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REVIEW

Reviewing estimates of the burden in disability-adjusted life years (DALYs) of tick-borne encephalitis in Slovenia

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ABSTRACT

Introduction: Tick-borne encephalitis (TBE) reflects an increasing burden and can affect public health policy. Vaccination could be the most effective option to reduce the disease burden, this review can support national recommendations for TBE vaccination in Slovenia.

Areas covered: This burden is relatively high in Slovenia and can be estimated by using an incidence-based disability-adjusted life years (DALYs) methodology. Notably, DALYs have been estimated for Slovenia in various studies. The present study summarizes the main differences and conclusions between two studies that dealt with the calculation of DALYs for TBE in Slovenia. The databases of PubMed and Embase were used to get information about publications that dealt with the TBE burden, using an incidence-based DALYs methodology, in Slovenia.

Expert opinion: Permanent sequelae contribute the most to the total burden in DALYs. Increasing vaccination in all ages and age groups can be the most effective and efficient strategy to reduce the burden of TBE and protect the whole population health.

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Tick-borne encephalitis (TBE); burden; disability-adjusted life years (DALYs); adults; children

1. Introduction

Analyses of the burden of a disease can help to guide health policy for vaccination against vaccine-preventable diseases [1], including tick-borne infections. Tick-borne encephalitis (TBE) is transmitted by the bite of infected ticks and/or through unpasteurized milk [2]. TBE is one of the most serious infectious diseases of the central nervous system and may lead to permanent neurological sequelae or even death. It reflects a growing burden in many parts of Europe as well as in other parts of the world [3]. Slovenia is one of the countries with the highest reported incidence rates of TBE in Europe [4]. Vaccination is the most effective protection against the disease and can avoid the consequences associated with TBE and reduce the burden. Although there are effective, safe and well-tolerated vaccines for adults and children against TBE available, vaccination is too low in many European countries, inclusive of Slovenia, to effectively reduce the burden [5]. The aim of the present study is to review two published calculations of the TBE burden, expressed in disability-adjusted life years (DALYs) and summarize the main differences and conclusions. The findings can support further development of optimized health policies and guidance on vaccination against TBE in Slovenia.

2. Literature search

PubMed and Embase were used to get information about publications that dealt with the TBE burden, using an incidence-based DALYs methodology, in Slovenia. Notably, four publications were identified: two full-length original

publications [6,7], one Letter to the Editor [8] and one full-length paper for the European Union and European Economic Area (EU/EEA) [9].

3. Publications reviewed

Only full-length original publications that have dealt with only the TBE burden and only in Slovenia are included, therefore more attention is given to the two publications [6,7]. The main dissimilarities that contribute the most to the different conclusions between these two publications are summarized in Table 1.

3.1. Šmit and Postma, 2015 [6]

3.1.1. Input data for the model

A novel model, using *Slovenian* percentages for specific health states [10,11] was developed, explicitly taking into account the differences between adults and children: 58% of adults [10], and 2.3% of children [11] with TBE develop permanent sequelae. These were divided by severity, as mentioned by clinical publications [10–13] into mild, moderate and severe sequelae. In adults 10% had mild, 46% moderate and 2% severe sequelae [6,10]. In children 0% had mild, 1.5% moderate and 0.8% severe sequelae [6,11]. Mild sequelae do not have a significant impact on patients' daily activities, social and working capacity. Moderate sequelae affect patients' daily activities, social and working capacity. In patients with severe neurological sequelae, social life and working capacity can be seriously affected and in a few cases, patients need institutional care.

Article Highlights

- TBE is one of the most serious infections of the central nervous system that may lead to permanent sequelae or even death.
- TBE cases with central nervous system problems are 4.5 higher than the officially reported number.
- TBE presents an increasing burden, optimally evaluated with DALYs that can support health policy for TBE vaccination.
- Permanent sequelae contribute the most to the total burden in DALYs.
- Vaccines are safe, well tolerated and cost-effective, being the most effective way to reduce the burden of TBE.
- Increasing vaccination in all ages and age groups can be the most effective and efficient strategy to reduce the burden of TBE and protect the whole population health.

This box summarizes key points contained in the article.

Specific disability weights for permanent sequelae were used as follows: mild at 0.023, moderate at 0.160 and severe at 0.629. Because TBE incidence can be considered to be underestimated [14,15], a methodology for calculating underestimation [16] was developed and used, with the resulting multiplication factor at 4.5 (range: 3.5–5.5) being included in the DALYs' calculations.

3.1.2. Results

The incidence rate of TBE was reported at 12 per 100,000 population in 2011, corresponding to a total burden in DALYs of 3,450 (167.8 per 100,000 population) for the whole of the Slovenian population. From the individual perspective, DALYs

per case amounts to 3.1. The impact of permanent sequelae reflects 94% of the total burden in DALYs per year, emphasizing the huge impact on patients' daily activities, social and working capacity. Within the total burden of permanent sequelae, the burden of moderate sequelae presents 77.6%, followed by the burden of severe sequelae (14.0%) and the burden of mild sequelae (2.4%). Furthermore, it was estimated that 85% of the *total* burden (in terms of % of total DALYs) is among the age group from 15 to 64 years (average over 2004–2011), reflecting the potentially major impact on productivity. Results of the probabilistic sensitivity analyses showed 0.95 likelihood that total DALYs are higher than 2,394.

3.1.3. Recommendations

It was suggested to prioritize prevention of TBE disease further and reallocate limited public health resources, for example, for an extended TBE vaccination for all groups, ages and regions, potentially free of charge or at a reduced price in Slovenia. In particular, continued awareness raising and corresponding increased vaccination coverage is needed to reduce TBE and improve the whole population health with these vaccines that have the potential to be highly cost-effective. Extended vaccination may result in major health benefits to the population as a whole as well as cost savings to the health-care system.

3.2. Fafangel et al., 2017 [7]

3.2.1. Input data for the model

A general model, as well as the 'BCoDE toolkit' software application to calculate DALYs for TBE, were used [9,17], taking into

Table 1. The main differences between the two studies that dealt with the calculation of DALYs for TBE in Slovenia.

Author and the year of publication	Šmit and Postma, 2015 [6]	Fafangel et al., 2017 [7]
Input data for the model:		
Incidence per 100,000 population	12	11.6
Health states from	Slovenian	Swedish, Lithuanian
Permanent sequelae	Adults (58%) Children (2.3%)	All ages (35.7–38.8%)
Severity of permanent sequelae	Adults Mild (10%) Moderate (46%) Severe (2%) Children Mild (0%) Moderate (1.5%) Severe (0.8%)	Not divided by severity, nor by adults and children
Disability weights for permanent sequelae	Mild (0.023) Moderate (0.160) Severe (0.629)	Not divided by severity (0.056)
Multiplication factor	4.5 (3.5–5.5)	Neither calculated nor applied
Results:		
Population perspective:		
DALYs	3,450	224.52
DALYs/100,000 population	167.8	10.95
Individual perspective:		
DALYs/case	3.1	0.23
Total permanent sequelae	94%	38%
Permanent sequelae by severity	Mild (2.4%) Moderate (77.6%) Severe (14.0%)	Not differentiated by severity
The highest burden	85% among the 15–64 year-olds (in terms of the total DALYs)	Among the 5–9 year-olds (in terms of DALYs per 100,000 stratum-specific population)
Recommendation for vaccination to reduce the disease burden	All ages, groups and regions free of charge or at a reduced price	Children

DALYs = disability-adjusted life years.

account percentages of health states which were taken from Swedish [12,18–20], Lithuanian [13] data for *adults*, which were also applied to *children*. From these data, calculations were done and conclusions were made for Slovenia. *Permanent sequelae* are actually the same as a *chronic post-encephalitic syndrome*. Although Fafangel et al. used chronic post-encephalitic syndrome, the term *permanent sequelae* will be used in the present discussion. According to Fafangel et al. 35.7% to 38.8% of *adults as well as children with the post-encephalitic syndrome* (that is not chronic, but lasts one year) developed permanent sequelae [7], while in the quoted clinical studies [12,18], 35.7% to 38.8% of *adults with TBE* developed permanent sequelae. This may have led to under-estimating the total burden of TBE in DALYs. The permanent sequelae were not divided by the severity into mild, moderate and severe [7] as it was mentioned in the quoted clinical publication [12]. The disability weights of 0.056 for permanent sequelae and 0.051 for symptomatic infections (acute first stage with symptoms similar to flu) were used, while this symptomatic infection does not have a significant contribution (only 0.3%) to the total DALYs. Considering that disability weights for permanent sequelae and for symptomatic infections (acute first stage with symptoms similar to flu) are nearly the same, it is to be concluded that the permanent sequelae have been quantified as the same severity as for the first phase of the disease with symptoms similar to influenza. Multiplication factors for under-estimation were neither calculated nor applied in the DALYs calculations.

3.2.2. Results

The mean annual incidence rate of TBE being 11.6 per 100,000 population was reported in the period from 2009 to 2013, corresponding to a total burden of 224.52 DALYs per year from the population perspective (10.95 per 100,000 population per year) for Slovenia. From the individual perspective, each case of TBE accounted for an average of 0.23 DALYs. The impact of permanent sequelae causing only 38% of the total burden in DALYs per year. The *highest* burden (in terms of DALYs per 100,000 stratum-specific population) is among the 5–9 year-olds.

3.2.3. Recommendations

It was recommended to design vaccination programmes targeting children where it was argued that the highest impact on reducing the burden of the disease could be achieved.

4. Discussion and conclusions

It is noted that the disease burden can be evaluated with DALYs as one measure that combines information on the incidence/prevalence, mortality and sequelae [1]. DALYs reflect lost years of healthy life as well as mortality directly [21] and may support health policy to improve population health [1].

The different values of 3,450 total DALYs [6] and 224.52 total DALYs [7] were noted while the highest burden also differed between both studies: among the 15–64-year-olds in Smit & Postma [6] and the 5–9-year-olds in Fafangel [7].

Notably, Fafangel et al. [7] might have under-estimated the total burden of TBE. The main reasons are:

- (i) permanent sequelae were taken from the post-encephalitic syndrome
- (ii) the severity of permanent sequelae were the same as for the first stage of the disease and assumed to mirror symptoms similar to flu
- (iii) multiplication factors to correct for under-estimation of TBE were not used.

Additionally, 36–39% for permanent sequelae were taken for all ages [7] rather than taking differences between adults and children into account [6]. However, a novel model was developed [6] and local data sources [10,11] for health states of the disease model were used, taking into account the difference between adults and children. Also, multiplication factors to correct under-estimation of TBE were calculated and used for DALYs calculations [6].

Seeing that permanent sequelae contribute the most to the total burden of the disease [6,7], this term will be used further on and compared with published clinical studies for Slovenia and other European countries where the European subtype of TBE virus is the most prevalent. To have a clear picture of the permanent sequelae, a review article on clinical studies was used as reference [22].

In studies up till 2010, the percentages of permanent sequelae in children vary between 0% and 10% (mostly defined as seizures, paresis, behavioural and mental disturbances). These studies are from Slovenia [11,23–27] Germany [28], Austria [29,30] and Switzerland [31].

These are low percentages compared to adults, in whom ≤63% of adults develop permanent sequelae, identified in eight European studies (references 1–8) performed from 1980 till 2018. In Slovenia, 58% of adults develop permanent sequelae [10], while in a recent study it is 33% [4]. These percentages are in the range of European studies. Permanent sequelae in these European studies are usually defined as hemiparesis, persistent cranial or spinal nerve paralysis, hearing loss; however, some included cognitive impairment as well [10,32–34]. In Poland, 55% of cognitive impairment in adults was reported [35]. In some studies [10,12,18] a range of 3 to 11% of persisting paralysis in adults was observed. The severity of TBE increases with the age and it is generally more severe in adults, having a bad outcome in terms of sequelae [26,36,37]. From 2012 till 2017, one Czech [38] and two small follow-up Swedish studies [39,40] reported 11 to 69% of cognitive impairment in children after TBE. In a small follow-up German study [41] 58% of children had not specified changes in the EEG and 26% of children had cognitive impairment after TBE.

In a European study [9], the burden of 31 infectious diseases, inclusive TBE, was calculated in the EU/EEA countries, including Slovenia. The TBE burden amounted to 0.69 DALYs per 100,000 population at the European level. The authors used a range of multiplication factor of 3.33–5 for TBE under-estimation, which is more or less the same (3.5–5.5) as calculated in the above discussed publication [6]. It was estimated that the highest burden is in the age group from 15–64 years [9], which confirms previous results [6].

A Letter to the Editor [8] in response to the Europe study [9], proposed further recommendations on the introduction of

a publicly reimbursed TBE vaccination for children at 3 years of age and for adults at 45–50 years of age in Slovenia.

A recent Slovenian clinical study [4] supports the use of the permanent sequelae from patients with TBE as was done in the discussed publication [6].

Although there are more differences between the two discussed studies, the present study concentrates only on the main differences between the studies that have the biggest influence on the conclusions. Therefore, that is a limitation of the present study.

Based on the above analysis, it can be concluded that permanent sequelae contribute the most to the total burden in DALYs for TBE. Further, a model using local disease epidemiological data for calculating the DALYs could give better insight into the national TBE burden for the national recommendation of TBE vaccination in Slovenia [6].

5. Expert opinion

In Slovenia, the TBE vaccine is free of charge only for those who are potentially exposed during fieldwork while the rest of the population has to pay for the vaccination although vaccination is recommended for the general population from the age of one [42,43].

Different policy options were considered for TBE vaccination in Slovenia, including:

- (i) prioritizing prevention of TBE disease further and reallocation of limited public health resources, for example, for an extended TBE vaccination for all groups, ages and regions, potentially free of charge or at a reduced price to improve the whole population health and vaccines can be highly cost-effective [6];
- (ii) vaccination programmes targeting children would have the highest impact on reducing the burden of the disease [7] and
- (iii) the introduction of publicly reimbursed TBE vaccination for children at 3 years of age and for adults at 45–50 years of age [8].

Austria is the only European country where an extended vaccination campaign was launched in 1981 and was the country with the highest recorded incidence of TBE in Europe before the campaign [6,44–46]. There, vaccination is free of charge only for people with occupational risk of TBE, while for the rest of the Austrian population a part of the costs is covered by the health insurance [44]. Vaccination coverage increased from 6% at the beginning of the programme to 88% in 2006, leading to reductions in TBE in all age groups. Between 2000 and 2006, about 2,800 cases were prevented in Austria [6,45].

In line with evidence on the effectiveness of the impact of the TBE vaccines for all ages in Austria [45,46], as well as that the burden is the highest among 15–65 years of age (in terms of the total DALYs) [6] and children (in terms of DALYs per 100,000 stratum-specific population) [7], it can be suggested that the best health policy option is prioritizing prevention of TBE disease further with the corresponding reallocation of limited public health resources for extended vaccination for all groups, ages and regions free of charge or partially covered

by health insurance at a reduced price. That would lead to reducing the burden of TBE and protect the whole population health in Slovenia, as was proposed [6].

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