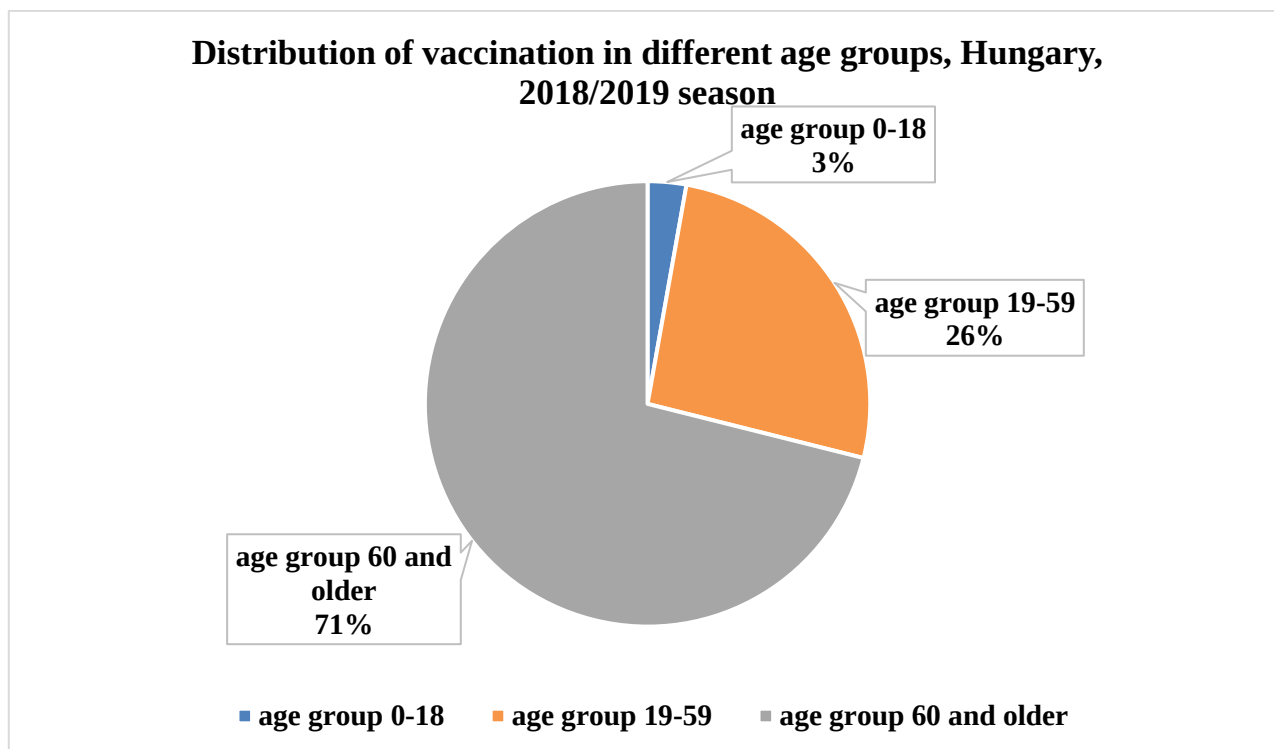


Figure 18. Distribution of vaccination in different age groups, Hungary, 2018/2019 season

Source: OWN EDIT VAJO RESULTS, 2020

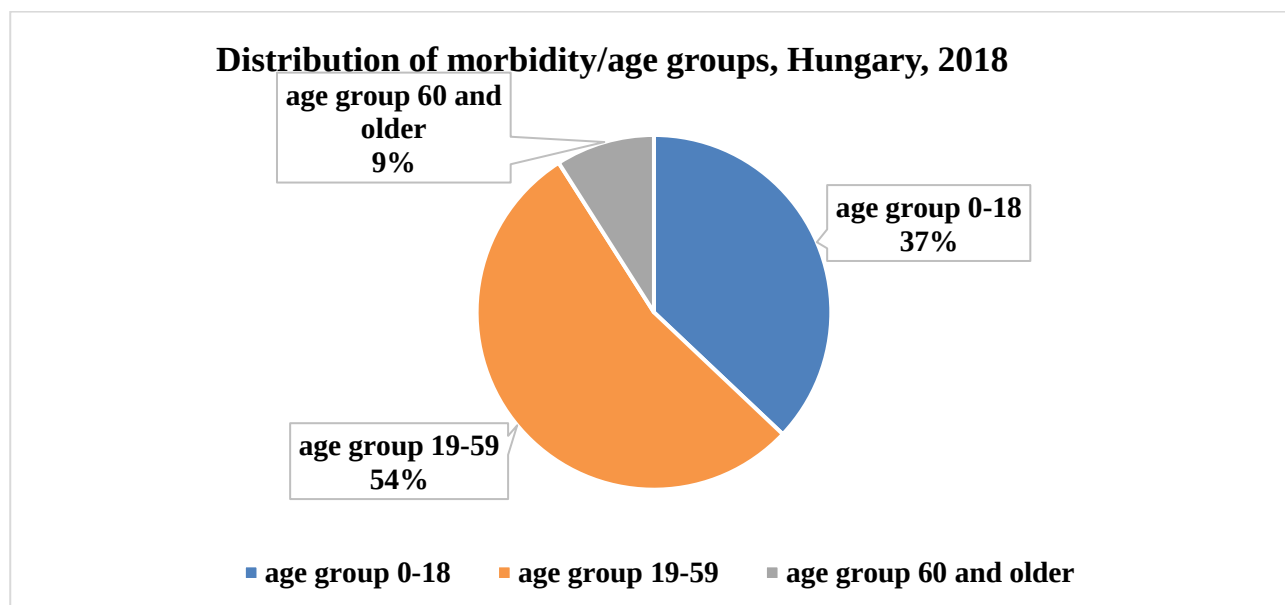


Figure 19. Distribution of morbidity/age groups, Hungary, 2018

Source: OWN EDIT VAJO RESULTS, 2020

Let us examine the ratios of vaccination and morbidity in the given age groups (*Table 9*).

Table 9. Vaccination and morbidity ratios/age groups in Hungary, 2018/2019 season

Age group	0-18	19-59	60 and older	Total
Vaccination (%)	1.1	3.5	19.8	7.3
Morbidity (%)	10.1	4.9	1.7	5.1

Source: OWN EDIT VAJO RESULTS, 2020

When interpreting these data, I can conclude the following:

Vaccination: 1.1% of the age group of minors, 3.5% of those economically active, and almost 20% of those 60 and older (19.8 percent) received vaccination.

As for morbidity data, 10.1 percent of the minors, 4.9 percent of the economically active, and only 1.7 percent of those 60 and older fell ill.

It can be seen that the direction of the vaccination rate and the morbidity data (compared to all members of this age group) is actually opposite.

A line chart of the data plainly shows the reverse direction. (Figure 20)

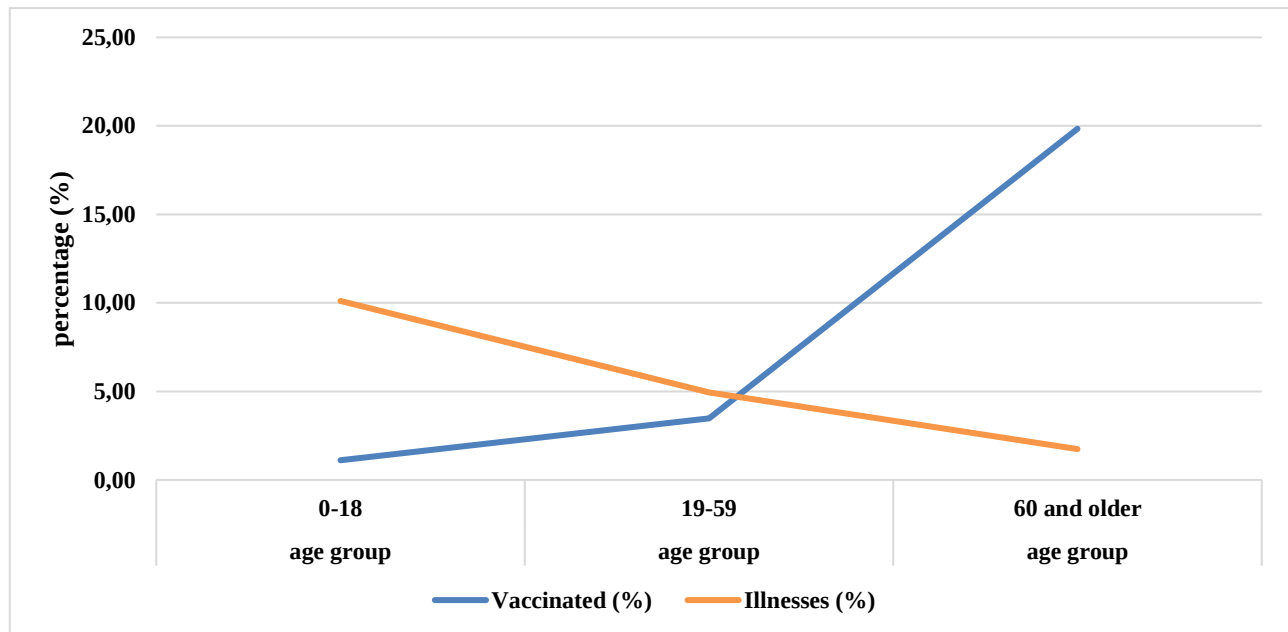


Figure 20. Vaccinated (%) and illnesses (%)/age group in Hungary, 2018/2019 season

Source: OWN EDIT VAJO RESULTS, 2020

When evaluating the numbers, we can say that 1.1 per cent of the minors were vaccinated, while more than 10 per cent (every tenth minor) became ill. Practically only one in ninety minors was vaccinated, yet one in ten fell ill.

As for the economically active, the vaccination rate is still below the proportion of the sick (3.5 percent and 4.9 percent, respectively). In this age group, every 29th person was vaccinated, but every twentieth became ill.

The most striking difference can be seen in the case of those 60 and older. Their vaccination rate is 19.8 percent, while morbidity is only 1.7 percent. Translated it into practical language it means that one in five people was vaccinated, resulting in only one in 58 people becoming ill.

Solely based on published professional views, I assumed that the effectiveness of vaccination is fifty percent. Now, however, based on the differences by age group, I can review the effectiveness on the basis of the facts or at least their magnitude.

Calculating effectiveness based on statistical data

Vaccination was very low in the minor's group with only 20,125 of 1,813,388 people being vaccinated.

At 100 percent effectiveness, all vaccinated persons – 20,125 – managed to avoid influenza, meaning they did not increase the morbidity data. The total morbidity in this age group is 183,253. Assuming that in the absence of vaccination, all those that received vaccination would have been infected by influenza then the number of incidents would have been $183,253 + 20,125 = 203,378$. Expressed as a percentage, the morbidity rate would have been 11.2 percent in this age group.

With zero vaccination effectiveness – that is, if vaccination has no effect on morbidity – the number of those that fell ill would have been identical with the number of those that actually developed influenza, that is, 183,253. It means that the morbidity rate in the age group of minors would have been between 10.1 and 11.2 percent regardless of vaccination.

If I examine the economically active and the 60 and older age groups, I will find that the age group of 60 and older shows similarity to the age group of minors based on their health status. Both age groups are at risk, the body of those in the elderly age group is already weakening, and the body of those belonging to the age group of the minors still needs to get stronger. Due to the different physical status of the active population, this age group shows the largest natural, successful immune response to the virus, the measurement and quantification of which would be far beyond the scope of this dissertation. Therefore, a comparison of the morbidity data of the minor age group with the morbidity data of the older age group provides a well-founded picture of the effectiveness of vaccination in contrast to the comparison of the data of the active age group.

Let us examine the age group of those 60 and older.

In the total Hungarian population, the number of people 60 and older (*Figure 21*) and the ratio of this age group to the total population between 2013 and 2017 (*Table 10*) developed as follows:

Table 10. Number and ratio of people 60 and older/years of 2013-2017, Hungary

Year	2013	2014	2015	2016	2017
Total population	9 908 798	9 877 365	9 855 571	9 830 485	9 797 561
60 and older (people)	2 364 420	2 411 429	2 472 802	2 521 684	2 559 600
Ratio of those 60 and older (%)	23.9	24.4	25.1	25.6	26.1

Source: CENTRAL STATISTICS OFFICE, 2013-2017; OWN EDIT VAJO RESULTS, 2020

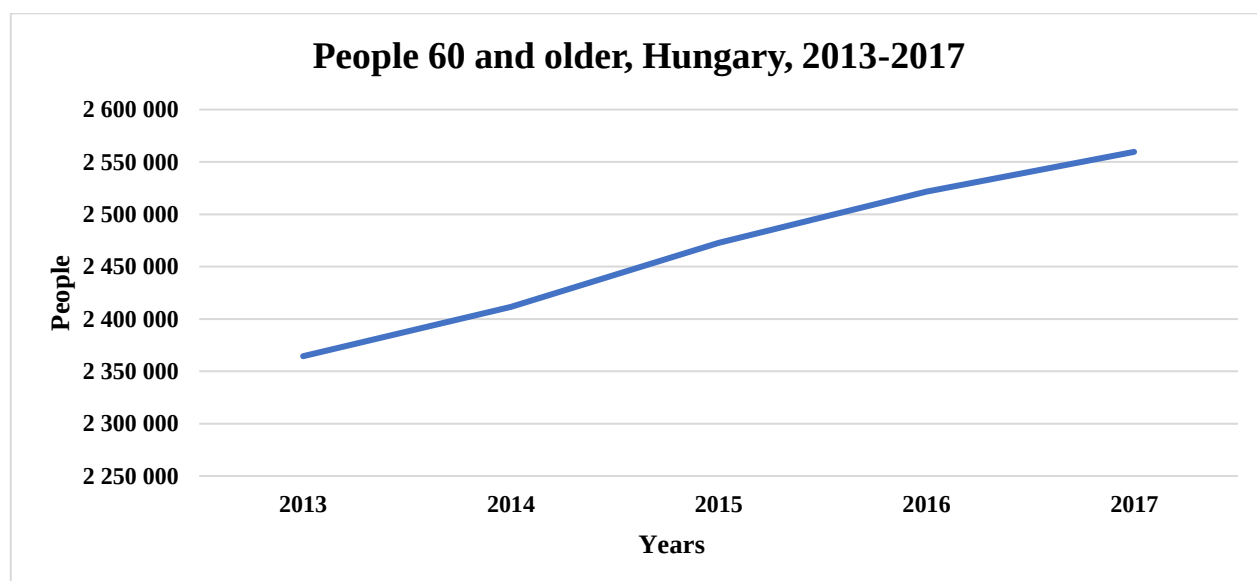


Figure 21. People 60 and older in Hungary, 2013-2017

Source: OWN EDIT VAJO RESULTS, 2020

It can be seen that the number of people 60 and older is steadily increasing year by year both in absolute and in relative terms (as the total population is decreasing at the same time). In four years the proportion of this age group increased by 2.3 percent.

One year later, in 2018, there were even more people (2,573,867) in the age group 60 and older. Based on their vaccine-independent morbidity rate of 10.1 to 11.2, the age group of minors should have had 260,218 and 288,788 incidents. In contrast, there were only 44,666 cases, which is 215,552 and 244,122 cases less than expected, which would have occurred if no vaccination had been applied.

This decrease in the number of cases occurred with 510,705 people 60 and older who were vaccinated. In other words, the vaccination of 510,705 people prevented influenza for 215,552 to 244,122 people. This justifies effectiveness between 42.2 and 47.8 percent based on calculated results. It matched the efficiency band approved of in the sector, i.e. it is considered a reliable result.

It is advisable that we use only one specific efficacy value herein based on the actual numbers for our calculations. I define this efficacy indicator on the basis of the methodology detailed below. The distinct subtasks of this methodology are defined as follows:

Task I: Defining the control group

The control group is the age group in which vaccination rate was low, so vaccination has an insignificant effect on morbidity. This is the group of minors where vaccination rate was the lowest (20,125 people, which is 1.11% of the total group). This age group was defined as the **control group**.

Task II: Defining the target group

The target group is the age group in which vaccination rate was high, consequently, vaccination has a significant impact on morbidity. This is the group of people over 60, where vaccination coverage was the highest (510,705 people, 19.84%). This age group was defined as the **target group**.

Task III: Efficacy calculation

With the help of efficacy calculation, I projected the morbidity of the control group onto the target group, then I compared the thus calculated value with the actual target group data. The difference between the calculated and the actual values show the number of non-occurred cases. Comparing this case number to all vaccinees in the target group, I get the vaccination efficacy indicator.

Steps of efficacy calculation in detail:

Step 1: I add up the actual total morbidity numbers of the control group and the number of avoided cases calculated from the number of vaccinees in the control group and the vaccination efficacy. I adjusted the number of vaccinees in the control group considering the actual vaccine efficacy, since in the lack of vaccination, there would have been cases in the control group with low vaccination rate. The adjustment is equal to the value of efficacy (multiplying the number of vaccinees by efficacy gives the number of avoided diseases).

Step 2: I divide the total number of cases in the control group calculated according to step 1 by the total number of the control group, which results in the calculated morbidity rate in the control group.

Step 3: I project the morbidity rate of the control group calculated according to step 2 to the total number of the target group, which shows how many cases would have occurred in the target group provided they had not been vaccinated at all.

Step 4: I subtract the actual number of cases in the target group from the morbidity number in the target group calculated without vaccination (calculated in step 3) to obtain the number of non-occurred cases in the target group.

Step 5: I divide the number of non-occurred (avoided) cases in the target group (see the previous point) by the number of actual vaccinees in the target group, so I get vaccine efficacy.

If I define the previous steps of efficacy calculation as a general mathematical model, I get the following equation:

$$E = \frac{\left(\frac{C_{ac} + (C_v * E)}{C_{tot}} * T_{tot} \right) - T_s}{T_v}$$

where:

E = Vaccine efficacy

C_{ac} = Number of actual cases in the control group

C_v = Number of vaccinees (vaccinees) in the control group

C_{tot} = Total number of control group

T_{tot} = Total number of target group

T_s = Number of actual diseases in the target group

T_v = Number of vaccinated of the target group

The control group is the group of minors, and the target group is the group of people over 60.

Currently, we have the unknown E on both sides of the equation, so the equation needs to be sorted.

I can derive the E-value from the formula as follows:

$$E * T_v = \left(\frac{C_{ac} + (C_v * E)}{C_{tot}} * T_{tot} \right) - T_s$$

$$(E * T_v) + T_s = \frac{C_{ac} + (C_v * E)}{C_{tot}} * T_{tot}$$

$$\frac{(E * T_v) + T_s}{T_{tot}} = \frac{C_{ac} + (T_v * E)}{C_{tot}}$$

$$\frac{(E * T_v) + T_s}{T_{tot}} * C_{tot} = C_{ac} + (C_v * E)$$

$$\frac{(E * T_v) + T_s}{T_{tot}} * C_{tot} - (T_v * H) = C_{ac}$$

$$(((E * t_v) + T_s) * C_{tot}) - (T_{tot} * T_v * E) = T_{tot} * C_{ac}$$

$$(E * T_v * C_{tot}) + (T_s * C_{tot}) - (T_{tot} * T_v * E) = T_{tot} * C_{ac}$$

$$(E * T_v * C_{tot}) - (E * T_{tot} * T_v) = (T_{tot} * C_{ac}) - (T_s * C_{tot})$$

$$E * ((T_v * C_{tot}) - (T_{tot} * T_v)) = (T_{tot} * C_{ac}) - (T_s * C_{tot})$$

$$E = \frac{(T_{tot} * C_{ac}) - (T_s * C_{tot})}{(T_v * C_{tot}) - (T_{tot} * T_v)}$$

Substituting the known value:

$$E = \frac{(2,573,867 * 183,253) - (44,666 * 1,813,388)}{(510,705 * 1,813,388) + (2,573,867 * 20,125)}$$

After performing the necessary mathematical calculations, I get the E-value, which is 44.68%; i.e., the vaccine efficacy is 44.68% based on statistics.

Substituting the specific numbers in the above model I get:

$$0.4468 = \frac{\left(\frac{183,253 + (20,125 * 0.4468)}{1,813,388} * 2,573,867 \right) - 44,666}{510,705}$$

The calculation steps show the following partial results:

- 1.) I add up the total actual illnesses in the group of minors (C_{ac} 183,253 people) and the number of cases in the vaccinated minors' group which cases would have occurred in the absence of vaccination, taking into account vaccine efficacy. Since vaccination efficiency is 44.68% as per the previous calculation, the number of avoided cases per the vaccinated people ($C_v = 20,125$ people) is $20,125 * 0,4468 = 8,992$.
- 2.) I divide the former value ($C_{ac} + C_v = 183,253 + 8,992 = 192,245$) by the total number of minors (C_{tot} : 1,813,388) to obtain the calculated morbidity rate for the minor group (10.60142%).
- 3.) I project the calculated morbidity rate of the minors (10.60142%) onto the target group, that is, the total number of people over the age of 60 (T_{tot} , 2,573,867 persons), so I get how many cases would have occurred if this age group is not vaccinated at all (272,866 people).
- 4.) From the number of cases in the age group of those over 60 without vaccination (272,866 people), I subtract the actual number of cases (T_s , 44,666 people) to obtain the number of non-occurred cases in the elderly group (228,200 people).
- 5.) I divide the number of non-occurred (avoided) cases in the elderly group (228,200 people) by the number of people actually vaccinated in the elderly group (T_v , 510,705 people), so I get the vaccine efficacy (44.68%).

The calculated value of efficacy can be used to determine the number of avoided cases as per age groups (vaccination * efficacy = number of non-occurring cases).

Accordingly, 8,992 cases were avoided in the age group of minors. Thus, in the absence of vaccination, there would have been $183,253 + 8,992 = 192,245$ cases in this age group, which would have resulted in a morbidity rate of 10.6014 percent of the total number of people in this age group. Projecting this morbidity rate for the elderly, there are 272,866 calculated cases compared to the 44,666 cases that actually occurred, which means 228,200 cases avoided. The latter age group results in effectiveness of 44.68 percent relative to the total number of those vaccinated which is thus supported and justified by adequate facts.

With the known effectiveness, the number of avoided cases can now be determined precisely for the active age group as well. 187,566 vaccines were administered in this age group. Considering the 44.68 percent effectiveness calculated above, the number of avoided cases is $187,566 * 0.4448 = 83,804$ cases.

In summary, the number of non-occurred cases of influenza illness achieved by means of vaccination (*3FLUART suspension for injection, seasonal influenza vaccine*) at the vaccination level in the influenza season of 2018/2019 is as follows (*Table 11, Figure 22*):

Table 11. Number of non-occurred cases of influenza/age groups in 2018/2019 season in Hungary

In the age group of minors	In the age group of active people	In the age group of the elderly (60+)	Total
8,992 cases	83,804 cases	228,200 cases	320,996 cases

Source: OWN EDIT VAJO RESULTS, 2020

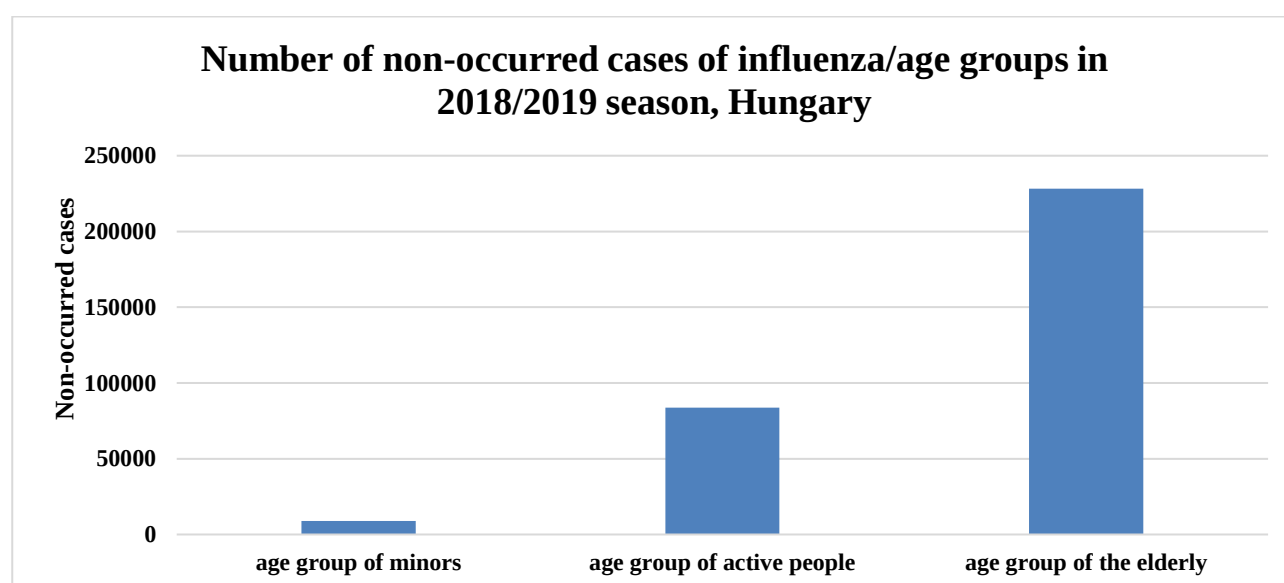


Figure 22. Number of non-occurred cases of influenza/age groups in 2018/2019 season in Hungary

Source: OWN EDIT VAJO RESULTS, 2020

4.2. Impact on the national economy

4.2.1. Avoided cases in the active and passive groups

In the previous chapter, on the basis of calculated data I managed to quantify how many non-occurred cases can be expected in the entire population, including minors, the active and the elderly. In the following, I would like to quantify the impact of these non-occurred cases on the national economy in Hungary.

To this end, I “start” into two directions. I first examine the economic benefits experienced in the age group of the active then I examine the age groups of the “passive” (minors and the elderly).

First of all, however, certain adjustments are needed. Since retirement age in Hungary is currently 65 years of age, and my age group is 60 and older, it is necessary to increase the age group of the active at the expense of the passive in terms of influenza cases that did not occur.

I take the distribution of those vaccinated by age group as help. In the elderly age group (60 and older), 510,705 people were vaccinated, of which the number in the 60-64 age group was 64,013, which corresponds to 12.534 percent. The calculated value of non-occurred cases among those 60 and older is 228,200; based on the former ratio it means 28,603 non-occurring cases in the age group of 60-64. That is, if I take the people between 18 and 64 years of age to be the active age group, the number of non-occurred cases is 83,804 previously calculated for the age group of 19-59 plus the relevant 28,603 cases from the age group of the elderly, i.e. a total of 112,407 cases.

Out of the 228,200 cases calculated for the elderly, 28,603 cases less i.e. 199,597 non-occurred cases are given for the age group of 65 and older. Thus, the total number of cases for the passive age group (the previous number plus the number of non-occurred cases in the minors age group) is $199,597 + 8,992 = 208,589$ cases.

To sum it up: the number of non-occurred cases (*Table 12*):

Table 12. Number and distribution of non-occurred cases by age groups, Hungary, 2018/2019 season

In the active age group	In the passive age group	Total
112,407 cases	208,589 cases	320,996 cases

Source: OWN EDIT VAJO RESULTS, 2020

The distribution shown in a pie chart is as follows (*Figure 23*):

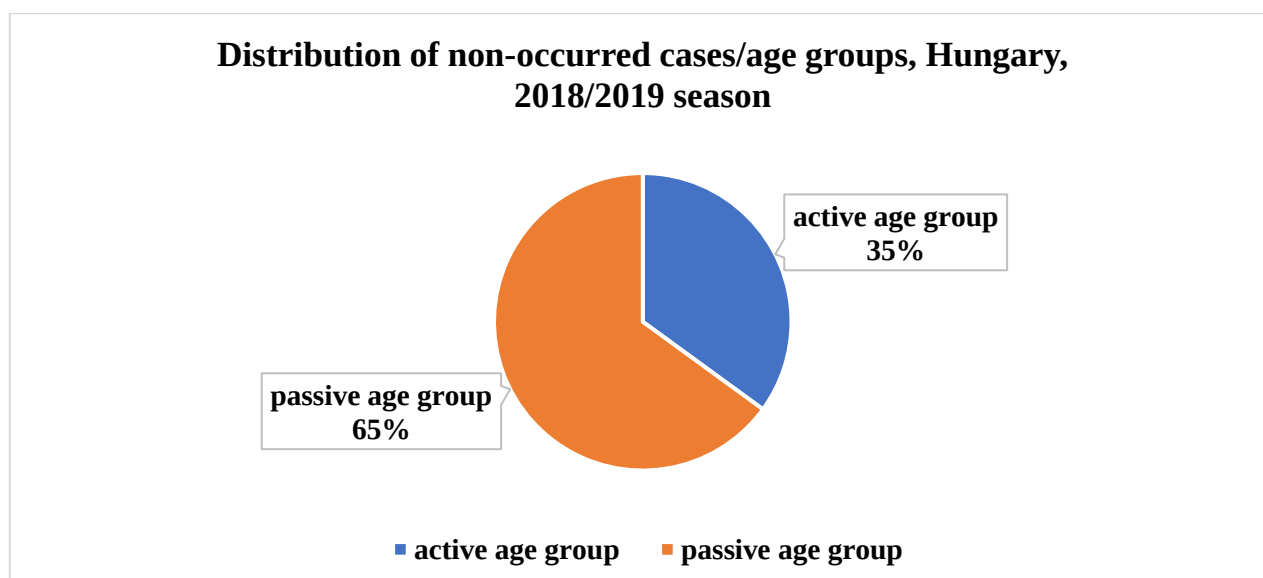


Figure 23. Distribution of non-occurred cases/age groups, Hungary, 2018/2019 season

Source: OWN EDIT VAJO RESULTS, 2020

After I managed to define the avoided diseases by age group, I am going to look at the expected course, duration and consequences of the disease.

4.2.2. Presentation of US data and comparison of US and Hungarian data

On September 27, 2018, the U.S. Centers for Disease Control and Prevention (CDC), the National Infectious Diseases Foundation (NFID), and other public health and medical groups held a joint press conference to launch the influenza vaccination campaign of 2018-2019 (CDC, 2018). Based on CDC data, the National Press Club of Washington (DCC) claims that more than 900,000 people were hospitalized and more than 80,000 people died of influenza during the exceptionally severe influenza season of 2017-2018 (which was one of the longest in recent years) in the US. These data highlight the severity of influenza and strongly draw attention to the hazards of influenza as well as the importance of vaccination. The burden influenza poses on the United States varies greatly depending on a number of factors, similar like in other countries. It is influenced by the characteristics of the spreading viruses, the timing of the season, the effectiveness of the vaccination, and the degree of vaccination. Although the impact of influenza varies, it also places a significant burden (even) on the health of people living in the United States each year.

Table 13. Data on symptoms, medical visits, hospital cases in numbers and proportion, USA, 2010-2019

Influenza season	Symptoms (M of people)	Medical visits (M of people)	Hospitalization (K of people)	Hospital cases (%)
2010-2011	21.0	10.0	290	2.9
2011-2012	9.3	4.3	140	3.3
2012-2013	34.0	16.0	570	3.6
2013-2014	30.0	13.0	350	2.7
2014-2015	30.0	14.0	590	4.2
2015-2016	24.0	11.0	280	2.5
2016-2017	29.0	14.0	500	3.6
2017-2018	45.0	21.0	810	3.9
2018-2019	35.5	16.5	491	3.0
Average	28.6	13.3	446.8	3.36

M – million, K - thousand

Source: CDC (Centers for Disease Control and Prevention, USA), 2010-2019

The CDC estimates that influenza has resulted in 9 million to 45 million illnesses, 140,000 to 810,000 hospitalizations, and 12,000 to 61,000 deaths annually in the United States since 2010, with an average of five to twenty percent of the population having influenza each year.

Influenza generates an estimated 31.4 million outpatients and more than 200,000 hospitalizations each year. The CDC website provides data on influenza cases, disease symptoms, medical visits, and hospital cases over the past nine years, as follows (*Table 13*) (CDC, 2019a).

The following bar graph (*Figure 24*) illustrates the annual change in the number of medical visits, hospital cases and the proportion of the latter:

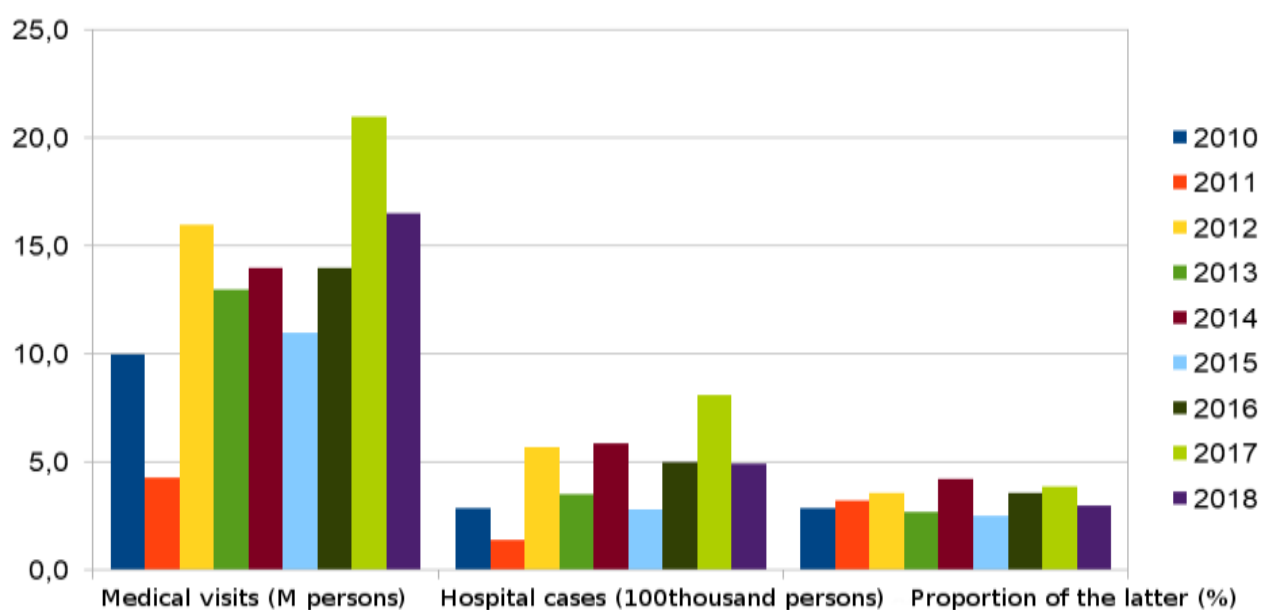


Figure 24. Medical visits, hospital cases and the proportion of the latter, USA, 2010-2018

Source: CDC (Centers for Disease Control and Prevention, USA), 2010-2019; OWN EDIT VAJO RESULTS, 2020

As of the end of October 2018, 185 child deaths were also reported to the CDC in the season of 2017-2018. Approximately 80% of these deaths occurred in children who had not received vaccination against influenza.

The U.S. population was 327.2 million in 2018. Based on the above CDC data, the ratio of medical visits is $13.3 \text{ million} / 327.2 \text{ million} = 4.1 \text{ percent}$. In Hungary, the proportion of those seeking medical treatment for influenza-like illnesses was $494,520 / 9,778,371 \text{ (total population)} = 5.1 \text{ percent}$.

The reason for the difference is that vaccination rate is higher in the USA, and – as it was demonstrated in the case of Hungarian data – the number of influenza-like illnesses decreases with the increasing rate of vaccination.

According to the CDC, the only best way to control influenza is by means of annual vaccination. Vaccination is recommended for people over six months of age. The influenza vaccine is available as an injection or nasal spray making it easily accessible to everyone.

No comparison based on the onset of symptoms can be done as there is no available estimate thereof in Hungary.

Nevertheless, the number of hospital cases relative to the number of doctor visits can be established. This number was between 2.5 and 4.2 percent in the past nine flu seasons. **Its average value is 3.36 percent.**

Expenditure

Influenza is estimated to cost USD 10.4 billion a year in medical expenses and an additional USD 16,300,000,000 a year in missed profits in the United States.

In addition, influenza results in approximately 17 million workday losses costing about USD 7 billion a year in sick-days and burdening productivity.

According to a report by the Challenger, Grey and Christmas Employment Consulting, employers' losses were over USD 21 billion due to lost productivity from employees due to the 2017-2018 influenza. In addition, an estimated 25 million employees were ill, while the average amount of wages lost due to missing replacements was USD 855.68 (Colleen Madden, 2018).

The 2018 report estimates that the average annual total burden of seasonal influenza on the U.S. healthcare system and society was USD 11.2 billion. Direct medical costs are estimated at USD 3.2 billion and indirect costs at USD 8 billion.

It was justified that US data are reliable and their comparison with the Hungarian data produces data of the same magnitude.

Accordingly, the extent of hospitalization in Hungary can also be estimated, i.e. how many of the patients need hospital care.

The average extent of hospitalization in the US was 3.36 percent compared to the number of doctor visits.

In Hungary, 494,520 people visited their doctor with influenza-like illnesses during the influenza season of 2018-2019. Projecting the US data to this figure, 16,616 hospitalizations were required in the whole period of the influenza season. Taking a 32-week flu season as a starting point, it means 520 patients per week nationwide (not evenly distributed). This value is by all means acceptable in terms of magnitude, which also confirms the correctness of the methodology.

Based on the calculated rate of hospitalization and the number of avoided illnesses I can now make a conclusion on the number of avoided hospitalizations (*Table 14*). It is as follows:

Table 14. Number of avoided cases and number of avoided hospitalization/age groups in 2018/2019 season, Hungary

Age group	Number of avoided cases	Number of avoided hospitalization
Active population	112 407	3 777
Passive population	208 589	7 009
Total	320 996	10 785

Source: OWN EDIT VAJO RESULTS, 2020

There are no reliable data on the duration of hospital care either, but I estimate that its duration – given the fact that hospital care is typically required due to complications – is an average of two weeks in any age group of the population.

4.2.3. Cost of hospital care per day

According to the data of the Central Statistics Office, the health expenditures of hospitals and nursing institutions amounted to HUF 906.5 million in 2016. The total number of days of care nationwide was 18,202,389 days. From the quotient of these two numbers, it can be stated that the health care expenditure per one day of care is HUF 49,801.

4.3. Economic impact

When having the flu, it is unfortunate to continue your work without treatment. On the one hand, flu patients' performance is characterized by inferior and less concentrated quality due to malaise, headache, and muscle ache, and on the other hand they can also infect their colleagues, which can multiply damage. In addition, a sick adult can spread the disease to their children and elderly parents (the same applies to sick children). A vaccinated adult does not contract the flu and does not infect anyone and can also avoid heavy costs of the treatment.

4.3.1. Economic impact on the active population group

As for the active population group, the economic impact can be measured in the number of lost working hours, which causes a loss of income for employees and additional costs for employers. In my model, I assume that employers are prepared to replace lost employees by involving new ones and by requiring extra working hours from existing employees in the case of seasonal influenza pandemic.

My calculation refers to the savings that can be derived from the number of non-occurred diseases i.e., it seeks to demonstrate the economic benefits that result from vaccination.

Unrealized loss of income for employees

As previously reported, 112,407 cases were avoided in the active age group thanks to influenza vaccination.

Assuming an average of one week of recovery period, the lost working time would be 112,407 weeks. An additional week per person for 3,777 people admitted to hospital, i.e. 3,777 weeks is added to it. This results in a total of 116,184 weeks of “non-lost” working time.

Assuming a five-day working week and an eight-hour working day, 116,184 weeks will result in savings of 580,920 working days and 4,647,360 working hours.

In December 2018, the average national gross earnings of full-time employees – in enterprises with at least five employees, budgetary institutions, and non-profit organizations observed by the CSO – were HUF 360,000, excluding public employees it was HUF 371,700 (KSH, 2019).

Calculated with a gross monthly average wage of HUF 360,000 including public employees, and monthly working hours of 172, the average hourly wage is HUF 2,093.

In terms of savings of 4,647,360 working hours, this represents a total gross earning of HUF 9,727 million for employees who “did not lose” these gross earnings.

If the employees had actually received a sick pay, they would have been entitled to sixty percent of this amount, i.e., HUF 5,836 billion. The profit of the employees was HUF 3,891 billion.

Savings for employers

One third of the previously calculated sick pay (HUF 5,836 billion) should be paid by employers. Avoided diseases thus save employers HUF 1,945 billion.

An additional saving for employers is that they do not have to pay overtime to replacement employees. The general rate for overtime is 50 percent. If 25% of the lost working hours can be replaced only by means of overtime, the payable extra overtime burden is:

$$9.727 \text{ billion} * 0.25 * 0.5 = \text{HUF } 1.216 \text{ billion}$$

The total savings at employers is: HUF 3,161 billion.

Budget savings

Sick pay not reimbursed by the employers is payable by the social security fund, which would be HUF 3,891 billion.

The number of patients in the active age group who are likely to not be hospitalized due to illnesses that did not occur because of vaccinations was 3,777. The healthcare expenditure per day of care is HUF 49,801. No distribution of this between the fixed and variable costs is available, but I estimate their ratio to be fifty to fifty percent. The 3,777 patients spend an average of two weeks in inpatient care. This is a total of 7,554 weeks, or a total of 52,878 days of care.

The variable cost per day of care is HUF 24,900. The quantifiable savings for those who avoid hospitalization are HUF 1,317 billion.

The total budget savings are HUF 5,208 billion.

Overall, it is apparent that gross earnings for the entire duration of non-occurred illnesses appear as an economic benefit. One-third of sixty percent of the total budget savings is the sick pay that the employer did not have to pay, the remaining two-thirds are unpaid benefits from social security funds, and forty percent of the total budget savings is the additional income for the employee. An additional economic benefit for employers is that they do not incur additional expenses for overtime due to lost working hours, and the budget is not burdened by the cost of hospital care.

The total economic benefits of influenza vaccination in the “active” population group are HUF 12,260 billion.

4.3.2. Economic impact on the passive population group

At first sight, one might think that no economic advantage is generated for the employers due to the absence of influenza-like illness. This is actually not true since in the case of minors one of the parents have to stay home from work anyhow during the one-week recovery period, which has the same consequences as for the active population.

The economic benefits of 8,992 illnesses among the minors:

The non-missed working time was 8,992 weeks. No further interruption is assumed for any possible hospital cases, as the parents do not have to stay home from work if their child is hospitalized.

Assuming a five-day workweek and an eight-hour working day, the above 8,992 weeks result in savings of 44,960 working days and 359,680 working hours.

Calculated with an already justified average monthly gross wage of HUF 360,000 and an average hourly wage of HUF 2,093, this saves a total of HUF 753 million – for the savings of 359,680 working hours – in gross earnings for employees who “did not lose” these gross earnings.

The difference between the possible sick pay and the non-lost earnings is HUF 301 million.

Savings for employers

One third of the previously calculated sick pay (HUF 452 million) is payable by the employers. Avoided diseases thus save HUF 151 million for employers.

The amount of savings per overtime: HUF 94 million.

The total savings for employers is HUF 245 million.

Budget savings

Sick pay not reimbursed by the employers is payable by the social security fund, which would be HUF 301 million.

The number of patients in the passive age group who are likely to not be hospitalized due to illnesses that did not occur as a result of vaccinations was 7,009, who spend an average of two weeks in inpatient care. This is a total of 14,018 weeks, or a total of 98,126 days of care.

The variable cost per day of care is HUF 24,900. The quantifiable savings for those in the passive group who avoid hospitalization are HUF 2,443 billion.

The total budget savings are HUF 2,744 billion.

The total economic benefits of influenza vaccination in the “passive” population group are HUF 3,290 billion.

Summary

The basic data and the results of the calculations derived above are summarized in the table below (*Table 15*).

Table 15. Economic benefit in case of actual vaccination strategy

Core data	Avoided	Hospitalization	One day of	Total	Total	Total	One hour of wage
	morbidity	number	healthcare day	lost time	lost time	lost time	
	number	cases	expenses				
	(people)	(people)	(HUF)	(weeks)	(workdays)	(hours)	(HUF)
Active population: 19-64 years of age	112 407	3 777	49 801	116 184	580 920	4 647 360	2 093
Passive population:							
0-18 years of age (lost time calculated for parents)	8 992			8 992	44 960	359 680	2 093
65 years and older	199 597						
Passive population total	208 589	7 009	49 801	8 992	44 960	359 680	
Total (active + passive)	320 996						

		Active	Passive	Total
	Economic impact	population	population	
1.	Income calculated for lost working time (billion HUF)	9.727	0.753	10.480
	Broken down into:			
	a) employee's loss 40% (billion HUF)	3.891	.301	4.192
	b) sick pay 60 % (billion HUF)	5.836	.452	6.288
	sick pay financed by:			
	ba) government budget 2/3 (billion HUF)	3.891	0.301	4.192
	bb) employer's budget 1/3 (billion HUF)	1.945	0.151	2.096
2.	Overtime imposed on employer (billion HUF)	1.216	0.094	1.310
3.	Hospitalization costs (billion HUF)	1.317	2.443	3.760
	Total (1+2+3)	12.260	3.290	15.550
	From which			
	Budget savings of government (1.ba+3.)	5.208	2.744	7.952
	Budget savings of employer (1.bb+2.)	3.161	0.245	3.406
	Employee's non lost income (1.a)	3.891	0.301	4.192
	Total (1+2+3)	12.260	3.290	15.550

Summarizing the above, it can be stated that the effectiveness of the vaccination (disease-preventing property) has an economic advantage of HUF 15,550 billion (fifteen billion five hundred and fifty million HUF) for the national economy, as a whole (*Figure 25*).

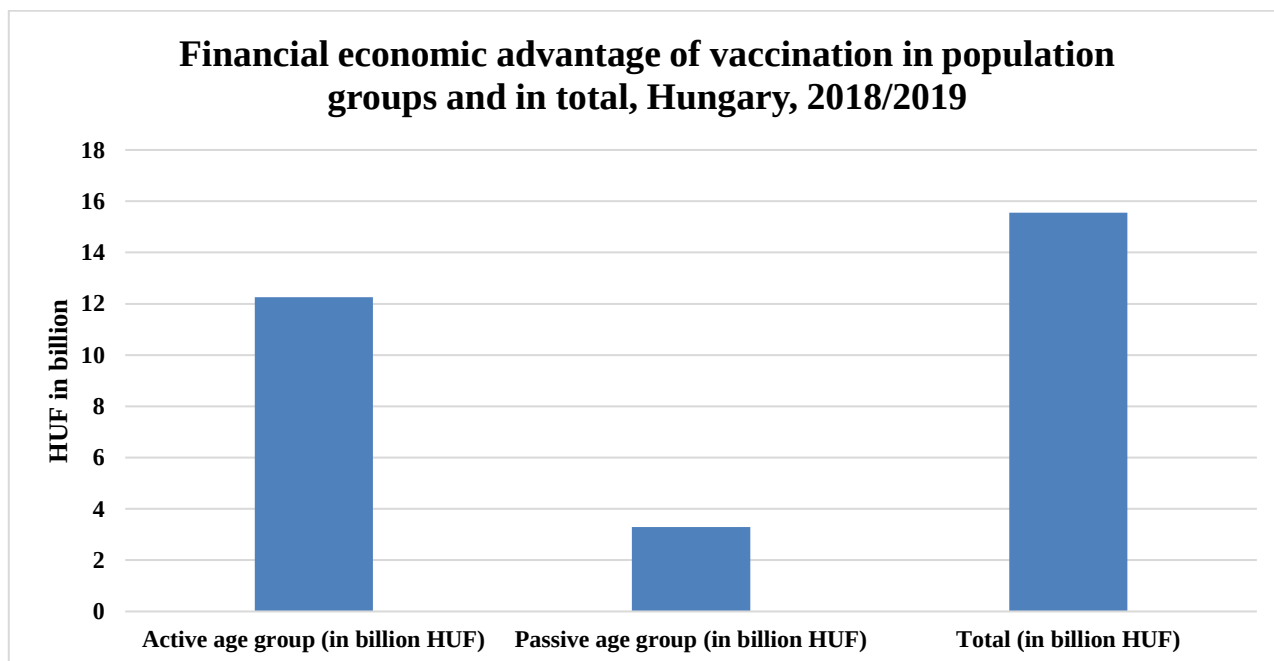


Figure 25. Financial economic advantage of vaccination in population groups and in total, Hungary, 2018/2019

Source: OWN EDIT VAJO RESULTS, 2020

The value of GDP (gross domestic product) in Hungary in 2018 was HUF 42,661,805 million, i.e. slightly rounded to HUF 42,662 billion. The economic benefit of influenza vaccination relative to GDP is 0.4 parts per thousand. This seems to be a minimal impact, yet it is of great importance in practice, as it was the first time that the positive impact of a vaccine on the economy has been quantified with mathematical equations based on specific statistics.

Recommended vaccination strategy

1. Major features of the recommended vaccination strategy

At the beginning of my study, I hypothesized that different vaccination strategies elicit different economic impacts. I pointed out that vaccination rates and morbidity rates vary in the different age groups of the population. I concluded that increased vaccination rates are followed by decreasing morbidity rates, which conclusion is supported by statistical data. I assumed that in terms of economic impact identical vaccination rates in the active age group and the age group of those over 65 would bring higher economic benefits.

One of the vaccination strategies presented herein is the currently applied strategy that focuses on the vaccination of the elderly. The other strategy, which I recommend, would provide a vaccination rate that is identical in the case of the active age group, the age group of those under 18, and the elderly. I define the economic benefits of the latter vaccination strategy herein by means of the same methodology as for the first vaccination strategy. Finally, I compare and analyze the results.

2. The cost of vaccination

When examining the economic impact, I consider vaccination costs only to the extent it is justified by the direct costs of higher vaccination rates.

As a consequence, the cost of vaccine availability is a fixed cost up to the quantity of the supplied vaccine, thus changes in vaccination rates affect this cost factor to the extent by which the vaccination rate exceeds the supplied vaccine quantity.

Vaccination cost remains unaffected by the cost of administering the vaccine, since the healthcare system in Hungary is functional anyway. Therefore, the staff required to administer the vaccine is always available and means no additional costs.

Based on the above, I consider the vaccination cost as a variable cost in my study only to the extent I mentioned above, and only with regard to the recommended vaccination strategy. I define the economic impact of influenza vaccination based on the number of cases avoided as a result of vaccination.

It is evident that while previously the economic benefit gained as a result of vaccination was HUF 15,550 billion, this economic benefit increased to 23,948 billion due to the higher vaccination rate. However, I previously pointed out that the cost of vaccination can only be considered a fixed cost up to the quantity supplied by the Hungarian manufacturer, and beyond that it is a variable cost.

3. The extent of the recommended vaccination

Previous chapters of my study detailed the statistical data that formed the basis for my calculations. Since I currently use the same statistical data as a starting point, I do not present the numbers in tables and graphs in this chapter. I present the calculation itself as well as the result.

There were 2,573,867 people in the age group of over 60 in 2018, out of whom 510,705 people, or 19.84 percent, were vaccinated.

If vaccination rate was the same in the age groups of both the minor and those active, the number of vaccinated minors would be $1,813,388 * 0.1984 = 359,776$. However, in real, the number of those vaccinated was 20,125. In the recommended model, the increase in the number of those vaccinated is 339,651.

The morbidity rate in the minor age group was 10.11 percent, therefore, vaccinating an additional 339,651 people would help avoid 34,339 illnesses. The number of incidents in this age group was actually 183,253, which would be reduced to 148,914 according to the recommended model. The number of avoided illnesses in the age group of minors increases from 8,992 to 43,331.

According to the same methodology, the number of those vaccinated as for the active age group is $5,391,116 * 0.1984 = 1,069,597$. In reality, the number of people vaccinated was 187,566. The increase in the number of those vaccinated is proposed to be 882,031.

The morbidity rate in the active age group was 4.95 percent, therefore vaccinating an additional 882,031 people would prevent 43,661 illnesses. The number of occurrences in this age group was actually 266,601, which would be reduced to 222,940 according to the proposed model. The number of avoided diseases in the active age group increases from 83,804 to 127,465.

The incident numbers do not change in the age group of those over 60, as we recommend projecting their vaccination rate to the age group of minors and the active. Accordingly, the correction between the age group of 19-64 and of those over 65 did not change.

4. Savings in case of the proposed vaccination strategy

Adding the increase in the number of avoided diseases compared to the previous values to the number of occurrences in the age group of minors and the active, then performing the calculation according to the previous methodology, we get the quantified economic impact with regard to the new data.

The outcome is summarized in the following table (*Table 16*).

Table 16. Economic benefit in case of recommended vaccination strategy

Core data	Avoided	Hospitalization	One day of	Total	Total	Total	One
	morbidity	number	healthcare expenses	lost time	lost time	lost time	hour of
	number	cases					wage
	(people)	(people)	(HUF)	(weeks)	(workdays)	(hours)	(HUF)
Active population: 19-64 years of age	156 068	5 244	49 801	161 312	806 560	6 452 480	2 093
Passive population:							
0-18 years of age (lost time calculated for parents)	43 331			43 331	216 655	1 733 240	2 093
65 years and older	199 597						
Passive population total	242 928	8 162	49 801	43 331	216 655	1 733 240	
Total	398 996						

		Active	Passive	Total
	Economic impact	age group	age group	
1.	Income calculated for lost working time (billion HUF)	13.505	3.628	17.133
	Broken down into:			
	a) employee's loss 40% (billion HUF)	5.402	1.451	6.853
	b) sick pay 60 % (billion HUF)	8.103	2.177	10.280
	sick pay financed by:			
	ba) government budget 2/3 (billion HUF)	5.402	1.451	6.853
	bb) employer's budget 1/3 (billion HUF)	2.701	0.726	3.427
2.	Overtime imposed on employer (billion HUF)	1.688	0.453	2.142
3.	Hospitalization costs (billion HUF)	1.828	2.845	4.674
	Total (1+2+3)	17.021	6.927	23.948
	from which			
	budget savings of government (1.ba+3.)	7.230	4.297	11.527
	budget savings of employer (1.bb+2.)	4.389	1.179	5.568
	employee's non lost income (1.a)	5.402	1.451	6.853
	Total (1+2+3)	17.021	6.927	23.948

It is evident that while previously the economic benefit gained because of vaccination was HUF 15,550 billion, this economic benefit increased to 23,948 billion due to the higher vaccination rate. However, I previously pointed out that the cost of vaccination can only be considered a fixed cost up to the quantity supplied by the Hungarian manufacturer, and beyond that it is a variable cost.

Publicly available data show that 1.3 million doses of vaccine is produced and supplied on an annual basis. During the influenza season of 2018/2019, 718,396 vaccines were administered, which means that only 55 percent of the available doses was used, and 45 percent was leftover. However, the recommended vaccination strategy suggests an even higher vaccination rate, with 359,776 in the case of minors, 1,069,597 in the active age group, and 510,705 in the age group of those over 60, which add up for a total of 1,940,078 people. This number exceeds the currently available annual dose number by 640,078 vaccines.

The manufacturing cost of the vaccine is not known; however, its range can be defined indirectly. A public supplement to its annual report of 2018, the vaccine manufacturer, the Fluart Innovative Vaccines Kft., shows that the net income generated from vaccine sales was HUF 1,512,501 thousand. Dividing the annual number of doses, that is 1,300,000 by this amount, we get HUF 1,164 / piece, which is the transfer price of the vaccine.

Multiplying this transfer price by the missing 640,078 pieces in the vaccination strategy recommendation, we get an additional HUF 745 million budget expenditure, which deteriorates the calculated positive economic impact. As a result, the calculated economic benefit of HUF 23,948 billion decreases to HUF 23,203 billion.

4.4. Summary of the impact on the national economy

The summary of economic benefits achievable by the two different vaccination strategies described above is shown in graph form below (*Figure 26*).

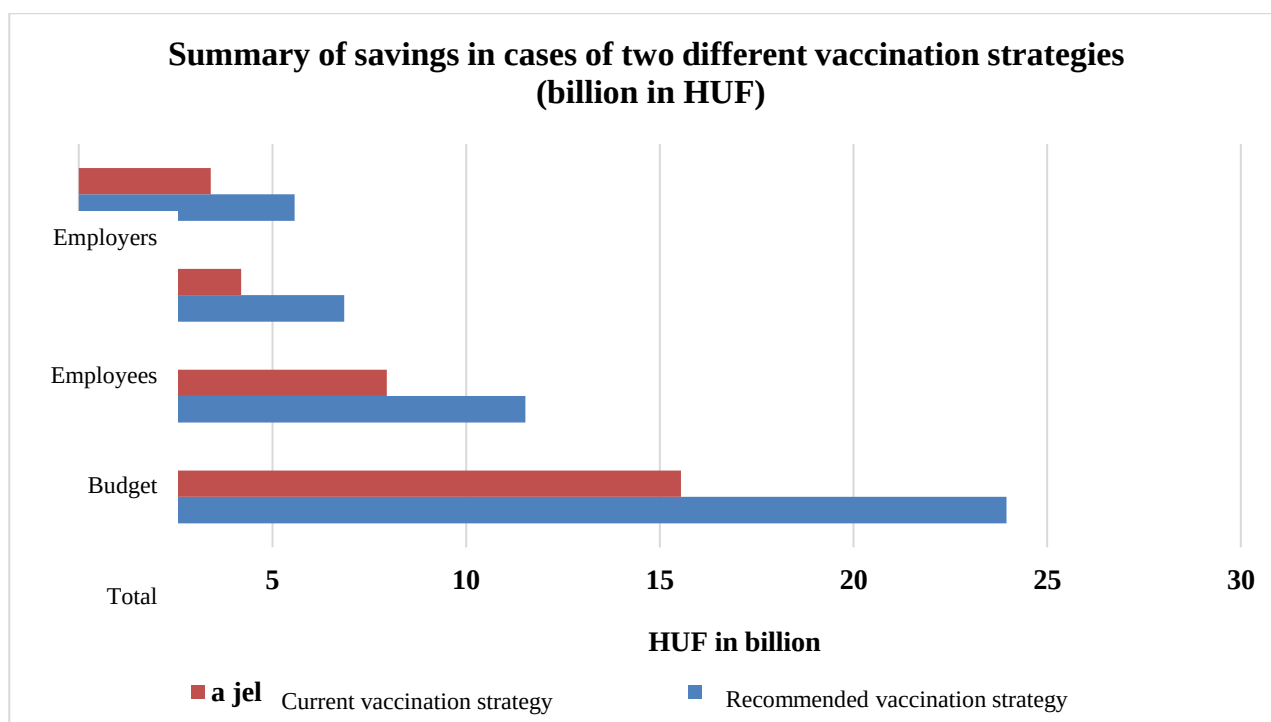


Figure 26: Summary of savings in cases of two different vaccination strategies (billion HUF)

Source: OWN EDIT VAJO, 2021

As a result of the higher vaccination rate, the economic impact calculated on the basis of the number of avoided cases consequently exceeds the savings achieved by means of the actual vaccination strategy by HUF 7.7 billion. This value also explains that the financial and social resources devoted to prevention can generate specific economic benefits in addition to the positive impact on life-quality.

4.5. QALY calculation

4.5.1. Calculating QALY based on the current vaccination strategy

A QALY (*Quality-Adjusted Life Years*) is a universal measure of health gains, which enables the comparison of different diseases and healthcare technologies. (AEEK, 2021)

It summarizes in a single indicator the changes of life-expectancy (mortality) and quality of life (morbidity).

When calculating QALY, life years gain is adjusted for qualitative weights, where 1 indicates ultimate health and 0 indicates death. Quality weights on the 0-1 interval scale reflect the preferences of people with relevant health conditions.

QALY is mostly used to compare the effectiveness and usefulness of different healing procedures.

In my study, I examined incidents occurring due to influenza and influenza-like illnesses and determined the incidents avoided thanks to influenza vaccination. Based on this as well as on the course of the disease, I could draw conclusions about the number of sick days avoided. Thus, data that help quantify QALY are practically available.

I concluded that in the age group of the economically active, a total of 116,184 weeks were saved because of vaccination, which virtually coincides the number of sick weeks (in a normal case the average course of the disease takes one week, plus an additional week in case of hospitalization).

In the passive age group, the number of sick days can be calculated based on the number of illnesses avoided, which does not correspond to the total time off work (since we examine the group of the economically passive). We assumed 208,589 avoided cases in this age group, and we assumed it probable that 7,009 persons out of these cases would have been hospitalized if they had fallen ill. This resulted in a “saving” of a total of 215,598 sick weeks.

In relation to the total population, the number of weeks avoided but otherwise would have been spent in illness due to the lack of vaccination was 331,782 weeks. Taking a year of 52 weeks, this period corresponds to 6,380 years.

Another measure that determines the value of QALY is quality weight, the value of which can be between 0 (death) and 1 (total health). Unfortunately, no data on the general health of the Hungarian population for the values 0 to 1 are available. However, as an international comparison, an article was published in *Vaccine*, 37th issue, on January 7, 2019, which analyzes the improvement of health in general because of vaccination (Leidner et al., 2019).

The article analyzes the cost-effectiveness of the immunization of the adult population based on articles. The writers of the article read and analyzed 1,688 references in literature. 140 articles out of the 1,688 dealt entirely with the cost-effectiveness of vaccination, including 48 articles that covered the cost-effectiveness of influenza vaccination. The contents of these publications were analyzed and summarized to draw conclusions about the extent to which vaccination improved life-quality as expressed in the QALY scale. The specific QALY values in each study were defined as a value of 0.5.

The QALY value of vaccination for life-quality cannot be determined more precisely in the context of this study. I assume that this value is close to 1 in the active age group, whereas it is somewhere below 1 in the age group of those over 65. It is not possible to state how far it is from the value of the active age group, but I assume that this value is over 0.5.

I assume that this quality value is reduced by 0.5 due to influenza and influenza-like illnesses, which corresponds to the above-mentioned literature. This value shifts the life-quality of certain individuals to poor and very poor conditions compared to the different baseline conditions that otherwise exist. I consider the 0.5 value for reduction to be justified based on the course of the disease.

Thus, both values required for QALY calculation are now available as well as the duration of the disease avoided and the qualitative weight. Accordingly, the QALY value is $6,380 * 0.5 = 3,190$ years.

It can be stated that the impact of influenza vaccination on the life-quality of the entire Hungarian population is 3,190 years on an annual basis: this is the number of years in total that can be saved in health by avoiding influenza.

4.5.2. Calculating QALY based on the recommended vaccination strategy

In an earlier part of my study, I quantified that the number of illnesses avoided would be much higher provided the active age group and the age group of under 18 were to receive the same rate of influenza vaccinations as the age group of the elderly. As a result, the number of quality life years measured in QALY would also increase. The extent is worth some consideration.

In the age group of the economically active, the recommended vaccination strategy would save a total of 161,312 weeks off work, which equals the number of sick weeks according to the calculation method used in the current vaccination strategy.

In the passive age group, the number of diseases avoided is 242,928 in the case of the recommended vaccination strategy, which means 8,162 cases of hospitalization. The two values together would add up to avoid 251,090 sick weeks in this age group.

Applying the recommended vaccination strategy, the total number of weeks avoided (but that would have been spent in disease due to the lack of vaccination) in the general population was 412,402 weeks, which corresponds to 7,930 years when taking years of 52 weeks.

Adjusting the QALY value by the quality weight that indicates the reduction of life quality, the QALY value is $7,930 * 0.5 = 3,965$ years.

For the current and recommended vaccination strategy, the difference between the calculated QALY values is 775 years. In other words, an additional 775 quality, healthy life years could be saved for the entire Hungarian population on a yearly basis provided the vaccination rate for age groups other than those over sixty were identical.

4.6. ICER calculation

ICER is the acronym for incremental cost-effectiveness ratio, which is used in full-scale economic analyses regardless of whether health benefits are measured in a clinical trial or a naturalistic study, or whether health benefits are expressed in natural units or quality years.

The cost-benefit ratio shows the cost increase per health benefit unit.

The assessment is based on a quotient, the incremental cost-effectiveness ratio (ICER), where the increase in cost and efficiency is compared to a benchmark, such as the cost-effectiveness rate of an already funded healthcare technology. $ICER = D \text{ cost} / D \text{ effectiveness}$ (D is the difference between the old and the new strategy in terms of both costs and results).

In our case, ICER means the following:

$$ICER = \frac{(C_n - C_o)}{(QALY_n - QALY_o)}$$

where

$C_n - C_o$ is the costs of the new and the old vaccination strategy

$QALY_n - QALY_o$ is the number of quality years gained as a result of the two different vaccination strategies.

I calculated and presented both values in former sections of my study. There is an additional cost of HUF 745 million between the old and the new vaccination strategy, and the number of years gained is 775 years. The ICER value is the quotient of these two numbers, i.e., HUF 961 thousand / QALY.

The outcome shows that we got extra health gains for the extra cost paid. This is usually characteristic of new health technologies / therapies.

In some developed countries, cost-effectiveness thresholds are set before approving healthcare technologies.

The below table summarizes these values based on the available data (in case of a range we indicated the lower value) (*Table 17*) (INOTAI ANDRÁS, 2009).

Table 17. Cost - effectiveness thresholds in some developed countries

Country	Currency	Threshold	Exchange rate	Threshold value
		foreign currency	2021.06.30	thousand HUF
Great-Britain	GBP	20 000	409,57	8 191
Australia	A\$	42 000	222,03	9 325
Netherlands	EUR	80 000	351,90	28 152
New Zealand	NZ\$	20 000	206,61	4 132
Sweden	SEK	500 000	34,76	17 380
USA	USD	100 000	296,04	29 604
Canada	C\$	20 000	238,40	4 768
Western Europe	EUR	44 000	351,90	15 484
WHO recommendation		1-3 x GDP/capita		
Hungary according to WHO recommendation	USD	16 470	296,04	4 876

Source: (INOTAI ANDRÁS, 2009); OWN EDIT VAJO, 2021

By converting the threshold value expressed foreign currency into Hungarian Forint, we obtain comparable data. Based on this, we can establish that the cost-effectiveness threshold ranges from 4 to 30 million ICER values in different countries. According to the WHO recommendation, the benchmark is GDP/capital times 1-3. GDP per capita in Hungary in 2019 was USD 16,470 / capita, which converted to Forint was HUF 4,876 thousand. It means that the recommended threshold in Hungary ranges from HUF 5 to 15 million. (IMF, 2020)

The ICER value we obtained does not reach HUF 1 million so it can be confidently stated that the need to introduce a new vaccination strategy is justified internationally, too.

In addition to the above the economic benefit generated by the extra vaccination is several times higher than the costs of implementation of the new vaccination strategy. Therefore the

balance is positive in terms of economical benefits, over the general improvement of people's health.

5. CONCLUSIONS, RECOMMENDATIONS

Conclusions

The goal I set in my dissertation has had no precedent either in the Hungarian literature: my intention was to present the impact of influenza vaccination on the economy and the national gross product.

My hypothesis was that greater emphasis should be placed on vaccinating the active (19-60 years of age), as well as the children and adolescent (3-18 years of age) population groups, while maintaining the supply of free vaccines to the age group of 60 and older that current Hungarian regulations define as one of the most vulnerable groups.

I managed to prove that the same level of vaccination coverage amongst children and adolescents and active population groups would lead to much greater economic benefits compared to the current vaccination strategy surplus.

The primary aim of my dissertation was to present the economic impact of the actual vaccination strategy which is focusing on the vaccination of 60 and older population group. After identifying the outcomes of the primary aim the next goal of my dissertation was to present the economic impact in case of a new suggested vaccination strategy, assuming that the same vaccination coverage would be applied in population groups of active (19-60 years of age) and children and adolescents (3-18 years of age) as in the elderly age group. I managed to justify this hypothesis with figures and facts.

For the specific calculation, I took data from the Central Statistical Office and the Influenza Surveillance System of the Epidemiology and Infection Control Department of the National Public Health Center as basic data, and I used international comparative data to determine the final result for factors with no available national data.

Based on the available basic data, I also had to make estimates during the calculation; I always carefully considered the circumstances and set the most accurate end-result as a purpose. One of the most important calculations was to find out how many cases of the disease were avoided through vaccination. There have been no former attempts in this regard so my dissertation can be considered innovative in this area.

I evaluated data from the influenza season of 2018/2019 in my dissertation. I analyzed the available data on population, vaccination and the number of diseases, and drew conclusions therefrom. It was a problem that the basic data appeared in different data sets for different age groups, so I had to find a consensus between them, and establish comparable age groups. Ultimately, I defined three distinct age groups: the age group of minors (0-18 years), the economically active (19-59 years) and the age group of 60 and older. These three age groups became well distinguishable by population, vaccination, and morbidity.

During the study period (2018/2019 influenza season), 1.1 percent of the minor age group, 3.5 percent of the economically active age group, and almost twenty percent (19.8%) of those 60 and older received influenza vaccinations. In terms of morbidity data, 10.11 per cent of the age group of minors, 4.95 per cent of the economically active age group, and only 1.74 per cent of those over the age of 60 became ill. It is evident that compared to all members of this age group, the rate of vaccination and the number of cases are strongly opposite.

The detailed data described the preventive effect and the effectiveness of vaccines. My calculation made on the basis of facts resulted in vaccine effectiveness of 44.68 percent compared to the fifty percent estimated by scientific literature.

The effectiveness value calculated on the basis of real data helped define the number of illnesses that did not occur due to vaccination: it is 8,992 cases in the minor age group, 83,804 cases in the active age group and 228,200 cases in the elderly age group, i.e. a total of 320,996 non-occurred illnesses.

Since there are no reliable national and processed data on the further history of patients visiting their doctor with flu-like symptoms, I applied international data in my work. The CDC report reflects data on influenza morbidity, the symptoms of the disease, medical visits, and the number of hospital cases over the past nine years. Based on the published data, the number of doctor visits and the number of subsequent hospitalizations could also be determined.

Based on the rate of hospitalization in the United States and the number of illnesses avoided in Hungary, I could draw conclusions on the number of hospital care that could be avoided in Hungary. This represents 3,777 hospital cases avoided in the active population group and 7,009 in the passive population group.

Based on the data of the CSO, the total health expenditure of hospitals and healthcare institutions as well as all days of care can be determined. From the quotient of these two numbers it can be stated that the health care expenditure per day of care is HUF 49,801.

When examining the impact on the gross national product, I calculated the loss of income for employees and the savings for employers and the budget. Overall, it can be concluded that gross earnings for the entire duration of non-occurred diseases appear as an economic benefit.

To summarize the results of my dissertation, it can be stated that the disease-preventing property of influenza vaccination has a total economic benefit of HUF 15,550 billion (fifteen billion five hundred and fifty million HUF) for the national economy. The value of GDP (gross domestic product) in Hungary in 2018 was HUF 42,661,805 million. The economic benefit of influenza vaccination in case of the present vaccination strategy as a share of the GDP is 0.4 parts per thousand.

Results might be achieved in case of the suggested vaccination strategy: the suggested vaccination strategy generates plus economic benefit both in active and passive population groups. The results clearly show that more than three-quarters of all economic benefits are generated in the active population group, although they only account for only one-third of non-occurred diseases. Consequently, higher degree of vaccination in the active population is strongly justified as the resulting economic benefit is cumulative in their case.

During calculations the same methodology was used for the suggested strategy as in case of the present one and it resulted almost 24 billion HUF. It means that the suggested vaccination strategy ensures more than 50% economic benefit compared to the current vaccination strategy. The economic benefit of influenza vaccination in case of the suggested vaccination strategy as a share of the GDP is 0.6 parts per thousand.

Recommendations

The data listed above on the disease caused by the influenza virus, the course and frequency of influenza infections, and the specific characteristics of influenza virus clearly accentuate the extreme hazards of the influenza virus and the disease it causes, the high level of national and global health risks due to the regularity of seasonal epidemics and pandemics, as well as the paramount importance of protection against the virus.

Since there are currently no widely used traditional drugs that could be used effectively against the influenza virus, the most effective way to control the virus and the disease is by means of vaccination.

The production and use of influenza virus vaccines produced by vaccine manufacturers using different technologies is therefore of strategic importance for all countries and the world's population.

Therefore, all nations and all vaccine manufacturers must make every effort to ensure that the vaccines they manufacture are the most effective in protecting against viral infection, regardless of the manufacturing technology or the composition.

It is necessary to extend the scope of vaccinations in order to prevent severe consequences that could easily become unpredictable. Vaccination should cover not only people in the hazard age groups and those already suffering from other diseases but also minors (they typically socialize in large “groups” where they can spread the virus effectively) and those in the active age group. The anti-vaccination sentiments typical of our age need to be addressed assertively. Vaccine acceptance can make a major contribution to mitigating the devastating consequences of a severe pandemic predicted by the WHO.

What are the possibilities of increasing vaccine acceptance?

WHO lists vaccine hesitancy among the 10 most dangerous global health threats in its study published in 2019. The importance of this problem is emphasized by many publications and studies available. Vaccination is referred to as one of the most important achievements of public health, yet there have always been certain groups (e.g., religious, political, scientific) that question its significance for some reason. Another problem is that information (and false information) is shared quickly in versatile communication channels, which might undermine confidence in vaccines or strengthen sentiments against immunization. There are several different reasons for vaccination hesitancy, the mapping of which is the first step toward increasing vaccine propensity and to persuading hesitant members of the population by effective means. (WHO, 2019a), (Larson et al., 2014), (MacDonald, 2015), (Schmid et al., 2017)

Literature data reveal that active participation by healthcare professionals and doctors in supporting vaccination, answering questions that arise, and providing information is essential.

According to a study conducted in Hungary, training and actively involving pharmacists in the recommendation of vaccinations would also contribute to increasing vaccine propensity not only in at-risk groups but also in the active adult population. (Yeung et al., 2016)

There should be campaigns to increase vaccine propensity so that professionals can share information and knowledge to hesitant people to build confidence and reinforce the importance of vaccination. In addition to explaining the patient information leaflet, they should also provide an overview of the vaccination procedure itself as well as its background.

The below list contains some but not all methods taken from literature that help increase vaccine propensity:

- Continuous training for healthcare professionals, doctors, and pharmacists
- Briefing, brochures and posters to GPs
- Informing parents
- More information on vaccines, the importance of vaccines, the influenza virus, and the disease, shared on social media (internet, tv, radio)
- Influencing perceptions of the effectiveness, safety, and adverse events of vaccines; consultation
- Free vaccination
- Sending reminders (phone, email)
- Easily accessible vaccines (designated vaccination points, simple and quick procedure without waiting times) (Yeung et al., 2016), (Brewer et al., 2017), (Twiddy, 2017)

6. MAIN FINDINGS OF THE DISSERTATION AND THE NEW AND NOVEL RESULTS THEREOF

Main Findings

While examining in my study the number of vaccines administered and number of influenza-like illnesses I have divided the total population of Hungary into three age groups: the age group of minors (0-18 years), the age group of economically active (19-59 years) and the age group of elderly (60 years and older).

From statistical data I have stated that in the 2018/2019 influenza season almost 20% of the age group of 60 years and older have been vaccinated with seasonal influenza vaccine, while the ratio of the illnesses in the same age group was only 1.7%.

The level of vaccination was the lowest in case of minors (1.1%), while at the same time the number of illnesses was the highest (10.1%). With the help of statistical data I managed to demonstrate, that there is an inverse relationship between the level of vaccination and the number of influenza-like illnesses, which leads to a conclusion that in case the level of vaccination is increased the number of illnesses is decreasing.

With comparison of data on illnesses of the least vaccinated group of minors against the highly vaccinated age group of 60 years and older I have determined the effectiveness of the vaccine against seasonal influenza through a mathematical calculation. The value I have reached is 44.68% which is in correlation with the efficacy data to be found in different sources of the scientific literature.

Based on this efficacy value I have made an estimation on the number of non-occurred illness cases avoided due to the vaccination. As a result of this estimation I have concluded that in 2018/2019 influenza season there were a total of 321,000d non-occurred influenza-like illness cases in Hungary.

By the age-group distribution of the above number of avoided cases I have quantified the economic benefit in billion HUF gained due to the non-occurrence of the illnesses. I have concluded that the vaccination triggered savings i.e., economic benefit in magnitude was 15,550 billion in terms of the Hungarian national economy. This savings value represents as a share of the GDP 0.4 parts per thousand.

In the next part of my study I have made a proposal on a new vaccination strategy where the focus should not be solely on the vaccination of the elderly but there is a need for increasing the level of vaccination of the whole population to the level of vaccination coverage of the age group of 60 years and older. In case of this suggested new vaccination strategy I have used the same methodology for calculations and I have concluded that with the implementation of a new vaccination strategy there would be further 78,000 cases avoided.

The positive impact on the national economy calculated with the higher number of avoided cases (taking into consideration the costs of the extra vaccination, as well) is 7,7 billion HUF higher compared to the benefits achievable by the current vaccination strategy, in figures 23,2 billion HUF. The share of the GDP has raised with 0.2 parts per thousand.

As a next part of my study I have determined the number of the Quality-adjusted Life Years (QALY) both in cases of the present and recommended vaccination strategies. In case of the present vaccination strategy it was 3,190 years while in case of the recommended one it turned out as 3.965 years, therefore the extra years of life value in case of the recommended vaccination strategy represents 775 years.

In the closing part of my study I have calculated the incremental cost-effectiveness ratio (ICER), as well, which represents 961,000 HUF/life years in Hungary. I have made a comparison of this value to the figures of some developed countries and with the WHO recommendation. I have concluded that the above Hungarian ICER data is below these threshold values and recommendation therefore it is justified that the newly suggested vaccination strategy is worth to be implemented both from the perspective of healthcare and economic aspects.

New and novel results

- Until now there were only medical-professional data available regarding the efficacy of vaccines against influenza. In my study I managed to prove the effectiveness of influenza vaccine on the basis of statistical data for the first time.
- On the basis of quantified efficacy the first time estimation has been made on the number of avoided cases due to the vaccination.
- Also, this was the first estimation on impact of the vaccination on national economy.

- Furthermore, there was the first quantification of Quality-adjusted Life Years (QALY) gained by the vaccination.
- Finally, the value of cost-increase necessary to reach one unit of health gains in course of protection against influenza was demonstrated for the first time in Hungary.

SUMMARY

I believe that my dissertation examining the impact of vaccination on economic performance is innovative as for both its approach and methodology. It does not match any type of health economics analysis (cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis), yet it is closest to cost-utility analysis. However, the methodology of the latter is not yet fully sophisticated, and there is little experience with it in Hungary. I hope my study can fit into the line of cost-utility analyses and serve as a basis for future economic analyses that go deeper than my dissertation.

In my dissertation I could prove my initial hypothesis that – in addition to maintaining the supply of free vaccines to the age group 60 and older being one of the vulnerable groups defined in the current regulations for influenza vaccinations – more emphasis should be placed on increasing vaccination in the active (18-60 years) and the pediatric and minors age groups (3-18 years).

The presented facts, numbers, the results of the calculations, and the conclusions drawn clearly show the preventive effect and effectiveness of vaccination, which was quantified for the first time in Hungarian literature. The economic benefit of influenza vaccination in case of present vaccination strategy as a percentage of GDP is 0.4 parts per thousand, while in case of the recommended vaccination strategy is as a percentage of GDP is 0.6 parts per thousand. These values might seem only mathematically small, but in reality it is quite significant.

Nevertheless, for the first time, the positive impact of a vaccine on the economy has been quantified on the basis of specific statistics.

In addition to the new viruses that are emerging today, the old enemy, the flu, is still the greatest threat. Even a one-year seasonal flu epidemic kills half a million people every year around the world. Drug researchers are working on a general influenza vaccine that would be able to catch the virus at the genetic level, making it much more effective than vaccines currently available on the market. Although many formulations are in the clinical trial phase, none of them offer fully universal protection. WHO experts believe that the most devastating disease with the most widespread consequences in the world could be a severe influenza pandemic.

It is necessary to extend the scope of vaccinations in order to prevent severe consequences that could easily become unpredictable. Even the CDC and EMA agrees that the only and best way to fight influenza is by means of annual vaccination. Vaccination should cover not only people in the hazard age groups and those already suffering from other diseases but also minors (they typically socialize in large “groups” where they can spread the virus effectively) and those in the active age group. The anti-vaccination sentiments typical of our age need to be addressed assertively. Vaccine acceptance can make a major contribution to mitigating the devastating consequences of a severe pandemic predicted by the WHO.

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LIST OF FIGURES

Figure 1.: Influenza virus properties, challenges and addressing them

Figure 2: Number of patients out of 100,000 people visiting medical doctors with influenza-like illnesses and number of influenza-positive samples in Hungary between week 40 of 2018 and week 20 of 2019

Figure 3: Number of patients out of 100,000 people visiting medical doctors with influenza-like illnesses and number of influenza-positive samples in Hungary between week 40 of 2016 and week 20 of 2017

Figure 4: Number of patients out of 100,000 people visiting medical doctors with influenza-like illnesses and number of influenza-positive samples in Hungary between week 40 of 2015 and week 20 of 2016

Figure 5: Number of patients out of 100,000 people visiting medical doctors with influenza-like illnesses and number of influenza-positive samples in Hungary between week 40 of 2014 and week 20 of 2015

Figure 6: Number of patients out of 100,000 people visiting medical doctors with influenza-like illnesses and number of influenza-positive samples in Hungary between week 40 of 2013 and week 20 of 2014

Figure 7: Number of patients out of 100,000 people visiting medical doctors with influenza-like illnesses and number of influenza-positive samples in Hungary between week 40 of 2012 and week 20 of 2013

Figure 8: Number of patients out of 100,000 people visiting medical doctors with influenza-like illnesses and number of influenza-positive samples in Hungary between week 40 of 2011 and week 20 of 2012

Figure 9.: Influenza-related morbidity in Hungary between 2013-2017

Figure 10.: Total mortality (number of people) in Hungary 2013-2017

Figure 11.: Population of Hungary between 2013-2017

Figure 12.: Number of influenza vaccines administered in Hungary between 2013-2017

Figure 13.: Influenza-related morbidity (k) between 2013 and 2017 in Hungary

Figure 14.: Number of people/age group vaccinated in 2018/2019 season in Hungary

Figure 15. Number of people/age group in 2019, Hungary

Figure 16. Number of people/age group visiting doctors with influenza-like symptoms in 2018/2019 season in Hungary

Figure 17. Distribution of population in Hungary, 2018

Figure 18. Distribution of vaccination in different age groups, Hungary, 2018/2019 season

Figure 19. Distribution of morbidity/age groups, Hungary, 2018

Figure 20. Vaccinated (%) and illnesses (%)/age group in Hungary, 2018/2019 season

Figure 21. People 60 and older in Hungary, 2013-2017

Figure 22. Number of non-occurred cases of influenza/age groups in 2018/2019 season in Hungary

Figure 23. Distribution of non-occurred cases/age groups, Hungary, 2018/2019 season

Figure 24. Medical visits, hospital cases and the proportion of the latter, USA, 2010-2018

Figure 25. Financial economic advantage of vaccination in population groups and in total, Hungary, 2018/2019

Figure 26. Summary of savings in cases of two different vaccination strategies (billion HUF)

LIST OF TABLES

Table 1.: Influenza incidence and prevalence data in Hungary, 2011-2019

Table 2.: Influenza vaccination (%)/year in Hungary between 2013-2017

Table 3.: Influenza-related morbidity rate (%)/year in Hungary between 2013-2017

Table 4.: People/age group vaccinated in 2018/2019 season in Hungary

Table 5.: Number of people/age group in 2019, Hungary

Table 6. Number of influenza-like illnesses in 2018/2019 season in Hungary

Table 7. Number and percentage of people visited doctor/age group in 2018/2019 season in Hungary

Table 8. Value data/age groups in Hungary, 2018

Table 9. Vaccination and morbidity ratios/age groups in Hungary, 2018/2019 season

Table 10. Number and ratio of people 60 and older/years of 2013-2017, Hungary

Table 11. Number of non-occurred cases of influenza/age groups in 2018/2019 season in Hungary

Table 12. Number and distribution of non-occurred cases by age groups, Hungary, 2018/2019 season

Table 13. Data on symptoms, medical visits, hospital cases in numbers and proportion, USA, 2010-2019

Table 14. Number of avoided cases and number of avoided hospitalization/age groups in 2018/2019 season, Hungary

Table 15.: Economic benefit in case of actual vaccination strategy

Table 16.: Economic benefit in case of proposed vaccination strategy

Table 17.: Cost-effectiveness threshold in some developed countries

ANNEX

ANNEX 1. 3Fluart seasonal influenza vaccine administered in 2017/2018 and 2018/2019 seasons to different population groups

<i>Application</i>	2017/2018					2018/2019				
	3Fluart (free of charge)					3Fluart (free of charge)				
	≥65 years	60-64 years	19-59 years	3-18 years	Total	≥65 years	60-64 years	19-59 years	3-18 years	Total
Patients with chronic respiratory disease, asthmatic patients		2.608	27.630	12.442	42.680		1 044	27 837	11 279	40 160
Patients with cardiovascular disease (excluding treated hypertension)		2.081	44.264	1.637	47.982		1 527	39 412	1 437	42 376
Patients with chronic kidney disease		146	4.315	248	4.709		85	2 683	93	2 861
Patients with chronic liver disease		80	2.712	120	2.912		175	4 147	324	4 646
Patients with diabetes		567	19.415	645	20.627		799	18 121	626	19 546
Patients with other metabolic diseases (except diabetics)		492	9.329	1.090	10.911		161	8 546	1034	9 741
Patients with congenital or acquired immunodeficiency (except tumor patients)		141	6.713	1.965	8.819		78	5 550	1 634	7 262
Persons who have been cared for a long time in institutions providing nursing, care, rehabilitation, temporary accommodation, residential homes or healthcare institutions	27.340	6.063	14.835	2.870	51.108	22 996	6 113	13 994	2 036	45 139
People 65 and older independent of their health	459.373				459.373	421 142				421 142
Healthcare professionals	1.980	3.370	31.617	287	37.254	1 640	3 684	30 359	485	36 168
Employees of social institutions	414	666	7.692	86	8.858	489	1 057	7 446	188	9 180
Pregnant women; women who plan to have children during the seasonal flu season			5.915	137	6.052			5 541	114	5 655
Children and adolescents receiving long-term salicylate treatment (due to the risk of Reye's syndrome)				107	107				163	163
Other	555	53.835	25.578	1.137	81.105	425	49 290	23 930	712	74 357
Total	489.662	70.049	200.015	22.771	782.497	446 692	64 013	187 566	20 125	718 396

ANNEX 2. 3Fluart seasonal influenza vaccine administered in 2010/2011, 2011/2012, 2012/2013, 2013/2014, 2014/2015, 2015/2016 and 2016/2017 seasons to different population groups

<i>Application</i>	<i>2010/2011</i>					<i>2011/2012</i>				
	<i>Fluval AB (free of charge)</i>					<i>Fluval AB (free of charge)</i>				
	<i>≥65 years</i>	<i>60-64 years</i>	<i>18-59 years</i>	<i>3-18 years</i>	<i>Total</i>	<i>≥65 years</i>	<i>60-64 years</i>	<i>18-59 years</i>	<i>3-18 years</i>	<i>Total</i>
Patients with chronic respiratory disease, asthmatic patients		25.629	42.578	25.750	93.957		24.066	38.694	24.568	87.328
Patients with cardiovascular disease (excluding treated hypertension)		88.492	83.108	4.651	176.251		79.749	75.104	2.969	157.822
Patients with chronic kidney disease		3.297	4.028	706	8.031		3.230	4.577	1.069	8.876
Patients with chronic liver disease		2.987	4.640	326	7.953		2.778	4.466	210	7.454
Patients with diabetes		26.189	28.849	1.524	56.562		27.053	31.215	1.119	59.387
Patients with other metabolic diseases (except diabetics)		8.865	17.304	2.411	28.580		8.435	15.953	2.456	26.844
Patients with congenital or acquired immunodeficiency (except tumor patients)		5.788	13.386	4.319	23.493		5.221	12.519	3.931	21.671
Persons who have been cared for a long time in institutions providing nursing, care, rehabilitation, temporary accommodation, residential homes or healthcare institutions	30.711	6.430	18.267	4.934	60.342	28.664	7.450	17.612	4.525	58.251
People 65 and older independent of their health	458.355				458.355	489.465				489.465
Healthcare professionals	2.444	4.607	49.526	527	57.104	2.791	5.298	51.673	395	60.157
Employees of social institutions	893	1.227	15.170	289	17.579	545	1.531	15.498	211	17.785
Pregnant women; women who plan to have children during the seasonal flu season			12.205	310	12.515			10.309	321	10.630
Children and adolescents receiving long-term salicylate treatment (due to the risk of Reye's syndrome)				450	450				238	238
Other	1.847	1.601	18.918	1.294	23.660	778	1.548	22.604	1.216	26.146
Total	494.250	175.112	307.979	47.491	1.024.832	522.243	166.359	300.224	43.228	1.032.054

<i>Application</i>	<i>2012/2013</i>					<i>2013/2014</i>				
	<i>Fluval AB (free of charge)</i>					<i>Fluval AB (free of charge)</i>				
	<i>≥65 years</i>	<i>60-64 years</i>	<i>19-59 years</i>	<i>3-18 years</i>	<i>Total</i>	<i>≥65 years</i>	<i>60-64 years</i>	<i>19-59 years</i>	<i>3-18 years</i>	<i>Total</i>
Patients with chronic respiratory disease, asthmatic patients		23.907	34.655	20.975	79.537		20.614	31.081	16.962	68.657
Patients with cardiovascular disease (excluding treated hypertension)		72.313	66.390	2.084	140.787		61.266	54.095	3.805	119.166
Patients with chronic kidney disease		2.769	3.426	587	6.782		2.729	3.142	532	6.403
Patients with chronic liver disease		2.281	3.660	91	6.032		2.138	3.200	163	5.501
Patients with diabetes		25.465	26.654	840	52.959		22.734	23.243	1.735	47.712
Patients with other metabolic diseases (except diabetics)		6.828	12.934	1.911	21.673		6.108	11.600	1.473	19.181
Patients with congenital or acquired immunodeficiency (except tumor patients)		4.324	10.602	3.099	18.025		4.744	9.343	2.645	16.732
Persons who have been cared for a long time in institutions providing nursing, care, rehabilitation, temporary accommodation, residential homes or healthcare institutions	27.328	6.914	17.021	4.562	55.825	29.449	7.077	15.056	4.361	55.943
People 65 and older independent of their health	484.873				484.873	460.446				460.446
Healthcare professionals	2.748	4.771	43.342	332	51.193	1.858	4.182	39.347	457	45.844
Employees of social institutions	391	1.553	13.402	248	15.594	2.025	1.656	11.395	211	15.287
Pregnant women; women who plan to have children during the seasonal flu season			8.643	355	8.998			7.115	248	7.363
Children and adolescents receiving long-term salicylate treatment (due to the risk of Reye's syndrome)				133	133				209	209
Other	679	1.551	20.925	1.308	24.463	302	2.561	24.322	2.457	29.642
<i>Total</i>	516.019	152.676	261.654	36.525	966.874	494.080	135.809	232.939	35.258	898.086

<i>Application</i>	2014/2015				
	<i>Fluval AB (free of charge)</i>				
	<i>≥65 years</i>	<i>60-64 years</i>	<i>19-59 years</i>	<i>3-18 years</i>	<i>Total</i>
Patients with chronic respiratory disease, asthmatic patients		1.289	28.215	12.004	41.508
Patients with cardiovascular disease (excluding treated hypertension)		1.749	53.075	1.797	56.621
Patients with chronic kidney disease		110	4.745	479	5.334
Patients with chronic liver disease		109	3.224	117	3.450
Patients with diabetes		888	22.291	729	23.908
Patients with other metabolic diseases (except diabetics)		180	9.983	1.068	11.231
Patients with congenital or acquired immunodeficiency (except tumor patients)		128	6.993	1.780	8.901
Persons who have been cared for a long time in institutions providing nursing, care, rehabilitation, temporary accommodation, residential homes or healthcare institutions	26.024	6.938	16.209	3.188	52.359
People 65 and older independent of their health	440.789				440.789
Healthcare professionals	1.255	3.791	31.402	314	36.762
Employees of social institutions	416	653	7.942	172	9.183
Pregnant women; women who plan to have children during the seasonal flu season			5.120	112	5.232
Children and adolescents receiving long-term salicylate treatment (due to the risk of Reye's syndrome)				297	297
Other	356	61.407	16.782	1.110	79.655
<i>Total</i>	468.840	77.242	205.981	23.167	775.230

<i>Application</i>	<i>2015/2016</i>					<i>2016/2017</i>				
	<i>3Fluart (free of charge)</i>					<i>3Fluart (free of charge)</i>				
	<i>≥65 years</i>	<i>60-64 years</i>	<i>19-59 years</i>	<i>3-18 years</i>	<i>Total</i>	<i>≥65 years</i>	<i>60-64 years</i>	<i>19-59 years</i>	<i>3-18 years</i>	<i>Total</i>
Patients with chronic respiratory disease, asthmatic patients		643	26.470	11.501	38.614		1.456	2.4423	9.900	35.779
Patients with cardiovascular disease (excluding treated hypertension)		1.729	46.194	1.566	49.489		1.389	38.583	1.444	41.416
Patients with chronic kidney disease		114	3.907	319	4.340		130	3.990	268	4.388
Patients with chronic liver disease		68	2.579	76	2.723		172	2.442	71	2.685
Patients with diabetes		449	1.9448	542	20.439		619	18.115	535	19.269
Patients with other metabolic diseases (except diabetics)		117	9.219	984	10.320		273	8.165	859	9.297
Patients with congenital or acquired immunodeficiency (except tumor patients)		50	7.060	1.631	8.741		117	5.706	1.340	7.163
Persons who have been cared for a long time in institutions providing nursing, care, rehabilitation, temporary accommodation, residential homes or healthcare institutions	28.236	7.301	15.482	3.035	54.054	27.923	7.311	14.790	2.320	52.344
People 65 and older independent of their health	432.431				432.431	407.546				407.546
Healthcare professionals	1.611	2.076	29.673	228	33.588	1.313	2.385	27.967	194	31.859
Employees of social institutions	438	792	8.332	130	9.692	347	655	7.313	81	8.396
Pregnant women; women who plan to have children during the seasonal flu season			5.468	109	5.577			4.451	119	4.570
Children and adolescents receiving long-term salicylate treatment (due to the risk of Reye's syndrome)				202	202				136	136
Other	2.754	55.027	22.972	1.319	82.072	1.189	48.498	18.932	688	69.307
Total	465.470	68.366	196.804	21.642	752.282	438.318	63.005	174.877	17.955	694.155

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DECLARATION

I hereby certify that Doctoral Candidate Péter Vajó carried out his work under the supervision of the above-mentioned Doctoral School between 2015 and 2019.

The Candidate made an independent contribution to the results included in the dissertation, and the dissertation is his independent work. I propose to accept the dissertation.

Debrecen, 5 January, 2022

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Dr. Zoltán BÁCS, PhD

Thesis Supervisor