CANCELLING OBLIGATORY MASS VACCINATION OF NEWBORNS AGAINST TB IN SLOVAKIA: PREDICTED DEVELOPMENT

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Abstract

The aim of the paper is to use modelling to predict possible changes in the incidence of active tuberculosis if mass vaccination of newborns in Slovakia is cancelled. Our secondary aim is to analyze the cost-effectiveness of mass primovaccination of newborns in Slovakia with BCG vaccine against tuberculosis (Bacillus Calmette-Guérin) as compared to no vaccination at all.

The model analyses the two above-mentioned scenarios in children aged 0 – 14 years for a period of 15 years. Our results show that the cost of preventing one case of active tuberculosis in children aged 0 - 14 years would be by € 784.30 less if mass vaccination of newborns is applied, when compared to the cancellation of mass vaccination.

The number of active tuberculosis cases would remain stable with a gradually decreasing trend if mass vaccination were to continue. If mandatory vaccination is cancelled, the number of active tuberculosis cases would be as much as five times higher in the model cohort.

Based on this analysis, we conclude that that it would be useful to model and monitor different strategies for general practitioners, paediatricians, pneumologists and epidemiologists to make a qualified decision how to proceed with BCG vaccination in Slovakia

Keywords: active tuberculosis epidemiology prediction, modelling, tuberculosis vaccination, cost effectiveness analysis

Introduction

Tuberculosis (or "TB", as it will be referred to hereafter) is a chronic communicable illness caused by the *Mycobacterium tuberculosis complex* bacterium. The illness may take on pulmonary or extra pulmonary form. The pulmonary form spreads primarily through the air. Infection is characterized by the occurrence of primary illness forms as early as in childhood. Massive infection in unvaccinated individuals results in severe disseminated forms of tuberculosis, for which it is expected that BCG vaccine offers up to 70-80% protection, in our conditions. Although a vaccinated person may fall ill with TB, the course of their illness will be as a rule less severe than that of an unvaccinated person.

The Slovak Republic has a comparatively low incidence of TB. The incidence of newly diagnosed cases of TB fell under 20/100 000 inhabitants in 2000, and then again under 10/100 000 inhabitants in 2009. This favourable trend continued in 2010, when the incidence was 8.17/100 000 inhabitants (443 new cases reported to the National TB Registry). In 374 of these cases, pulmonary tuberculosis was involved, while 69 cases dealt with extrapulmonary TB. Of this total number of TB cases, 11 cases of TB were reported in children (0-14 years of age). The epidemiological situation of TB differs significantly in the various regions of Slovakia (*Figure 1*), with the highest incidence being in the Prešov (PR) and Košice (KE) Regions.

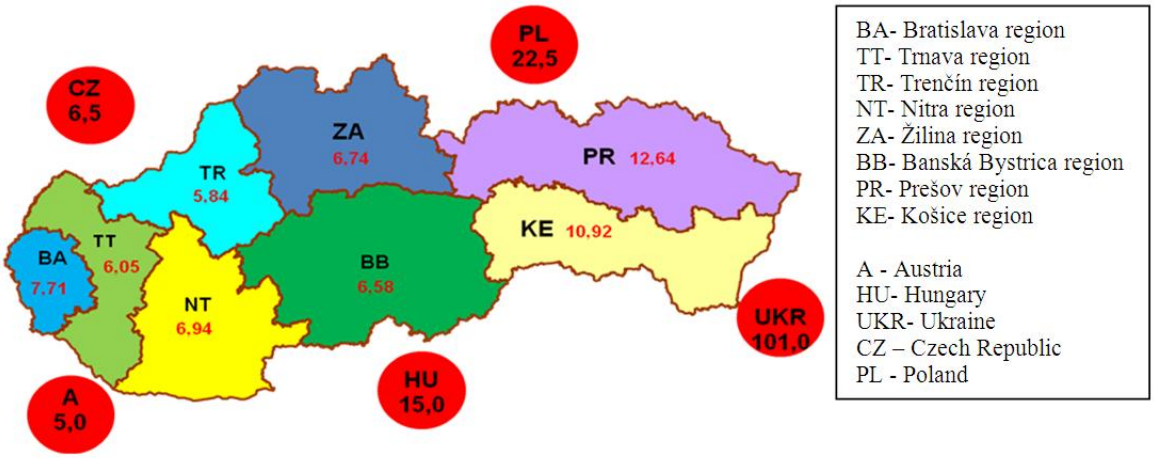

Fig 1: *Epidemiological situation of TB incidence in Slovakia in 2010*

Existing tuberculosis management is based on WHO recommendations. It entails quick diagnosis of affected persons, their prompt isolation, effective directly-observed treatment (DOTS – short course), and an active search for infected persons that have come into contact with tuberculosis. Two-phase treatment regimens are used in treatment of childhood tuberculosis, consisting of initial phase (2 months) and continuous phase (4 -6 months). The categories of treatment regimens are designed according to the extent of the disease, bacteriology, and whether a newly diagnosed disease, a relapse, treatment failure, treatment after discontinuation or a chronic disease is concerned. Standard treatment regimens in children include basic antituberculotics (isoniasid, rifampicine, streptomycine). Treatment should cure the patient and leave them with minor residual changes; yet full recovery is not frequent. Patients with latent infection are treated to prevent the eruption of a clinically manifested form of the illness.

TB primovaccination of newborns in Slovakia

In 1953[1], the National Program for Tuberculosis Control was implemented. One of its elements, Act no. 4/1952 Coll., instituted mandatory vaccination of children, adolescents, and adults aged 0 to 30 against tuberculosis, in five-year intervals. Aside from these mandatory yearly cohorts, various at-risk population groups were selectively vaccinated as well. The vaccine used was called Prague Liquid Vaccine, also known as Šula's vaccine, made from the Danish vaccine 725-901. It was considered to be weak, although its effectiveness was estimated to be approx 70%. One of its advantages in practice was the low frequency of adverse effects it entailed.

The institution of mandatory vaccination and revaccination against TB was accompanied by a decrease in the incidence of new TB cases in children (*Figure 2*).

[1] Authors' note: In 1953, the Slovak Republic was part of Czechoslovakia.

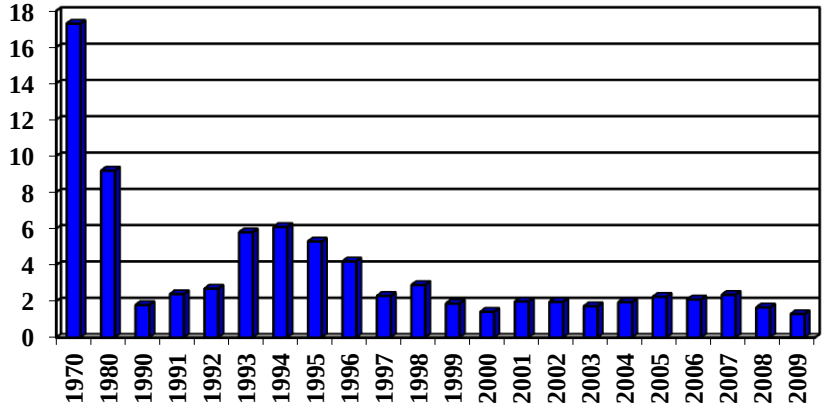

Fig 2: *Newly diagnosed cases of tuberculosis per 100 000 children (aged 0-14)*

The principles of vaccination against tuberculosis differ in each country depending on its epidemiological situation. For this reason, beginning in 1974, it was possible to make new changes in Slovakia (*Table 1*). In the following years, mandatory mass primovaccination continued, while the number of revaccinations was gradually reduced. Outside of the vaccination calendar, tuberculin-negative at-risk individuals were revaccinated if they came into direct contact with an infectious source.

Table 1*: Principles of BCG vaccination policy in 1953-2010*

Year	Characteristics
1953	Start of mandatory primovaccination of newborns, revaccination of MTX II negat. in 5-year intervals (up to 30 years of age)
1974	Mandatory primovaccination of newborns, revaccination of MTX II negat. at ages 7, 13, and 18.
1996	Mandatory primovaccination of newborns, revaccination of MTX II negat. at age 11 Revaccination of contacts outside the vaccination calendar
2010	Revaccination of MTX II negat. at age 11 discontinued
	Revaccination of contacts outside the vaccination calendar
2012	Mandatory vaccination of newborns cancelled. Contacts of active TB cases vaccinated and employees in high risk profession.

By Decree of the Ministry of Health of the Slovak Republic no. 273/2010 Coll. (MoH 2010), the mandatory revaccination of tuberculin-negative children against tuberculosis at age 11 was discontinued based on the recommendations of specialists in the field of pneumophtiseology. By Decree of the Ministry of Health of the Slovak Republic no. 544/2011 Coll. (MoH 2011) obligatory primovaccination has been cancelled. This decree became to be effective from January 1st, 2012.

Aim of the study

The aim of the study was to create model mapping changes in the epidemiological situation that are to be expected after a change in vaccination strategy and such a change in health policy valid from January 1st, 2012. Our supplementary aim was to analyze the incremental cost-effectiveness of mass BCG primovaccination of newborns in Slovakia as compared to no vaccination.

Model and Structure

From the TRIPDATABASE, MEDLINE, PUBMED, and COCHRANE databases, as well as other resources of institutions such as the WHO, ECDC (European Centre for Disease Control), and CDC (Centre for Disease Control), we created an overview of published cost-effectiveness analyses of vaccination against TB since 1990. Our study is based on a worldwide overview of such analyses published in 2006 [1]. Secondly, a study of the impact of various vaccination strategies on the incidence of severe forms of TB in children with low and moderate prevalence (i.e. up to 30 positive cultivations from sputum per 100 000 children aged up to 5 years) [2]. Our cost-effectiveness analysis of the primovaccination of newborns against TB used a principles defined by an analysis made in Japan [3].

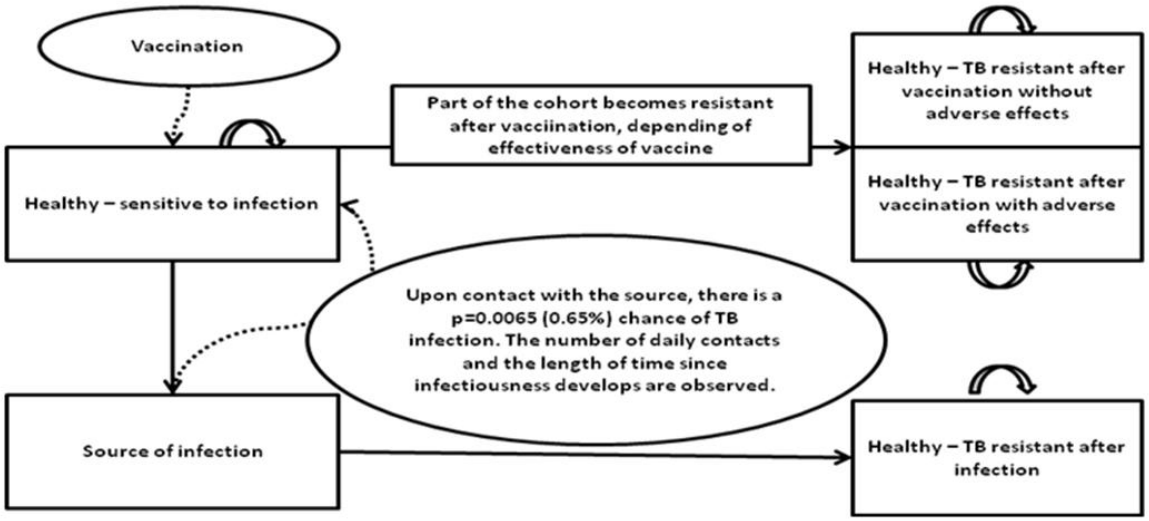

Fig 3: *Structure of the model used in analysis of primovaccination of newborns against TB in Slovakia*

Model Inputs

Clinical effectiveness of the vaccine

The model uses a 63.3% vaccine effectiveness [4] in relation to preventing the onset of active TB. According to Slovak experts, this value is closest to the conditions observed in Slovakia.

Expected duration of protection

We used the maximum expected duration of the protections that effective vaccine offers to prevent the onset of active TB, which is 15 years [4].

Number of newborns in the cohort

In 2007, the Statistical Office of the Slovak Republic (hereafter referred to as the "SO") published a prognosis of population development in several projections [5]. Consulting with the SO of the Slovak Republic, we decided to use the so-called young projection for input as the number of newborns in cohorts for the years 2012 to 2027, because this projection was closest to real numbers in the years 2007 to 2010.

Incidence of TB in the vaccinated cohort

The data on incidence in the vaccinated cohort for 2006 to 2010 was calculated according to the number of cases per age [6] and the number of children in each year at ages 0

to 14 [7]. Based on experts' recommendation we calculated the average rate of incidence for the given ages that was used for future as well (*Table 2**: Incidence of active TB in children aged 0-14** 2*).

***Table 2**: Incidence of active TB in children aged 0-14*

YEAR	0-4	p	5-9	p	10-14	p	total	
2006	11	4.18338E-05	6	2.18409E-05	6	1.802E-05	23	2.64179E-05
2007	7	2.6245E-05	3	1.12232E-05	6	1.8926E-05	16	1.88004E-05
2008	4	1.46762E-05	6	2.28733E-05	4	1.328E-05	14	1.6745E-05
2009	2	7.13837E-06	5	1.92224E-05	4	1.37442E-05	11	1.3232E-05
2010	4	1.39744E-05	4	1.53668E-05	3	1.05665E-05	11	1.32457E-05
Average	6	2.07736E-05	5	1.81053E-05	5	1.49074E-05	15	1.76882E-05

Incidence of TB in the unvaccinated cohort

At present there is no data available on the vaccination rate of patients with active TB with BCG vaccine. Because of this, and also due to the high percentage of vaccination rate of children in (up to 98.8%), we operated under the assumption that all children who manifest active TB were vaccinated as newborns, and the outbreak of TB was related to their vaccination. The incidence of TB in the unvaccinated cohort ($I_{tb/unvac}$) was calculated by the following equation:

$I_{tb/unvac}$ *= (incidence in vaccinated individuals) x* ($\%_{adh}$*) / (1-VE)*

Type of analysis and perspective

The primary parameter of cost-effectiveness is the direct cost of preventing 1 case of active tuberculosis in children aged 0 to 14. We used a cost-effectiveness analysis with a horizon of 15 years, as this time period is considered to be the maximum duration of the vaccine effect used in Slovakia with a clinical effectiveness of 63.3% [4].

The cost-effectiveness analysis took a population approach, which studied the impact of two different strategies on the cohorts of children aged 0 to 14 born in the years 2012 to 2027.

The first strategy, mass vaccination of newborns, was compared with the second one, discontinuing primovaccination of newborns against TB altogether.

Our analysis uses the structure and method of a model analysis calculated in Japan [3], which anticipated a dynamic upsurge in the count of TB cases due to its spread through other contacts.

We used the perspective of health insurance companies, and therefore included in our analysis only those direct costs for health care which are covered by health insurance companies.

Economy

We applied the cost of primovaccination for each year to a modelled cohort of newborns from 2012 to 2027 (*Table 3:*).

The price of 1 dose was at most € 0.303 [8]. Only the cost for the vaccine itself was included in the cost of primovaccination. We calculated the total costs for primovaccination (C_{vac}) as the sum of the cost for vaccinating a specific cohort (C_{coh}) and the costs for treating adverse effects (C_{AE}). Thus, $C_{vac} = C_{coh} + C_{AE}$.

The cost of one cohort vaccination was determined from the number of individuals in a cohort (N_{coh}), the estimated vaccination rate ($\%_{adh}$), and the cost of the vaccine itself (C_{vac}).

The costs of treating adverse effects (AE) were calculated from their average occurrence rate for each vaccinated portion of the cohort, and the average cost therapy required to treat them (C_{AEther}). The mean chance of AE occurring (p_{AE}) was determined by reports from 2006 to 2010 summarized by the Public Health Authority of the Slovak Republic (hereafter referred to as the "PHA").

The price of treating AE was based on the prices for treating diagnoses A18.2 and A18.4 in 2009. Because of uncertain financial developments in the future, we used a 0.3% annual price growth for the years until 2027. Costs for treating AE consist of hospital expenses, ambulatory treatment and costs of pharmacological interventions, if necessary, and therefore a 0.3% price growth underestimates future expenses significantly. Average costs for TB treatment are taken from data provided by health insurance companies in 2009. Similarly, a 0.3% annual price growth rate was applied to the calculation up to 2027.

***Table 3**: Total costs for vaccinating cohorts*

	2012	**2013**	**2014**	**2015**	**...**	**2027**
C_{vac}	20 415.11 €	20 505.31 €	20 544.61 €	20 544.60 €		19 476.17 €
C_{coh}	17 505.06 €	17 551.74 €	17 546.47 €	17 499.10 €		15 260.83 €
C_{AE}	2 910.05 €	2 953.57 €	2 998.14 €	3 045.49 €		4 215.34 €
$\%_{adh}$	97.73%	97.73%	97.73%	97.73%		97.73%
N_{coh}	58 949	59 118	59 118	58 982		52 090
$C_{\_AEther}$	18.92 €	19.15 €	19.44 €	19.79 €		31.02 €
C_{vac}	0.30 €	0.30 €	0.30 €	0.30 €		0.30 €
p_{AE}	0.27%	0.27%	0.27%	0.27%		0.27%
C_{TBl}	1 097.55 €	1 110.78 €	1 127.54 €	1 147.99 €		1 799.20 €

We calculated the total number of active cases of TB prevented attributable to vaccination in the child population in Slovakia aged 0 to 14.

We based our assumptions on the clinical effectiveness of the vaccine (VE), duration of protection offered by the vaccine (d), incidence of TB in vaccination (from which $I_{tb/unvac}$ was calculated), the percentage of vaccinated individuals, and discount rate (r). In Slovakia, at the time of our calculations, the discount rate was fixed by a decree [9] at 5% both for costs and gains.

Calculations were made in Microsoft Excel, and the number of prevented cases (NP_{TB}) was determined mathematically by the following formula:

$$NP_{TB} = ((N_{coh} \times \%_{adh} \times VE) / (1 - \%_{adh} \times VE)) \times \sum_{\{k = 1 \rightarrow d\}} ((I_{tb/unvac} / (1+r)^{k-1})$$

To calculate the number of vaccinated individuals necessary to prevent one active case of TB (NNT), we used a calculation involving the number of newborns in a cohort ($\%_{adh} \times N_{coh}$) and the total number of prevented cases (TP_{NB}).

$$NNT = (\%_{adh} \times N_{coh}) / TP_{NB}$$

The total number of prevented cases was thus given by the equation: $TP_{NB} = P_{TB} + P_{TTB}$
These equations were used in the same manner as in the Japanese analysis [3] our analysis is based on. However, contrary to the aforementioned Japanese analysis, we included cases of TB meningitis in the number of active TB cases.

The number of prevented cases (P_{TB}) was swelled by the number of cases prevented by isolating the source, i.e. the containment of infection in the environment of a source (P_{TTB}), as expressed by the following equation:

$P_{TTB} = P_{TB}$ *x number of contacts over infectious period x 0.0065 [prevalence of TB in contacts]*

The number of contacts in the infectious period we worked with was age-specific, as attested by a study observing the number of contacts in one day. The average number of contacts in the age group 0 – 4 was 10.21; in the age group 5-9 years old it was 14.82 contacts per day; in the age group 10-14 it was 18.22 contacts per day, and in the whole monitored group (in the age 0- 14 years old) it was measured 14 contacts per day in the average [10]. The number was multiplied by the number of days between the outbreak of active TB and the time of diagnosis and isolation of the source.

Description of achieved results

We modelled two scenarios – continuous mass vaccination and cancelling mass vaccination. In them we modelled incidence of active TB in them. Continuing mass TB vaccination of newborns would be translated in 16 active TB cases in 2012 in children aged 0-14 years. This number will decrease year by year and in 2027 we would expect 14 active TB cases.

Cancelling mass vaccination would be translated in 36 active TB cases in 2012 in children aged 0-14 years. This number will decrease year by year and in 2027 we would expect 50 active TB cases.

In summary the expected number of prevented cases from 2012 to 2027 would be 899 without discounting (*Table 4**: Number of discounted prevented cases in compared strategies for 2012 – 2027***4). It is naturally understood that discontinuing primovaccination will not help to prevent any new cases of active tuberculosis.

Table 4*: Number of discounted prevented cases in compared strategies for 2012 – 2027*

Scenario	Discounted number of prevented cases	Prevented cases without discount
Mass primovaccination	653	899
Primovaccination discontinued	0	0

The numbers of prevented cases are discounted in the basic scenario. These numbers helped simulate the development of TB in Slovakia for the compared strategies (

*Fig **4: Expected incidence of active TB in children aged 0-14** 4*). This comparison showed that cancelling mass vaccination could increase the incidence from existed 2 per 100 000 up to 12 per 100 000.

This assumption was based on the same approach in detection and isolation of active TB as it's applied in Slovakia now.

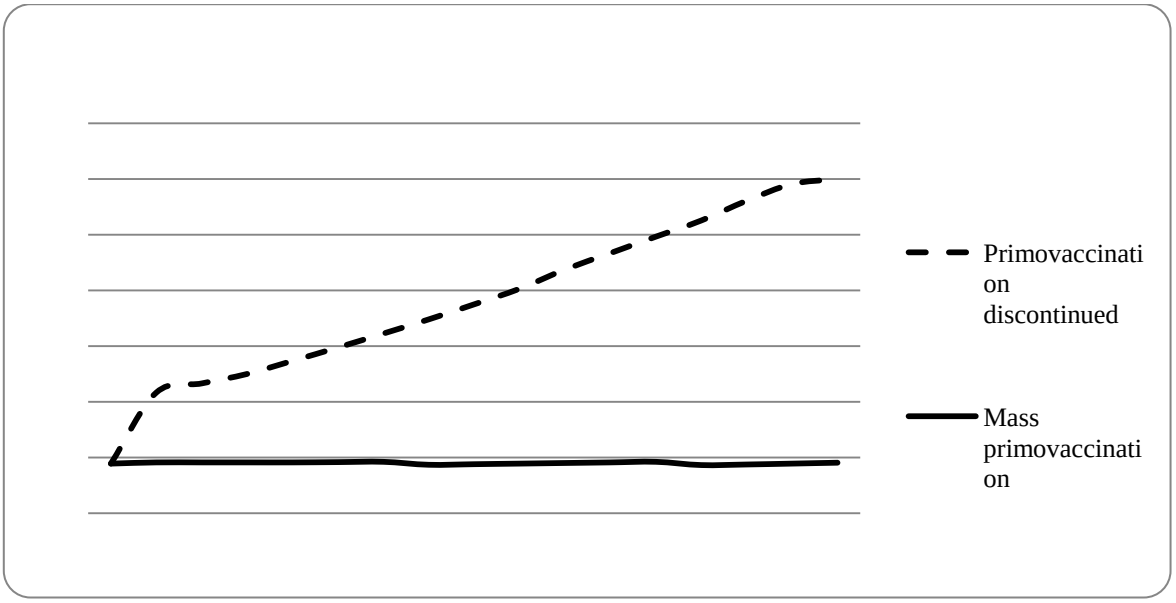

***Fig 4**: Expected incidence of active TB in children aged 0-14 (number of cases per 100 000 children)*

Modelled numbers of active TB cases together with modelling related costs were used for cost effectiveness analysis (*Table 5 and 6*).
We carried out a deterministic one-way sensitivity analysis as well focusing at:

- Vaccine effectiveness (40 – 80%)
- Number of days to diagnose TB in which the source of TB is infectious (7 – 21 days)
- Number of daily contacts (4 – 24)
- Discount rate for future benefits (0 – 3.5 %)
- Incidence of adverse effects (0.13 – 0.40%)

***Table 5**: Incremental cost effectiveness ratio I.*

Strategy	**Basic scenario**	**Vaccine effectiveness**		**Interval of infection**	
ICER in € per 1 prevented case of TB		40%	80%	7 days	21 days
Mass vaccination vs no vaccination	-784.30	-897.98	-766.63	-518.71	-944.54

***Table 6**: Incremental cost effectiveness ratio II.*

Strategy	**Number of daily contacts**		**Discount rate**		**Incidence of adverse effects**	
ICER in € per 1 prevented case of TB	min	max	0%	3.5%	0.13%	0.4%
Mass vaccination vs no vaccination	-341.37	-982.17	-568.86	-718.82	-813.05	-753.30

Incremental cost effectiveness is in all scenarios below zero as less costly and more effective.

Either basic scenario or tested scenarios in sensitivity analysis, all were located in dominant segment. The most sensitive factors are number of days to diagnose active TB and number of daily contacts.

Conclusion

Our modelling assumed that cancelling obligatory vaccination against TB would cause in remarkable increase in the number of active TB cases.

This expected trend could be influenced by the implementation of specific strategies targeted on fast identification of active TB and quick isolation of this patient. Yet this hypothesis should either be modelled or tested in a pilot project within a geographical area were TB incidence is much higher in comparison to the nationwide average.

The cost-effectiveness analysis of newborn primovaccination against tuberculosis in the Slovak Republic was carried out from the perspective of the payer, using a cost-of-illness method in combination with minimization-of-cost analysis through a vaccine effectiveness model with a horizon of 15 years. It has been shown that at current pricing the mass vaccination is a cost-effective strategy.

The strategy of discontinuing vaccination of newborns altogether is assessed as less effective and more costly.

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