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<b>Conceptualization</b>	Ideas; formulation or evolution of overarching research goals and aims.		X							X
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13 **Discussion Points:**

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1. Where do we stand in our current knowledge of the burden of Tick borne Encephalitis in Europe?

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2. How is Tick Borne Encephalitis contracted and who are the populations at risk?

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3. There is no current treatment available as of now. Vaccinations remain the most effective tool to combat the lethal complications of the disease.

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4. What are the current vaccination recommendations of Tick Borne Encephalitis in Europe?

19

5. What are the steps we can take to raise awareness of the increasing incidence and burden of Tick Borne Encephalitis?

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1 **ABSTRACT.**

2 **Background**

3 Tick-borne encephalitis (TBE) is a central nervous system disease that is posing a growing public health  
4 challenge in Europe. Its disease burden, despite carrying a significant global impact, is still relatively  
5 unexplored. This study aims to outline a regression model of how the increasing cases will influence the  
6 burden of TBE in the upcoming years, using YLDs (years lived with disability) and DALYs (Disability-adjusted  
7 life years), and address climate change as a determinant.

8 **Methods**

9 Information regarding the number of cases, YLDs and DALYs of TBE was collected from European countries  
10 using available surveillance data from 2012 to 2020. Number of TBE cases and burden projections were  
11 created until 2025, using a linear regression model. The total reported cases of TBE cases in this timeframe,  
12 age-group and gender distribution were inserted and modeled in ECDC BCoDE Toolkit, a software application  
13 that calculates the burden of communicable diseases, YLDs and DALYs of each year. A non-systematic  
14 bibliographic search was conducted exploring the impact of climate change on TBE.

15 **Results**

16 Our findings showed a linear growth in number of TBE cases (74.3% increase), DALYs (71.3%), YLDs  
17 (71.75%) in European countries from 2012 to 2020. By 2025, these factors are likely to increase by 141%  
18 (95% CI: [108%,175%]), 134% (95% CI: [91%,177%]) and 134% (95% CI: [98%,172%]) compared to 2012,  
19 respectively ( $p < 0.0001$ ).

20 **Conclusions**

21 The likelihood of morbidity and mortality increase of TBE, as well as climate-related changes in tick activity,  
22 highlight that prompt action is necessary by introducing preventive measures in European populations.

23

24 **Key Words:** Climate change, Encephalitis, tick-borne, Epidemiology, Europe, Global Burden of Disease, Public  
25 health, Surveillance

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## 1 INTRODUCTION.

2

3 Tick-borne encephalitis (TBE) is a central nervous system disease that has been increasingly spreading in  
4 Europe from its traditional endemic areas in China, Mongolia, and Russia. It is caused by a virus of the family  
5 Flaviviridae and can lead to a wide range of clinical manifestations.<sup>1, 2</sup> The majority of patients, approximately  
6 70% to 85%, who contract the infection are asymptomatic, which may imply a significant number of  
7 undiagnosed cases. However, about 75% of patients infected with the European TBE virus subtype have  
8 experienced a biphasic disease course.<sup>3</sup> The initial phase is related to viremia and patients display  
9 nonspecific symptoms such as fever, myalgia, arthralgia, fatigue, general malaise and anorexia. This phase  
10 lasts for two to seven days which is then followed by amelioration or an asymptomatic interval of about a  
11 week. The second phase then follows, in which 50% of adults present with meningitis, 40% with  
12 meningoencephalitis and 10% with meningoencephalomyelitis. The symptoms of meningitis include the  
13 classic triad of high fever, headache, nausea and vomiting, as well as photophobia and vertigo reported by  
14 some patients. Encephalitis typically manifests with impaired consciousness, ranging from somnolence to  
15 stupor. Meningoencephalomyelitis is usually characterized by flaccid paralysis.<sup>3</sup> The virus life-cycle occurs  
16 through consistent interactions among intermediate hosts, such as rodents and deers, and ticks, *Ixodes*  
17 *ricinus* being the most common in Europe and *Ixodes persulcatus* in the eastern and Siberian regions.<sup>4</sup> The  
18 main route of infection in humans is through a tick bite, while contracting the infection via consumption of  
19 infected unpasteurised dairy products is less common.<sup>5</sup> There is still no specific antiviral therapy to combat  
20 TBE. Mainstay options are supportive or, in severe cases, require hospitalization in intensive care units with  
21 ventilatory support. Although many patients with TBE will recover, up to one third will suffer from long-term  
22 complications such as nonparalytic encephalitis and chronic TBE.<sup>2</sup> Due to limited therapeutic options,  
23 preventive measurements such as vaccinations are essential to reduce the devastating outcomes of TBE.

24 Similarly, the coronavirus disease 2019 (COVID-19) pandemic has revealed several neurological  
25 consequences in which symptoms of COVID-19 encephalitis mimic that of TBE.<sup>6</sup> Majority of Covid-19 patients  
26 are asymptomatic or mildly symptomatic; however, there have been overlap in neurological manifestations of  
27 this infection with TBE in severely ill patients, such as encephalopathies with or without psychosis,  
28 encephalitis, acute disseminated encephalomyelitis and myelitis. TBE is a disease that easily preventable with  
29 vaccinations. In a similar fashion, the COVID-19 vaccines have significantly decreased morbidity and mortality  
30 of the disease, allowing for the prevention of these devastating neurological complications.<sup>7</sup>

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32 Recently, TBE has posed a growing health risk to populations in western European countries and climate  
33 change has been likely to contribute to the increase in its incidence partly because it alters and expands the  
34 niche of tick, which is a disease vector.<sup>8-12</sup> We hypothesized that the increase in the likelihood of arthropod-  
35 borne diseases will consequently lead to a rise in the overall burden of TBE.<sup>13</sup>

36 Our study aims to: (I) illustrate the increasing number of TBE cases since 2012; (II) assess the burden of TBE  
37 through assessment of YLDs (Years lived with disability) and DALYs (Disability adjusted life years); (III)

- 1 predict the future trend through a linear regression model; and (IV) evaluate climate change as a driving factor
- 2 in the increasing burden.
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## 1 METHODS

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3 We used the online Surveillance Atlas of Infectious Diseases of the European Centre for Disease Prevention  
4 and Control (ECDC) to obtain number of TBE cases from 2012 to 2020 in Europe.<sup>14</sup> The Surveillance Atlas of  
5 Infectious Diseases is a tool that presents the latest data obtained through The European Surveillance  
6 System (TESSy) from the Member States on several infectious diseases. The total reported cases (2012-  
7 2020), age-group and gender distribution, were then inserted and modeled in the ECDC BCoDE Toolkit, a  
8 software application that allows the calculation of the burden of disease of a variety of communicable  
9 diseases, to calculate YLDs and DALYs of each year.<sup>15</sup> DALYs and YLDs allow for a measure of disease  
10 burden and injury in a population. One DALY represents the loss of the equivalent of one year of full health  
11 and similarly, one YLD represents the equivalent of one healthy year lost due to disability.<sup>16</sup> Of note, when  
12 data collection at the EU level was initiated, twenty countries reported their TBE cases, whereas, by the year  
13 2020, reported cases from five more countries were included. Our data analysis did not include these  
14 additional reports as the Paired Wilcoxon Signed-Rank test deemed these additions insignificant.

15 On both raw data plots (Figure 1) we observed that the number of TBE cases, YLDs, and DALYs follow the  
16 increasing trend from 2014. Therefore, we decided to use observations from 2014 to estimate the maximum  
17 likelihood chances of each variable. A linear regression model was created for each dataset in RStudio, and  
18 we used metrics such as Residual Standard Error, R-squared, t-statistics and the F-statistics to confirm that  
19 the models fit the data. Residual Standard Error and F-statistics were used to measure how well the  
20 regression model fits the dataset. Linear regression was used because it was the simplest model that we  
21 could use with seven data points. Moreover, we utilized R-Squared, which indicates the proportion of variation  
22 in the dependent variable that has been explained by the model. Finally, we used t-statistics to test for the  
23 significance of the "year" variable in each model. To assess the overall model significance, a two-sided p-  
24 value was obtained with a cut-off set up to 0.05, as outlined in Table 1.

25 To understand the possible effects of environmental alterations, on the life cycle of tick species and  
26 consequently on the rising number of TBE cases, we performed a structured, non-systematic bibliography  
27 search of the PubMed database. We included reviews, laboratory, observational and modeling studies that  
28 focused primarily on the link between climate change and changes in tick and TBE distribution in Europe.  
29 Case reports, case series and surveys were excluded. The search strategy included (((ticks) OR (TBE)) OR  
30 (tick-borne encephalitis)) AND ((climate change) OR (global warming)). 413 articles were identified, from  
31 which we included only those in English. No publication date restrictions were applied, and we did not  
32 consider articles describing solely other tick-borne diseases. The first search was performed on the 14<sup>th</sup> of  
33 October 2021 and updated thereafter. The literature screening and the selection was carried out  
34 independently by three reviewers. Additionally, well-structured reviews on TBE and/or ticks and climate  
35 change were consulted, and its cross-references screened. Altogether, three reviewers identified 10 articles  
36 that were most relevant to our analysis.

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1 **RESULTS.**

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3 While in 2012 there were 2142 reported cases of TBE in Europe, in 2020 there were 3734 cases, indicating a  
4 74.3% rise in eight years. Regarding the disease burden in the EU, from 2012 to 2020, DALYs increased from  
5 488 to 836 (71.3% increase) and similarly, YLDs from 325 to 558 (71.7% increase).

6 The raw data suggest a linear relationship between consecutive years and all three variables (Figure 1). The  
7 value of the R-squared coefficient in all three models is above 0.9, which indicates that the variability of the  
8 response variables is well explained by the year. The R-squared coefficient of TBE reported cases model from  
9 2012-2020 is 0.9384 (95% CI: 0.8784058, 0.9911942). The R squared value for YLDs versus year model is  
10 0.9228 (95% CI: 0.8564565, 0.9891435) and DALYs versus year model is 0.9232 (95% CI: 0.8571859  
11 0.9892141).

12 The regression model created of the estimated number of new cases revealed 3985 cases in the year 2021,  
13 and a rise to 5176 cases in 2025 (95% CI: 4453-5899). The DALYs was predicted to increase from 882 in  
14 2021, to 1143 in 2025 (95% CI: 931-1354). Finally, the predicted YLD value was found to be 589 in 2021, and  
15 then 763 in 2025 (95% CI: 644-883). The estimated values of new cases, DALYs and YLDs in 2025  
16 corresponded to a 141% (95% CI: [108%,175%]), 134% (95% CI: [91%,177%]) and 134% (95% CI:  
17 [98%,172%]) increase from the values of 2012, respectively. The confidence intervals and values calculated  
18 for each predicted year is outlined in Table 1 and Figure 2.

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## 1 DISCUSSION.

2 Since the initiation of the data registry amongst the EU/EFTA countries in 2012, the number of TBE cases  
3 showed an overall major increase of 74.3% by 2020, based on the latest available information.<sup>14</sup> This was  
4 accompanied by an increased disease burden quantified by DALYs and YLDs. Therefore, based on our  
5 projections, a 175% increase in TBE cases from 2012 is possible by the year 2025, highlighting the need for  
6 prompt action. A contributing factor to the expansion of TBE is the continuous spread of ticks' species, which  
7 has largely been associated with climate variability.

8 Climate change has been suggested to have a direct influence on the epidemiology of vector-borne disease.<sup>13</sup>  
9 A predicted increase of 1.0 - 3.5 degrees Celsius is estimated by the year 2100, potentially causing an  
10 increase in the likelihood of many vector-borne diseases. TBE is not an exception and is becoming a public  
11 health concern.<sup>8, 13</sup> According to previous studies, the changes in the density and distribution of the tick  
12 population, particularly the shift to previously hostile areas and the associated increase in tick-borne pathogen  
13 transmission, are influenced by climate variability, most notably rising temperatures.<sup>10, 11</sup>

14 Environmental changes are thought to be a selective pressure inducing the adaptation in both ticks'  
15 physiology and behavior. Laboratory and field studies have shed some light on the biological mechanism that  
16 potentially underlies this alteration in density and distribution, as ticks are susceptible to temperature and  
17 humidity.<sup>17, 18</sup> It was shown that rising temperature causes acceleration of the cycle development and the  
18 production of eggs. Furthermore, the incubation period and stages of the tick life cycle have a shorter duration  
19 when exposed to higher temperatures.<sup>18, 19</sup> Altogether, that could boost transmission risk through increased  
20 vector population within a favorable temperature range and as a result, an increased TBE morbidity in the  
21 EU/EFTA can be expected.

22 Correspondingly, models which use satellite data to represent a change in environmental factors important for  
23 sustaining foci of TBE, suggest that climate change could be partly responsible for increasing number of  
24 cases in Europe.<sup>12, 20, 21</sup> Indeed, Species Distribution Modeling of the climatic niche of the most important  
25 vector of TBE in Eurasia (tick *Ixodes ricinus*) shows an increase of a climatically suitable area between 2050  
26 and 2080 of about two times greater than the current area.<sup>20</sup> Furthermore, a rise in temperature and a  
27 decrease in moisture in the summer is likely to cause a shift of distribution of TBE into higher-latitude and  
28 higher-altitude regions progressively through the 2020s, 2050s and 2080s.<sup>21</sup>

29 The shift estimated by the models is supported by already observed northern longitudinal extension of ticks in  
30 Sweden and expansion of the ticks population into higher altitudes in Central Europe in Czech Republic.<sup>10, 11</sup>  
31 Both examples demonstrate an establishment of the tick population in the new, previously hostile area for  
32 their survival and development.

33 However, it is important to take into consideration that estimating the impact of global warming quantitatively  
34 on the epidemiology of TBE is difficult, due to the complex interplay between biotic and abiotic factors that  
35 influence hosts, arthropods and pathogens. Additionally, we must consider climate-related changes in human  
36 behavior, such as more time spent outdoors due to increased number of warmer days, which contributes to  
37 the rising number of TBE cases by putting people directly at risk of infection.<sup>9, 22</sup>

1 Our study has some limitations. For instance, it included combined data that were collected from individual  
2 countries in the EU/EFTA, which have different reporting systems and preventive measures. Additionally,  
3 ECDC has reported under-ascertained infections and under reporting across countries, limiting the number of  
4 reported cases used in our study. Data collected are limited to the years 2012-2020 as ECDC initiated EU  
5 surveillance of TBE cases in 2012. Having a larger dataset with a unified data-collecting protocol would allow  
6 us to confirm with better accuracy that the linear trend was chosen correctly. Therefore, the projected  
7 increasing trend may not be representative of a longer period of time. Most importantly, the five-year  
8 estimations are solely based on yearly statistical data that we collected without consideration of any other  
9 variables. Moreover, we conducted nonsystematic bibliographic search when exploring climate change as a  
10 plausible driving factor in increasing TBE burden. Due to these confounding factors, we suggest that future  
11 TBE-related projections be studied in countries at risk and more systematic approach to be undertaken when  
12 examining causative factors.

13 Our study explored the increasing number of TBE cases in Europe since 2012, in relation to the expansion of  
14 endemic areas and the prolongation of tick activity season, which in turn is enlarging the disease burden. We  
15 offered a simplified model, based on limited data, which showed the likely continuation of this trend in the  
16 coming years, with the aim to increase countries' awareness of this largely preventable disease. At present,  
17 vaccination policies vary with nations, and low vaccine coverage for populations at risk is a definite factor for  
18 increase morbidity. In Austria, for instance, mass vaccination campaign that began in 1981 and reached a  
19 coverage of 82% for its entire population by 2015 dramatically reduced annual cases compared to pre-  
20 vaccination era, whereby Austria held the highest recorded TBE-related morbidity in Europe.<sup>23</sup> By contrast,  
21 the Czech Republic, where surveillance of TBE is similar to Austria, only 10% of its at-risk population was  
22 vaccinated by the year 2000, and an opposite trend was observed when cases continued to rise each year,  
23 highlighting the effectiveness of an extensive TBE vaccine coverage. In addition, in some countries the risk of  
24 TBE is underestimated, likely due to low awareness of physicians.<sup>24</sup> Amongst preventive measures,  
25 individuals partaking in outdoor activities should be informed that long sleeve clothing, insect repellents and  
26 prompt eventual tick removal, are effective ways to avoid TBE infection. Moreover, strategies for effective  
27 locally adapted sustainable vector control, as indicated in the WHO document *Global Vector Control*  
28 *Response 2017-2030*, are essential to diminish TBE impact. Apart from raising public awareness regarding  
29 the risks of tick bites, vaccinations in endemic areas remain the most crucial and powerful preventive tool  
30 available for protection against TBE, as previously mentioned.<sup>25</sup> WHO recommends to establish public  
31 immunization strategies and provide vaccinations to all age groups in areas where the disease is highly  
32 endemic, defined as an incidence of clinical disease of  $\geq 5$  cases/per 100,000 population per year.<sup>26</sup> Since  
33 definitive therapeutic options are not yet available to treat TBE, it is of key importance that primary prevention  
34 measures are implemented to control transmission and infection, especially in the regions and countries that  
35 have experienced the largest increase in TBE cases.

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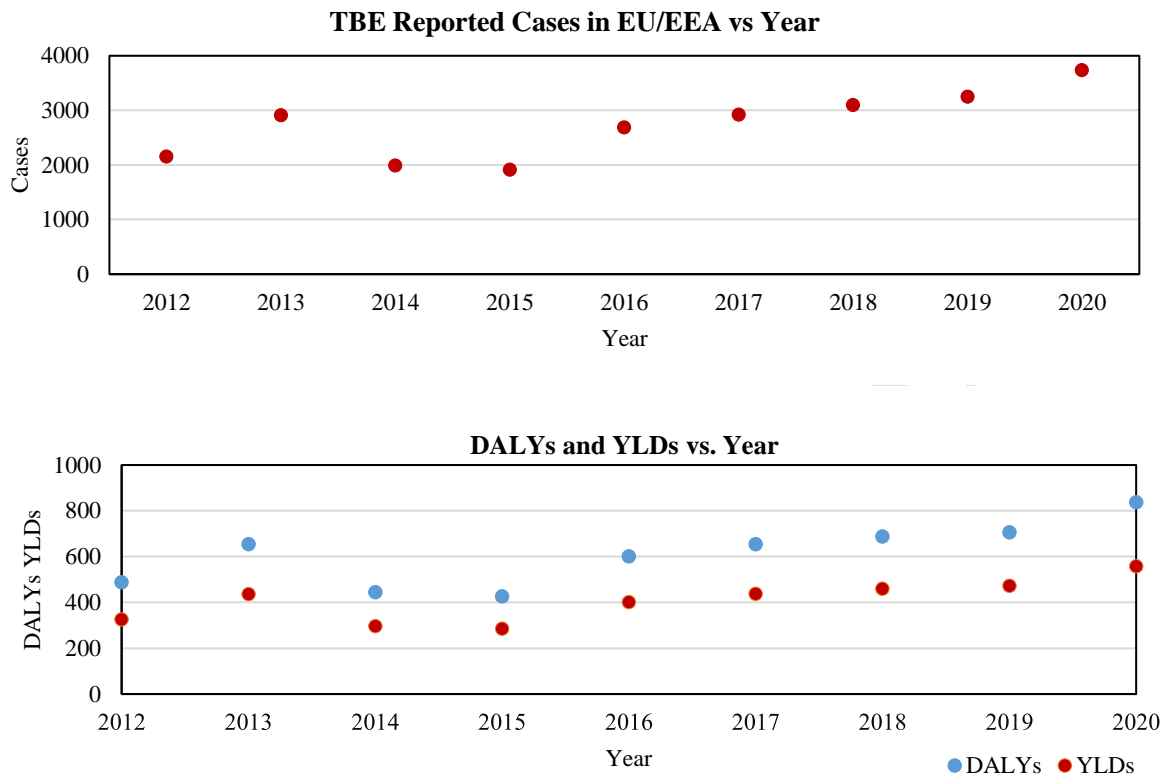
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1 **FIGURES AND TABLES.**

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3 **Figure 1.** Historical Data Indicating the Number of Reported Cases in EU/EEA (above) and DALY and YLD  
4 (below), from 2012 to 2020

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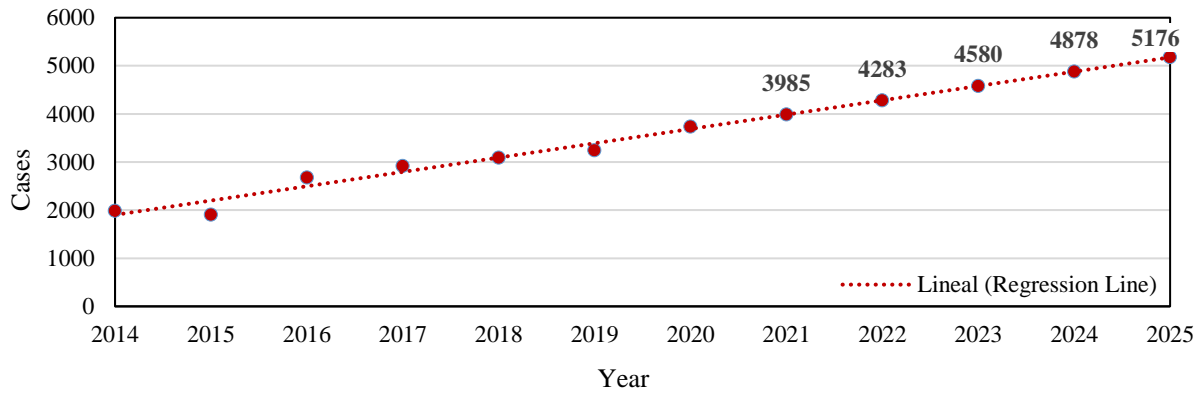
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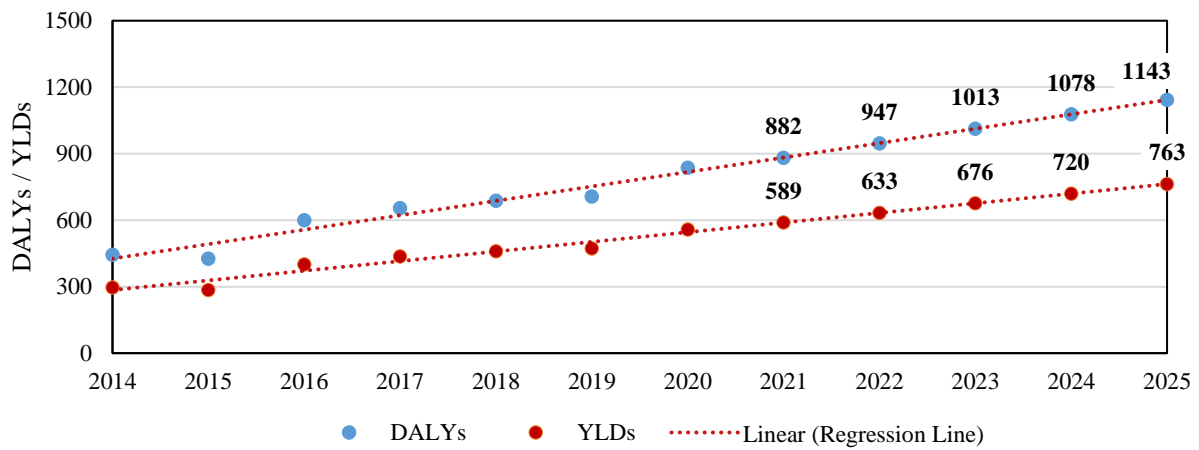
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1 **Figure 2.** Tendency Line Demonstrating Likelihood Increase in New Cases from 2021 to 2025 (above) and  
 2 Predicted Rates of DALYs and YLDs from 2021 to 2025 (below)  
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- 1 **Table 1:** Regression models characteristics, demonstrating P-value and Residual Standard Error and
- 2 Estimated Values for Number of New TBE Cases, YLDs and DALYs from 2021 to 2025.

Linear regression model	TBE New Cases vs. Year	YLDs vs. Year	DALYs vs. Year
Year	<p><b>p-value [F-test]</b> &lt;0.0001</p> <p><b>RSE = 180.50</b></p>	<p><b>p-value [F-test]</b> &lt; 0.0001</p> <p><b>RSE = 29.80</b></p>	<p><b>p-value [F-test]</b> &lt;0.0001</p> <p><b>RSE = 44.42</b></p>
2021	<p><b>3985</b> (95% CI: 3593 - 4377)</p>	<p><b>589</b> (95% CI: 524 - 654)</p>	<p><b>882</b> (95% CI: 733 - 1032)</p>
2022	<p><b>4283</b> (95% CI: 3811- 4755)</p>	<p><b>633</b> (95% CI: 555 - 710)</p>	<p><b>947</b> (95% CI: 785 - 1110)</p>
2023	<p><b>4580</b> (95% CI: 4026 - 5135)</p>	<p><b>676</b> (95% CI: 585 - 768)</p>	<p><b>1013</b> (95% CI: 835 - 1191)</p>
2024	<p><b>4878</b> (95% CI: 4240 - 5517)</p>	<p><b>720</b> (95% CI: 614 - 825)</p>	<p><b>1078</b> (95% CI: 883 - 1272)</p>
2025	<p><b>5176</b> (95% CI: 4453 - 5899)</p>	<p><b>763</b> (95% CI: 644 - 883)</p>	<p><b>1143</b> (95% CI: 931 - 1354)</p>

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