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Cost-effectiveness of a potential anti-tick vaccine with combined protection against Lyme borreliosis and tick-borne encephalitis in Slovenia

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ABSTRACT

This study assessed cost-effectiveness of a potential anti-tick vaccine that would protect against both Lyme borreliosis (LB) and tick-borne encephalitis (TBE) in a highly endemic setting of Slovenia.

A Markov model was developed to estimate cost-effectiveness of a vaccine with potential combined protection against LB and TBE from the societal perspective. The model expressed time in annual cycles, followed a target population through their lifetime, and applied an annual discounting of 3%. A target population entered the model in a susceptible state, with time dependent probabilities to acquire LB/TBE. Disease manifestations were either resolved within one cycle, or a patient developed LB/TBE sequelae. The vaccination consisted of initial immunization and one revaccination. Estimates of LB/TBE direct and indirect costs, and data on natural course of LB/TBE were obtained from Slovenian databases. Effectiveness of the vaccine with potential combined protection against LB/TBE was derived from studies on existing TBE and LB vaccines, while utility estimates were collected from various literature sources.

A vaccine with potential combined protection against LB/TBE was predicted to have an incremental cost of €771,300 per 10,000 vaccinated persons, an incremental utility of 17QALYs and a base-case incremental cost-effectiveness ratio (ICER) of 46,061€/QALY. Vaccine cost, effectiveness and discount rates were identified as the most influential model parameters. A wholesale price for a vaccine shot of €9.13 would lead to cost savings followed by health gains for the vaccination strategy.

The base-case ICER was below commonly accepted thresholds of cost-effectiveness, indicating that a combined LB/TBE vaccine might be a cost-effective option in Slovenia. With early Health Technology Assessment becoming increasingly important, this analysis still represents a rare example of cost-effectiveness assessment prior to market authorisation. Although obviously in such a situation some key parameters are unknown, our model sets up a tool to analyse pharmacoeconomic criteria that can help development of a cost-effective health technology, in this case a combined tick-borne diseases vaccine.

1. Introduction

Lyme borreliosis (LB) and tick-borne encephalitis (TBE) are the most common tick-borne diseases in Europe (ECDC, 2011), resulting in at least 85,000 cases of LB and 2000–2600 cases of TBE per year (ECDC, 2011, 2014; ECDC, 2016). There are pronounced geographical differences, with the annual incidence ranging from 0 to 350/100,000 and 0–22/100,000 for LB and TBE, respectively. Regions of Central and Eastern Europe, the Baltic states and Scandinavia are the most affected (ECDC, 2016; Rizzoli et al., 2011; Süss, 2011).

In Slovenia, a small Central European country, average of 5400 cases of LB and 200 cases of TBE were reported annually in the period 2008–2014; the corresponding incidence of 260/100,000 and 10/100,000 exceed the respective averages European estimates by 25–30 times (ECDC, 2012; Rizzoli et al., 2011; The National Public Health Institute of the Republic Slovenia, 2018).

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LB can be successfully treated by timely antibiotic therapy. However, a failure in the diagnosis and a delay of the treatment can lead to more severe disease manifestations and sequelae (Stanek et al., 2011). For TBE no etiologic treatment is available (Bogovic and Strle, 2015). A recent Slovenian study estimated that as much as 30% of TBE patients develop sequelae, while 0.75% die due to TBE (Fafangel et al., 2017). Sequelae can result in further outpatient visits and hospitalizations, expensive care and premature retirement, which altogether contribute to the high costs of LB and TBE in endemic regions. As a reference, direct annual costs of LB treatment alone were estimated at $0.7–1.3 billion in the United States (Adrion et al., 2015). Also, the quality of life decrement of TBE patients in Slovenia was assessed to be 167.8 disability adjusted life years (DALY) per 100,000 people, indicating a high TBE disease burden in comparison to other infectious diseases (Šmit and Postma, 2015).

In recent decades, vaccines against TBE became part of immunization programmes in many endemic countries and established one of the highest field effectiveness among vaccines (Kunz, 2003; Heinz et al., 2007). In contrast, a LB vaccine was withdrawn shortly after its market authorisation in the United States in 1998 (Poland, 2011). Currently, two LB vaccines are in the early phase of clinical trials (Wressnigg et al., 2013; Comstedt et al., 2014), but it is unclear whether they will reach the market. A single vaccine that could inhibit transmission of multiple pathogens from the tick vector to humans would be ideal. This could be achieved by a vaccine targeting the tick rather than the individual tick-borne pathogens. To date a tick vaccinogen for such a vaccine does not exist. However, identification and development of an anti-tick vaccine, that could prevent bacterial, viral and protozoal tick-borne diseases, including LB and TBE, has been the subject of the ongoing Anti-tick Vaccines to Prevent Tick-borne Diseases in Europe (ANTIDotE) - project (www.antidote-fp7.org) (Sprong et al., 2014).

Assessments of TBE or LB vaccines' cost-effectiveness have been conducted for economic and epidemiological settings of Slovenia, Austria, Estonia, Sweden and the United States (Askling et al., 2015; Hsia et al., 2002; Jürisson et al., 2015; Meltzer et al., 1999; Shadick et al., 2001; Šmit, 2012). Even though the studies varied in analysis perspective, model structure and outcome measures, cost-effectiveness predominantly depended on disease incidence and the specific risk distribution across age groups. Economic evaluations of vaccines (or drugs) are often performed at the moment of market entry or even only when explicitly considered for inclusion in a country's immunization program. Recently, early economic evaluation of vaccines, within the context of early Health Technology Assessment (HTA), has become an increasingly important step in the process of including vaccines in the immunization programs across developed countries (Bryson et al., 2010; Ricciardi et al., 2015). For example, the Joint Committee of Vaccination & Immunization (JCVI) from the United Kingdom has the horizon scanning of new vaccines yet in development embedded as a structural component of its HTAs (Raftery, 2014). Early HTA with cost-effectiveness as a core element, is important for: (i) better understanding of the potential for reimbursement by the health authorities, and marketing for the developers and producers of the vaccines, and (ii) contributing to planning, financing and understanding health impacts of new vaccines for national authorities such as, for example, the Ministry of Health and JCVI in the United Kingdom (Raftery, 2014).

This study aims to estimate cost-effectiveness of a potential vaccine with combined protection against LB/TBE in Slovenia, a country where both LB and TBE are highly endemic. The pharmacoeconomic evaluation of such a potential vaccine can be utilised as a helpful tool for both vaccine developers and healthcare decision makers to better understand the vaccine's economic impact and public health value.

2. Methods

2.1. General model settings

To estimate cost-effectiveness of a potential vaccine with combined protection against LB/TBE in Slovenia, a Markov model was developed in the statistical software R, version 3.0.2 (R Development Core Team, 2008). The model compared costs and health utilities of the current situation with no specific prevention strategies, and vaccination of a target population with a vaccine with potential combined protection against LB/TBE. The analysis of the two approaches was conducted from the societal perspective, considering direct and indirect costs. Costs were expressed in €, and health utilities in quality adjusted life years (QALY) gained, enabling estimates of incremental cost effectiveness ratio (ICER) measured in €/QALY as the main outcome of the analysis. The time in the model runs in annual Markov cycles, while total time horizon covers the average lifetime of the Slovenian population (Statistical office of the Republic of Slovenia, 2018a). Finally, costs and utilities estimated by the model were discounted at an annual rate of 3%, conforming to the local pharmacoeconomic guideline (Uradni list Republike Slovenije, 2013).

2.2. Model structure

The model synthesized natural courses of LB and TBE through clinically relevant stages of the diseases, defined as mutually exclusive Markov health states (Fig. 1A and B). Both compared cohorts entered the model at age 18, the youngest age eligible for LB/TBE vaccination, and were followed until the age of 81, which corresponded to an expected life length in Slovenia (Statistical office of the Republic of Slovenia, 2018a). Patients moved through the model states in accordance with transition probabilities (Table 1) that were estimated from data of the National Institute of Public Health of the Republic of Slovenia and/or a register of Lyme borreliosis Outpatient Clinic (LBOC) of the University Medical Centre Ljubljana (The National Public Health Institute of the Republic Slovenia, 2018; Data available at LBOC, 2018).

At the beginning cohorts were in a health state "Susceptible" where they could remain, contract LB and/or TBE according to specific time dependent probabilities for these diseases (p_LB, p_TBE), or die. Patients who develop LB do not gain a permanent immunity (Stanek et al., 2011); thus, all such patients moved back to the susceptible state in the Markov model. In contrast, patients who acquired TBE were interpreted to have a life-long protection (Data available at LBOC, 2018).

LB and TBE were represented by two periods, active disease and sequelae. The specific manifestations of active LB were: erythema migrans (EM), which could be solitary or multiple, borrelial lymphocytoma (BL), Lyme neuroborreliosis (LNB), Lyme carditis (LC), Lyme arthritis (LA) and acrodermatitis chronica atrophicans (ACA). The manifestations of active TBE were: meningitis (Me), moderately severe meningoencephalitis (modME), severe meningoencephalitis and meningoencephalomyelitis (sevME), and hospitalization in intensive care unit due to TBE (TBE ICU). In our model, all listed disease manifestations were interpreted as transitory and were either resolved within one year, or patients proceeded to sequelae of LB/TBE (Fig. 1A and B).

Sequelae were defined as symptoms/signs present one year after diagnosis and treatment of LB or TBE. Sequelae of LB were specified as EM, LNB, ACA and LA sequelae. Since available Slovenian data sources suggested that LC and BL are very rare and infrequently result in sequelae (Data available at LBOC, 2018) these manifestations were interpreted as not developing long-term conditions. Recovery from the sequelae was allowed in the model to fully capture the complexity of the disease. According to detailed follow-up data (Data available at LBOC, 2018) 50% of patients with EM, 25% with LNB, 20% with LA, and 10% with ACA who had LB sequelae fully recover within 5 years (Table 1). Unlike LB, none of the patients with TBE sequelae (specified as Me, modME and sevME sequelae) were expected to fully recover in

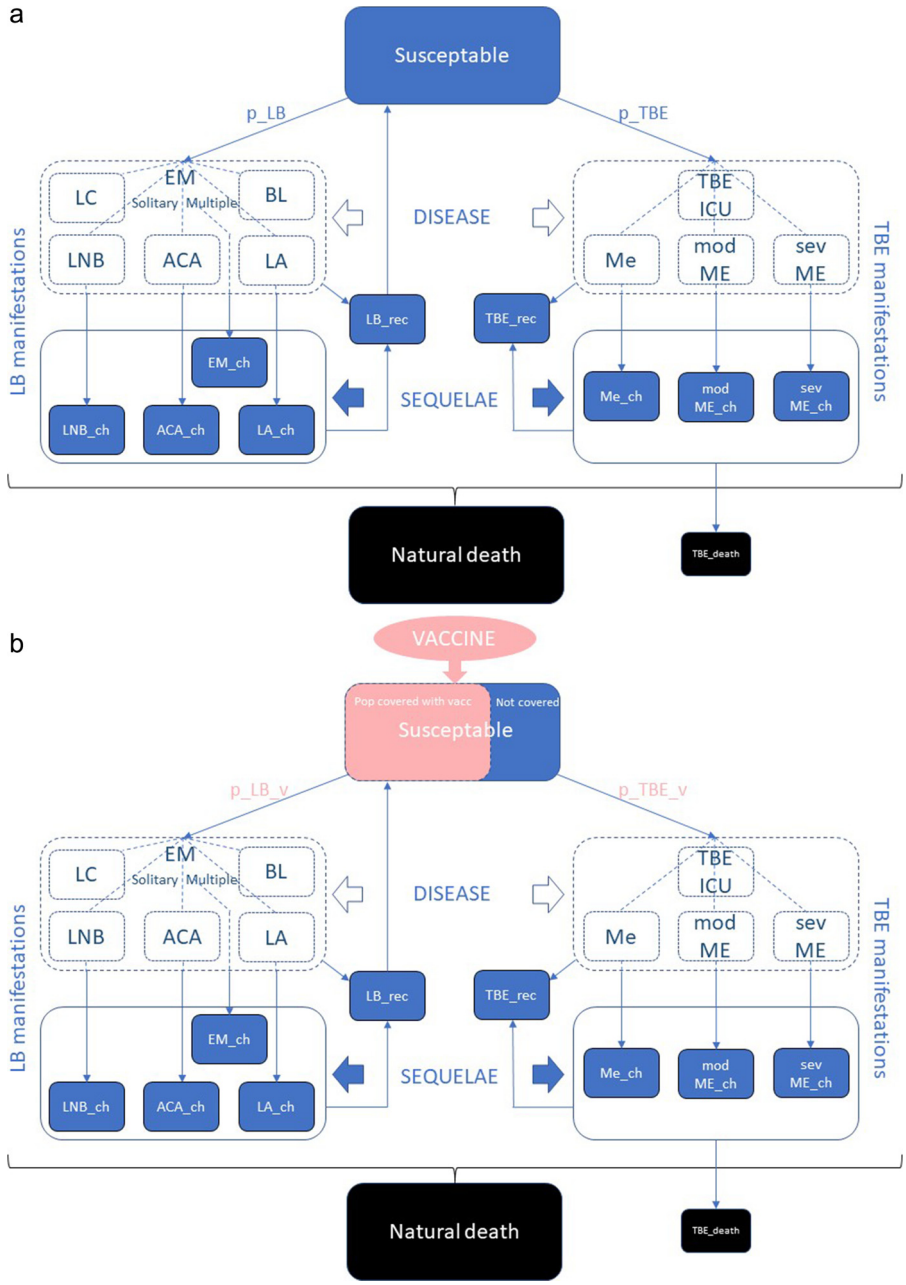

Fig. 1. A) Model scheme without the vaccination. B) Model scheme with the vaccination.

the model (Data available at LBOC, 2018); they were only redistributed from more to less severe TBE sequelae (Fig. 1A and B, Table 1).

Finally, death from any cause was possible from any of the Markov states and equal to the age-dependent natural mortality rate in Slovenia (Statistical Office of the Republic of Slovenia, 2018a). Disease-specific mortality was ascribed only to TBE sequelae state and estimated at 2.3% for TBE patients older than 60 years (Logar et al., 2006). All time dependent probabilities used in the model have been presented in the table of Supplemental material 1.

2.3. Vaccination

Vaccination affected the vaccinated cohort within the model only in lowering probabilities of contracting LB/TBE (p_LB_v, p_TBE_v in Fig. 2B). The model allowed selection of different vaccination coverages and accordingly modified probabilities of contracting LB/TBE. Persons who acquired disease despite the vaccination were interpreted to have the same probabilities for disease progression as those not vaccinated. No herd immunity was assumed.

As the subject of this study was a potential vaccine, its main parameters, costs and effectiveness, were unknown and they had to be assumed. To cope with this uncertainty, several scenarios with different costs and effectiveness of the vaccine were analysed.

In the base case analysis, we assumed a cost of €50 for a dose of a potential LB/TBE vaccine and a schedule consisting of one initial administration and one booster three years later. Our estimate of the vaccine costs was conservatively based on current cost of an existing TBE vaccine in Slovenia (Šmit, 2012) multiplied by two. We chose a two vaccine dose scenario because all published cost-effectiveness and most of effectiveness studies on LB/TBE vaccines reported their outcomes after two or maximum three vaccine shots (Hsia et al., 2002; Shadick et al., 2001; Šmit, 2012). However, an extensive set of different vaccination schedules has been tested in a sensitivity analysis (5 different scenarios with total of 3–18 vaccine shots per lifetime).

Table 1
List of input parameters.

Parameter	Base case value	Range used in sensitivity analysis[1]	Reference
Vaccination			
Vaccination population coverage	100%	80–100%; a special scenario includes coverage of 12.4%, recorded for TBE vaccination in Slovenia ;	Assupmtion, Grgič-Vitek and Klavs, 2011
Vaccination schedule	2 shots (first year) in total	several special scenarios in sensitivity analysis	Assumption
Cost of a vaccine shot	€ 50	€40–60	Assupmtion
Effectiveness of a vaccine against LB	85.00%	74.00–86.00 % (within 95% CI)	Shadick et al., 2001
Effectiveness of a vaccine against TBE	98.70%	97.98%–99.09% (within 95% CI)	Heinz et al., 2007
Time parameters			
Time horizon	64 annual cycles (from age 18 till age 81)	51–77	Statistical office of the Republic of Slovenia, 2018a
Discount rate for costs/ effectiveness	3.0%	2.4–3.6% (+ several special scenarios)	Uradni List Republike Slovenije, 2013
Model probabilities			
Probability of contracting LB (any form)	0.00009–0.000303 (detailed age-depenent data provided in Appendix)	± 20%	The National Public Health Institute of the Republic Slovenia, 2018
Probability of contracting TBE (any form)	0.0000151–0.0000353 (detailed age-depenent data provided in Appendix)	± 20%	The National Public Health Institute of the Republic Slovenia, 2018
Probability of natural death	0.00039–0.05814 (detailed age-depenent data provided in Appendix)	± 20%	Statistical office of the Republic of Slovenia, 2018a
TBE specific mortality	age-dependent, 0% age18–60, 2.3% > 60	± 20%	Logar et al., 2006
Proportion of EM pt among LB pt	0.90000	0.72000–1.00000	Data available at LBOC, 2018
Proportion of LNB pt among LB pt	0.07730	0.06184–0.09276	Data available at LBOC, 2018
Proportion of ACA pt among LB pt	0.07890	0.06312–0.09276	Data available at LBOC, 2018
Proportion of BL pt among LB pt	0.00640	0.00512–0.00768	Data available at LBOC, 2018
Proportion of LA pt among LB pt	0.03390	0.02712–0.04068	Data available at LBOC, 2018
Proportion of LC pt among LB pt	0.00320	0.00256–0.00384	Data available at LBOC, 2018
Proportion of Me pt among TBE pt	0.34400	0.27520–0.41280	Bogovic et al., 2014
Proportion of modME among TBE pt	0.46500	0.37200–0.55800	Bogovic et al., 2014
Proportion of sevME among TBE pt	0.19100	0.15280–0.22920	Bogovic et al., 2014
Proportion of EM sequelae that proceeds from EM	0.08000	0.06400–0.09600	Data available at LBOC, 2018
Proportion of LNB sequelae that proceeds from LNB	0.12000	0.09600–0.14400	Data available at LBOC, 2018
Proportion of ACA sequelae that proceeds from ACA	0.55000	0.44000–0.66000	Data available at LBOC, 2018
Proportion of LA sequelae that proceeds from LA	0.15000	0.12000–0.18000	Data available at LBOC, 2018
Proportion of Me sequelae that proceeds from Me	0.52620	0.42096–0.63144	Data available at LBOC, 2018
Proportion of modME sequelae that proceeds from modME	0.09250	0.07400–0.11100	Data available at LBOC, 2018
Proportion of sevME sequelae that proceeds from sevME	0.50260	0.40208–0.60312	Data available at LBOC, 2018
Proportion of pt with TBE requiering ICU treatment	0.03000	0.02400–0.03600	Data available at LBOC, 2018
Proportion of EM sequelae that fully recovers	0.50000	0.40000–0.60000	Assupmtion
Proportion of LNB sequelae that fully recovers	0.25000	0.20000–0.30000	Assupmtion
Proportion of ACA sequelae that fully recovers	0.10000	0.08000–0.12000	Assupmtion
Proportion of LA sequelae that fully recovers	0.20000	0.16000–0.24000	Assupmtion
Costs			
Direct medical costs			
Cost of treating EM	€ 313.00	€250.40–375.60	Data available at LBOC, 2018
Cost of treating EM sequelae	€ 31.00	€24.80–37.20	Data available at LBOC, 2018
Cost of treating BL	€ 676.00	€540.80–811.20	Data available at LBOC, 2018
Cost of treating ACA	€ 1591.00	€1272.80–1,909.20	Data available at LBOC, 2018
Cost of treating ACA sequelae	€ 110.00	€88.00–132.00	Data available at LBOC, 2018
Cost of treating LNB	€ 4328.00	€3462.40–5,193.60	Data available at LBOC, 2018
Cost of treating LNB sequelae	€ 118.17	€94.54–141.80	Data available at LBOC, 2018
Cost of treating LC	€ 4876.00	€3900.80–5,851.20	Data available at LBOC, 2018
Cost of treating LA	€ 480.00	€384.00–576.00	Data available at LBOC, 2018
Cost of treating LA sequelae	€ 480.00	€384.00–576.00	Data available at LBOC, 2018
Cost of treating Me	€ 1235.00	€988.00–1,480.00	Data available at LBOC, 2018
Cost of treating modME	€ 2915.00	€2332.00–3,498.00	Data available at LBOC, 2018

(*continued on next page*)

Table 1 (*continued*)

Parameter	Base case value	Range used in sensitivity analysis[1]	Reference
Cost of treating sevME	€ 11,100.00	€8880.00–13,320.00	Data available at LBOC, 2018
Cost of treatment in ICU	€ 20,400.00	€16,320.00–24,480.00	Data available at LBOC, 2018
Cost of treating Me sequelae	€ 70.00	€56.00–84.00	Data available at LBOC, 2018
Cost of treating modME sequelae	€ 122.00	€97.60–146.40	Data available at LBOC, 2018
Cost of treating sevME sequelae	€ 28,592.00	€22,873.60–34,310.40	Data available at LBOC, 2018
Indirect costs			
Average gross monthly salary in Slovenia	€ 1687.00	€1349.60–2,024.40	Statistical office of the Republic of Slovenia, 2018b
Average number of work absence days due to TBE	48	38.40–57.60	Bogovič, 2012
Average number of work absence days due to LB	**4.35**	3.48–5.22	Data available at LBOC, 2018
Utilities			
1Utility of EM	0.800	0.960–0.640	Shadick et al., 2001
5Utility of LA	0.690	0.552–0.828	Shadick et al., 2001
4Utility of LC	0.610	0.488–0.732	Shadick et al., 2001
3Utility of LNB	0.520	0.416–0.624	Shadick et al., 2001
6Utility of ACA	0.800	0.640–0.960	Assumption
2Utility of BL	0.800	0.640–0.960	Assumption
Utility of Me	0.977	0.782–1.000	Šmit, 2012
Utility of modME	0.840	0.672–1.000	Šmit, 2012
Utility of sevME	0.371	0.297–0.445	Šmit, 2012
Utility of ICU	0.190	0.152–0.228	Šmit, 2012

Abbreviations: LB – Lyme Borreliosis; TBE – tick borne encephalitis; EM – Erythema migrans; LNB – Lyme neuroborreliosis; ACA – Acrodermatitis chronica atropicans; BL – Borrelial lymphocytoma; LA – Lyme arthritis; LC - Lyme carditis; Me – Meningitis; modME – moderately severe meningoencephalitis; sevME – severe meningoencephalitis and meningeoencephalomyelitis; ICU – intensive care unit.

Another important assumption was made for the vaccine effectiveness. As there were no data on the effectiveness of a potential vaccine with combined protection against LB/TBE, in the base case analysis we ascribed reported effectiveness rates estimated separately for (old) LB and TBE monovalent vaccines. The 98.7% field effectiveness reported for TBE vaccine (Heinz et al., 2007) was used as an effectiveness rate against TBE in a potential vaccine. Information on LB vaccines, which was much scarcer and mostly limited to 2–3 year follow-up periods, indicated effectiveness rate between 62% and 85% (Shadick et al., 2001). The latter was used as an effectiveness rate in our base case analysis, while the former was tested in the sensitivity analysis, together with lower and upper confidence intervals of all reported effectiveness rates against LB and TBE.

2.4. Costs and utilities estimates

All costs in the model were collected from the local Slovenian sources and expressed in 2016 € (Table 1). Each of the defined Markov health states had an annual estimate of direct costs based on the local Slovenian data. To get LB and TBE specific indirect costs, the proportion of days lost due to LB or TBE (48 and 4.35 days for TBE and LB, respectively (Bogovič, 2012; Data available at LBOC, 2018)) was multiplied by the average yearly salary (Statistical office of the Republic of Slovenia, 2018b).

To express health benefits in QALYs, the model required separate estimates of health utilities per each defined Markov state (Table 1). While quality of life of most of the LB and TBE states could be described with the estimates from published sources (Shadick et al., 2001; Šmit, 2012), there were no data on ACA and BL. Conservatively, we assigned utilities of the least damaging LB state, i.e. EM, to both ACA and BL.

2.5. Sensitivity analysis

Univariate sensitivity analysis (SA) was conducted by varying each of the 64 input parameters in the model ± 20% or, when possible, within established 95% confidence intervals to ascertain their impact on the main cost-effectiveness estimate (ICER). As 62 of 64 parameters presented point estimates without available 95% confidence intervals (Table 1), a simultaneous variation of all parameters within their ± 20% ranges through a standard probabilistic sensitivity analysis would result in potentially imprecise outcomes. Notably, potential probabilistic sensitivity analysis would create confidence intervals around the base case cost-effectiveness estimate that would predominantly depend on the arbitrary selected range of input parameters, leading to non-informative uncertainty estimates. Therefore, the impact of the most uncertain parameters was additionally tested outside the predefined parameter ranges through the scenario analyses. The most uncertain parameters included the schedule of vaccination (5 scenarios), vaccine effectiveness rates (1 scenario for LB vaccine effectiveness), costs of a potential LB/TBE vaccine (3 scenarios), discount rates (3 scenarios), indirect costs (1 scenario), TBE mortality (1 scenario) and time horizon of the analysis (1 scenario). More detailed description of all listed scenarios is provided in Table 2.

3. Results

3.1. Base case

A potential vaccination with an anti-tick vaccine that would combine protection against LB and TBE in Slovenia resulted in a total costs estimate of €95.10 per person, while the current “no vaccination” strategy equalled to €17.97 per person (Table 3). Of the total costs per person in the vaccinated population, €94.35 went to the costs of vaccines and only €0.75 per person to the treatment of LB/TBE that occurred despite vaccination. As all costs in non-vaccinated population related to the LB/TBE treatment costs, the vaccine prevented €17.22 of €17.97 treatment costs. Incremental costs required to introduce a potential LB/TBE vaccination was estimated at €77.13 per person (Table 3). Main utilities’ estimates in the base case setting were 25.9962 QALY and 25.9946 QALY per person for vaccinated and non-vaccinated populations. The vaccination lowered time spent in disease and sequelae phases of LB/TBE, which led to total utilities increase estimated at 0.0017 QALY per each person in the vaccinated population and a base case ICER at €46,061/QALY (Table 3).

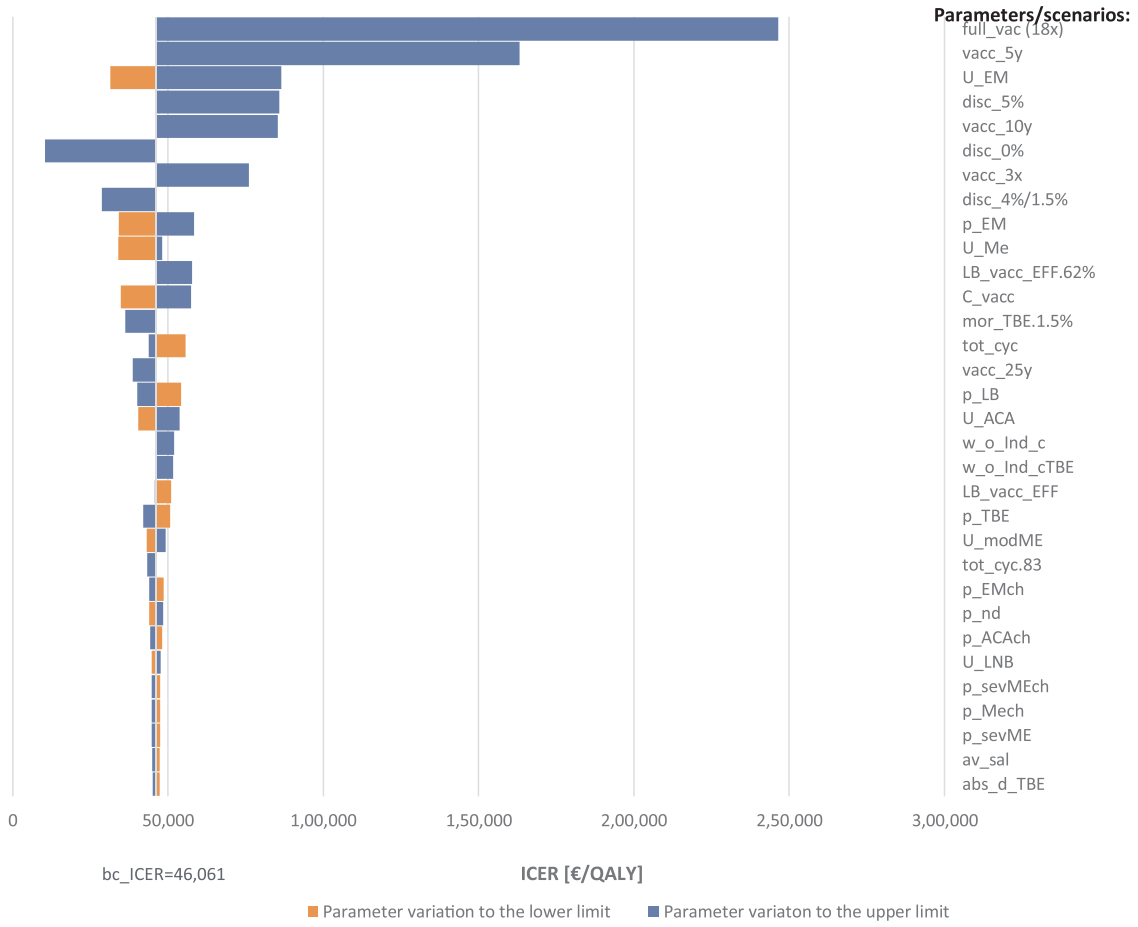

Fig. 2. Tornado diagram.

Abbreviations used for parameters/scenarios in Fig. 2: full_vac(18x) - full vaccination scenario considers 18 vaccine shots; vacc_5y - vaccination each 5 years; U_EM - utility of state Erythema migrans (EM); disc_5% - discounting costs and utilities at 5%; vacc_10y - vaccination each 10 years; disc_0% - no discounting of costs and utilities; vacc_3x - 3 vaccine shots during first year followed with no vaccination after that; disc_4%/1.5% - discounting of costs at 4% and utilities at 1.5%; p_EM - proportion of EM patients among Lyme borreliosis (LB) patients; U_Me - utility of state Meningitis; LB_vacc_EFF.62% - vaccine effectiveness against LB set at 62%; C_vacc - cost of vaccine; mor_TBE.1.5% - mortality of TBE set at 1.5% for all ages; tot_cyc - total number of cycles in the model; vacc_25y - vaccination each 25 years; p_LB - probability of contracting LB; U_ACA - utility of state Acrodermatitis chronica atrophicans (ACA); w_o_Ind_c - scenario without indirect costs included; w_o_Ind_cTBE - scenario without indirect costs for tick-borne encephalitis (TBE); LB_vacc_EFF - vaccine effectiveness against LB; tot_cyc83 - scenario with the model lasting 83 cycles; p_EMch - proportion of patients with EM that have sequalae; p_nd - probability of natural death; p_ACAch - proportion of patients with ACA that have seqalae; U_LNB - utility of state Lyme neuroborreliosis; p_sevMEch - proportion of patients with severe meningoencephalitis (sevME) that have sequalae; p_Mech - proportion of patients with meningitis that have sequalae; p_sevME - proportion of patients with sevME among patients with TBE; av_sal - avarage annual salary in Slovenia; abs_d_TBE - annual number of days absent from work due to TBE.

3.2. Sensitivity analysis

Parameters and predefined scenarios affecting the base case ICER by more than €1,000/QALY are shown in Fig. 2 and in the details in the table of Supplemental material 2.

Changes to the vaccination schedule would have the greatest impact on the ICER. Notably, in the scenario with 18 vaccine shots during a person's lifetime, the ICER increases from €46,061/QALY to €246,456/QALY. Vaccination every 5 years, every 10 years or only 3 times in total would result in ICERs of €163,117/QALY, €85,280/QALY and €75,921/QALY, respectively. Comparably important parameters seem to be discount rates and utility value of the EM state. Variation ± 20% of utility of EM changed ICER from €86,409/QALY to €31,400/QALY. Discounting of both costs and utilities at 5% would increase ICER to €85,775/QALY, while no discounting would result in an ICER at €10,301/QALY. Differential discounting of costs at 4% and utilities at 1.5% led to an ICER of €28,709/QALY. All other parameters/scenarios affected the ICER to a considerably smaller extent (Fig. 2, Supplemental material 2).

Using the presented cost-effectiveness model, it was possible to establish vaccine prices needed to achieve certain predefined cost-effectiveness levels under base case values of all other parameters (Table 4). A price of a vaccine shot set at €55.71 would enable cost-effective ICER according to the World Health Organisation merits (WHO Commission on Macroeconomics and Health, 2001), which equals to 3 GDP/c or 52,500/QALY in Slovenia (Statistical office of the Republic of Slovenia, 2018b). The vaccination would be considered a very cost-effective option with an ICER at 1 GDP/c or €17,500/QALY if the vaccine would cost €24.66. Finally, keeping all other parameters fixed at the base case value, a vaccine cost of €9.13 would render the vaccination against LB/TBE pharmacoeconomically dominant in comparison to no vaccination strategy, meaning that it would result in health gains followed by cost savings.

4. Discussion

The present study assessed cost-effectiveness of a potential vaccination against LB and TBE with a single anti-tick vaccine in a highly endemic setting of Slovenia. For the first time, it synthesizes natural courses of LB and TBE in a single mathematical model substantiated

Table 2
List of special scenarios conducted in the analysis.

Parameter (number of scenarios)	Description of a parameter in each of special scenarios
Vaccination schedule (5)	3 vaccine shots in first year followed by a shot each 5 years (until the age of 60), then each 3 years (18 shots in total) 1 vaccine shot each 5 years 1 vaccine shot each 10 years 1 vaccine shot each 25 years 3 vaccine shots in the first year
Vaccine effectiveness against LB (1)	lower effectiveness rate from the literature (62%)
Vaccine price (3)	vaccine price that provides cost-effectiveness (ICER < €52,500/QALY) vaccine price that provides high cost-effectiveness (ICER < €17,500/QALY) vaccine price that provides pharmacoeconomic dominance (C ≤ 0, E > 0, ICER ≤ 0)
Discount rates (3)	discount rates at 5% discount rates at 4% differential discounting (4% for costs and 1.5% for utilities)
Indirect costs (1)	indirect costs excluded
TBE mortality (1)	TBE mortality of 1.5% for all ages
Time horizon	time horizon prolonged to 100 years

Table 3
Base case cost-effectiveness results[1].

Outcome	Vaccination arm	No intervention arm
Costs [€]:		
Vaccination cost	94.35	0.00
Treatment cost of LB disease	0.42	2.80
Treatment cost of LB sequelae	0.06	0.42
Treatment cost of TBE disease	0.02	1.79
Treatment cost of TBE sequelae	0.04	3.00
Indirect costs (absenteesm)	0.20	9.95
Total costs per person [€]	*95.10*	*17.97*
Difference in costs (Vacc.-No Interv.)	*77.13*	
Utilities [QALY]:		
Obtained in state susceptable	25.9951	25.9768
Obtained in LB disease	0.0007	0.0049
Obtained in LB sequelae	0.0002	0.0016
Obtained in TBE disease	0.0001	0.0079
Obtained in TBE sequelae	0.0000	0.0033
Total utilities per person [QALY]	*25.9962*	*25.9946*
Difference in utilities (Vacc-No Interv)	*0.0017*	
Incremental cost effectiveness ratio [€/QALY]	***46,061***	

Legend – 1-Base case concerns the set of all input parameters at their main values as provided in second column of Table 1.

Table 4
Determination of a vaccine price required to achieve different cost-effectiveness levels.

Cost-effectiveness level	ICER [€/QALY]	Price of a vaccine shot [€]
Base case	46,061	50.00
Vaccination being cost-effective[1]	52,500	55.71
Vaccination being very cost-effective[2]	17,500	24.66
Vaccination being dominant strategy[3]	< 0 (ΔC < 0, ΔE > 0)	9.13

Legend: 1-according to the WHO a limit for cost-effectiveness is 3 GDP/capita - 52,500€/QALY in Slovenia; 2-according to the WHO a limit for high cost-effectiveness is 1GDP/capita - 17,500€/QALY; 3-pharmacoeconomic dominance of an intervention relates to the situation when an intervention delivers additional health benefits followed by reduction of costs.

with the high quality epidemiological data, and provides a framework for effectiveness/cost-effectiveness examination of future preventive/curative approaches that would target these tick-borne diseases. It is one of the rare studies to examine health economics of an upcoming preventive strategy on which main parameters, such as a vaccine cost and effectiveness, are still unknown.

Cost-effectiveness evaluations of the monovalent TBE vaccine considered the vaccine cost-effective in Slovenia, Austria and Estonia with ICERs between €15,000 and €61,000/QALY, while it was judged as not cost-effective for Sweden (Askling et al., 2015; Jürisson et al., 2015; Šmit, 2012). All three studies on LB vaccine from the United States suggest that in highly endemic regions the LB vaccine would prove more cost-effective than in regions with lower LB incidence (Hsia et al., 2002; Meltzer et al., 1999; Shadick et al., 2001). However, only one of the studies estimated cost-effectiveness through the generically comparable outcome of $/QALY, reported ICER of $62,300/QALY (~54,000 €/QALY)and considered the vaccine to be cost-effective (Meltzer et al., 1999).

It has been estimated that a potential LB/TBE vaccine, as defined in the present study, would bring 0.0017 QALY per person in the whole Slovenian population for an investment of €77.13 per person, leading to the cost-effectiveness estimate of €46,061/QALY. This makes the LB/TBE vaccination a cost-effective strategy in Slovenia according to the criteria of WHO (WHO Commission on Macroeconomics and Health, 2001). However, several major uncertainties exist, that are predominantly inherent to the early state of vaccine development in which this study was undertaken. Different vaccine schedules and varying discount rates resulted in particularly large variations in the ICER. Since the final vaccine schedule could be established only years after the vaccine's authorisation, we tested a wide range of schedules (2–18 shots) that resulted in five-fold different ICERs (€46,000–€250,000/QALY).

Discounting is a more general problem in a long-term cost-effectiveness modelling of which a vaccination is a typical example. As most preventive strategies incur costs immediately and bring benefits later during a lifetime period, lower discounting of health benefits presents more favourable cost-effectiveness results. In our study a discounting range from 0 to 5% changed the ICER from €10,000/QALY (highly cost-effective) to €85,000/QALY (not cost-effective). It is debatable whether the base-case discount rates of 3% for costs and utilities applied in this analysis (Uradni list Republike Slovenije, 2013) accurately address people's preferences for costs and benefits. Namely, a recent critical review on discounting in 84 cost-effectiveness studies of different vaccines suggested that lowering and delay of discount rates, or differential discounting (higher for costs than for utilities) may lead to more realistic cost-effectiveness estimates (Jit and Mibei, 2015).

One of the main purposes of the presented analysis was to inform the anti-tick vaccine developers and manufacturers on thresholds of vaccine price and effectiveness that would lead to an acceptable cost-effectiveness for the vaccination strategy in an endemic setting, such as Slovenia. If a potential anti-tick vaccine achieves the effectiveness of separate TBE and LB vaccines, price that leads to a favourable cost-effectiveness ranges between €25 and €50 per shot, and prices below €9 provide cost savings. On the other hand, failure to achieve cited effectiveness rates against LB and TBE or potential improvement beyond these rates, would accordingly change the pricing frame for a potential anti-tick vaccine. Finally, due to relatively higher incidence of LB in comparison to TBE, the model outlined effectiveness against LB as much more influential for cost effectiveness of a potential LB/TBE vaccine.

Since the major cause of uncertainty in our study concerns its hypothetical nature, with exact costs and effectiveness of the vaccine still being core unknown variables, all findings should be interpreted with caution and understanding of the parameters' uncertainty. Nonetheless, we note that the study provides a valuable tool for future health technology evaluations with a comprehensive and flexible model that can

be utilised in pre-registration phase of any combined LB/TBE prevention strategy, and with the ability to support and enhance the understanding of the reimbursement potentials of the combined vaccine to the developer, producer and authorities.

The present study also has several other limitations. For example, there is a lack of (reliable) data on 5-year recovery rates from LB sequelae. Therefore, we relied on the best estimates of experienced clinical experts (Data available at LBOC, 2018).

To conclude, we analysed the cost-effectiveness of a potential anti-tick vaccine that would combine protection against LB and TBE in Slovenia. Inherent to early HTA, some key parameters were unknown. Yet, the model provides a tool to analyse health economics of any future LB/TBE vaccination strategy in highly endemic regions for one or both diseases, advices authorities in planning immunization programs and provides the insights into potential price/effectiveness combinations that could be feasible and attractive to both the manufacturers and the authorities. The base-case ICER was below commonly accepted thresholds of cost-effectiveness, indicating that a potential LB/TBE vaccine might be a cost-effective option in Slovenia under specific assumptions for these key parameters. The results should be taken with caution, as they are prone to significant structural and parameter uncertainty which is again inherent to the early-HTA context in which we analysed the potential vaccine.

Conflict of interest statement

JM received honoraria from AstraZeneca and Sanofi, all fully unrelated to this research. JH is the coordinator of the Fp7-funded ANTIDotE project (see below). HS and PB have no conflicts of interest to declare. MJP received grants and honoraria from various pharmaceutical companies, inclusive those potentially interested in developing, producing and marketing tick-borne diseases' vaccines. Also, MJP reports stock ownership of Ingress Health (Rotterdam/Wismar, The Netherlands/Germany) and Pharmacoeconomics Advice Groningen (PAG Ltd; Groningen, The Netherlands) and advisorship of Asc Academics (Groningen, The Netherlands). MJP is member of the Joint Committee of Vaccination & Immunization (JCVI), obviously opinions stated in this paper are his personal ones and not necessarily JCVI's. FS is an unpaid member of the steering committee of the ESCMID Study Group on Lyme Borreliosis/ESGBOR.

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Appendix A. Supplementary data

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