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Research paper

The impact of active case finding among high-risk populations on the decline of tuberculosis incidence

Aleksandra Tomczak, Dominika Warmjak, Aneta Wiśniewska

Faculty of Mathematics and Computer Science, University of Warmia and Mazury in Olsztyn, Poland

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Abstract

Introduction: Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. In 2019 the WHO reported approximately 10 million TB cases and 1.4 million deaths worldwide. TB still remains one of the leading causes of death in humans. Brazil is one of 30 countries with the highest TB burden with 96,000 new cases and 6,700 deaths reported in 2019. From 2015 the TB incidence is increasing by 2%–3% annually. It means that TB control programs need to be improved.

Aim: Our aim is to show the impact of active case finding of TB cases among a high-risk subpopulation on decline of the incidence in the general population.

Material and methods: We use a SIS-type compartmental mathematical model to describe the disease dynamics. We consider the population as a heterogeneous population which differ in disease transmission risk. Using best-fit techniques we compare the actual data with the model. For the fitted parameters we calculate the basic reproduction number and estimate the TB trends for the next few years applying several preventative protocols.

Results and discussion: Using numerical simulations we examine the impact of ACF on the disease dynamics. We show that active screening among high risk subpopulations can help to reduce TB spread. We show how the reproduction number and estimated incidence decline depend on the detection rate.

Conclusions: Active screening is one of the most effective ways for reducing the spread of disease. However, due to financial constraints, it can only be used to a limited extent. Properly applied detection can limit the spread of the disease while minimizing costs.

Corresponding author: Aleksandra Tomczak, Faculty of Mathematics and Computer Science, University of Warmia and Mazury in Olsztyn, Sloneczna 54, 10-710 Olsztyn, Poland.
E-mail address: aleksandra.tomczak@matman.uwm.edu.pl

1. INTRODUCTION

Tuberculosis (TB) is a communicable disease caused by *Mycobacterium tuberculosis*. In general, TB affects the lungs (pulmonary TB) but can also affect other parts of the human body (extrapulmonary TB). According to the WHO, one-third of the global population has been infected (may be considered as a reservoir of the infection). It is estimated that 5%–10% of the latent TB can be later developed and activate causing the infection. In 2019 the WHO reported about 10 million TB cases and 1.4 million deaths worldwide.[1] TB is one of the top 10 causes of death worldwide and is the leading cause of death from a single agent (more than HIV/AIDS).

The epidemic of HIV in the 1990s showed that the global incidence rate of TB during the 1990s was increasing. The WHO and Stop TB Partnership responded by increasing the targets for TB control within the United Nations Millennium Development Goals, setting a strategy for decreasing the TB incidence and death rate by 2015. The strategy was based on the fast diagnosis and treatment of active TB cases. One of the most important elements of the strategy was preventative therapy, in particular for TB/HIV co-infected people. One of the internationally agreed targets was the eradication of TB by 2050, meaning that the annual incidence of the disease should be less than 1 case per 1 million of population. Despite the existing recommendations, work on the development of an effective vaccine, and research aimed at increasing the effectiveness of treatment, achieving this goal seems doubtful.

The United Nations Sustainable Development Goals and the WHO End TB Strategy agreed target for the period 2016–2030 is an 80% reduction in the TB incidence rate by 2030 compared with 2015, with two milestones: a 20% reduction in 2020; and a 50% reduction in 2025. TB deaths to be reduced by 90% by 2030 compared with 2015, with two milestones: a 35% reduction in 2020 and a 75% reduction in 2025.[1]

Brazil is one of 30 countries with the highest incidence of TB worldwide. In 2019 the WHO estimated there to be 96,000 new cases of TB, including 11,000 HIV-positive cases, which is equivalent to 45.20 cases per 100,000 population (incidence rate), together with 6,700 deaths caused by TB, including 1,200 HIV-positive cases, which is equivalent to 3.15 per 100,000 population (excluding HIV-positive: 2.59 per 100,000). Brazil has formulated their own targets for TB elimination and control (Brazilian National Plan to End Tuberculosis as a Public Health Problem). Although the TB incidence rate in 2015 decreased by 33% compared to 1990, from 2015 it is increasing by 2%–3% annually, while the total incidence is increasing by 4%–5% annually. The increasing incidence rate means that the WHO and End TB Strategy targets become unachievable; the result being that the control programs need to be improved.[2]

In disease control, mathematical modelling plays an important role. In the past several decades, many mathematical models of disease dynamics have been formulated, analyzed and examined. The first models were formulated by Kermack and McKendrick in the 1920s and 1930s[3]. These models have inspired many researchers to investigate new models. Mathematical models for TB dynamics and control have been used since the 1960s[4]. Nowadays, the numerical methods for data fitting give a proper combination of theoretical analysis and practical applications by exploring the effects of population growth, disease spread, randomness, and age structures using computer simulations. Computer simulations of mathematical models, which are built under realistic assumptions and compared with epidemiological and demographic data, allow disease controllers to test many control protocols and reject those strategies that seem ineffective or economically unjustified. What is more, they are able to take into account several control strategies (isolation, treatment, vaccination, active screening etc.) and model the possible synergy effects, which are unpredictable.[4–8]

It is obvious that in a given population there are groups characterized by significantly higher transmission, e.g. the homeless; the irresponsible; the uneducated and so on. The relationship between TB and homelessness has been known for over 100 years,[9] Homelessness, as a special form of poverty, increases the risk of contracting tuberculosis many times.[10,11] Moreover, homeless people, despite the advanced stage of the disease, are often not treated, which results in intensive disease transmission. It is estimated that the homeless population has an incidence rate 10 to 85 times higher compared to the rest of the population[2,11–13] and their period of infection may be several times longer. It is known that the homeless spread the disease not only to each other, but also transmit the disease to the general population more intensively.[14–16] For example, it is estimated that 6% of Brazilians live in crowded and inappropriate conditions (for example, favelas) and 1.2 million people are either homeless or 'precariously housed.' It is estimated that in Brazil, the prevalence of homeless among all TB cases is 2.5%–3.0%[17,18] with the prevalence odd rate (OR) 5.49 (the corresponding 95% confidence interval (CI) 5.29–5.70).[17] A similar prevalence among the homeless was reported in Warmia and Mazury region in Poland in 2004, before the first active case finding (ACF) campaign was carried out.[12]

2. AIM

In this paper we analyze the actual data for TB in Brazil. Using mathematical modelling compared to the data, we estimate model parameters to predict further TB dynamics in Brazil. We follow the concept of Romaszko et al.[19] We estimate the basic reproduction number and propose a new strategy of disease control. By dividing the population into two groups which are characterized by two different risks of disease spread, we study the effects of active screening of TB cases in a high-risk population. Our aim is to show the impact of ACF of TB cases among a high-risk subpopulation on decline of the incidence in the general population. We show that active detection in the high-risk group gives much better results at a much lower cost.

3. MATERIAL AND METHODS

3.1. Mathematical model

In this section we describe a mathematical model of TB dynamics. The analyzed model is a compartmental model, where the population is being divided into epidemiological compartments and individuals can be transferred from one compartment to another. As TB confers no immunity against reinfection, individuals can transfer from the susceptible class S to the infective I and then back to the susceptible class. Such models are called SIS models.

Following the idea from Romaszko et al.[19] and Choiński et al.[20] we divide the population into two groups with different rates of disease spread. We use a SIS-type criss-cross model for non-homogeneous population formulated and analyzed by Bodzioch et al.[21] Our aim is to show the differences between the disease dynamics in a homogeneous and heterogeneous populations. As it was shown by Bodzioch et al.,[21] the disease control is possible only if the population is considered as a heterogeneous group.

Following the notation in Bodzioch et al.[21], we denote by S_i susceptibles and by I_i infected, $i = 1,2$. The first class S_1, I_1 is the class of non-homeless people, while the second one, S_1, I_2, indicates the homeless one. Susceptibles classes are increased at recruitment rate C_i. By μ_i we denote the natural mortality rate and by α_i – disease related death rate. Parameters γ_i reflect the recovery parameter, where $1/\gamma_i$ is the mean duration of the infectious period. The model description can be constructed as follows by the system of four differential equations:

$$\dot{S}_1 = C_1 - \beta_{11}S_1I_1 - \beta_{12}S_1I_2 + \gamma_1I_1 - \mu_1S_1,$$
$$\dot{I}_1 = \beta_{11}S_1I_1 + \beta_{12}S_1I_2 - (\gamma_1 + \alpha_1 + \mu_1)I_1,$$
$$\dot{S}_2 = C_2 - \beta_{22}S_2I_2 - \beta_{21}S_2I_1 + \gamma_2I_2 - \mu_2S_2,$$
$$\dot{I}_2 = \beta_{22}S_2I_2 + \beta_{21}S_2I_1 - (\gamma_2 + \alpha_2 + \mu_2)I_2,$$

where β_{ij} are disease transmission parameters. Note that, if $\beta_{12} = 0$ and $\beta_{21} = 0$, we have two models for two isolated homogeneous populations. The basic reproduction number, denoted by R_0, for such model is

$$R_0 = \frac{1}{2}\left(\beta_{11}\frac{C_1}{\mu_1 k_1} + \frac{\beta_{22}C_2}{\mu_2 k_2} + \sqrt{\left(\frac{\beta_{11}C_1}{\mu_1 k_1} - \frac{\beta_{22}C_2}{\mu_2 k_2}\right)^2 + \frac{4\beta_{12}\beta_{22}C_1C_2}{\mu_1\mu_2 k_1 k_2}}\right)$$

where $k_i = \mu_i + \alpha_i + \gamma_i$, $i = 1,2$.

It is known, that the epidemic dies out if $R_0 < 1$, and may spread if $R_0 > 1$.

Table 1. Estimated epidemiological burden of TB in Brazil in 2015–2019 (in thousands).[1]

Year	Population	Incidence	95% CI	Mortality	95% CI
2019	211,000	96	82–111	6.7	6.1–7.5
2018	210,000	95	81–110	6.7	6.0–7.4
2017	209,000	91	78–105	7.0	6.2–7.8
2016	208,000	87	74–100	7.3	6.3–8.3
2015	206,000	84	72–97	7.7	6.4–9.5

Table 2. Nominal parameter values.

Name	Value	Unit	Role	Reference
C_1	$3{,}000 \times 10^3$		recruitment rate	[26]
C_2	41×10^3		recruitment rate	[26]
μ_1	0.6063×10^{-2}	year^{-1}	natural mortality rate	[26]
μ_2	0.2746×10^{-1}	year^{-1}	natural mortality rate	[26]
α_1	0.8036×10^{-1}	year^{-1}	disease related death rate	[1]
α_2	0.1228	year^{-1}	disease related death rate	[25]
γ_1	1.8163	year^{-1}	recovery rate	estimated
γ_2	0.5241	year^{-1}	recovery rate	estimated
β_{11}	0.2134×10^{-9}		disease transmission rate	estimated
β_{12}	0.1839×10^{-6}		disease transmission rate	estimated
β_{22}	0.1412×10^{-6}		disease transmission rate	estimated
β_{21}	0.1015×10^{-7}		disease transmission rate	estimated
δ	[0,1]	year^{-1}	detection rate	

3.2. TB control

In general, there are three ways to control the spread of TB: (1) vaccination, (2) prevent progression from latent infection to active, (3) treat active cases. In this paper our aim is to consider an additional way to control the spread of this disease: active screening. We include in the model an additional term δ, which reflects the proportion of the detected infected individuals. We denote by delta the detection rate per person per year. It is called 'patient detection rate' and can be treated as an additional treatment rate and is a standard measure of detection in the literature.[22] We consider active detection only in the second subpopulation of homeless people, as the screening in the high risk population gives much better results than in the general population.[19]

It is obvious that the higher the detection rate, the more the incidence of the decrease. Of course, the detection parameter cannot grow indefinitely. We therefore assume that the detection parameter is from zero (no intervention) to two per one infected person per year. We analyze the effectiveness of the intervention depending on parameter δ.

3.3. Numerical simulations

We use epidemiological and demographical data available in the WHO report, the Brazilian Ministry of Health and the Brazilian Institute of Geography and Statistics. As the epidemic has changed many times in Brazil in recent years,[23,24] we use data from the 2015–2019 period (see Figure 1 and Table 1). Since 2015, we can observe a clear increase in incidence: in the total cases as well as in the incidence rate. The prevalence of homeless among all TB cases is 2.5%–3.%,[17,18] while the number of homeless people is 0.5% of the total population. The mortality in the population can be estimated based on WHO[1] and Ranzani et al.[17] According to the literature, the mortality among homeless people is up to twice higher than in the general population.[25] All nominal parameters values are listed in Table 2.

The values of demographic parameters and the prevalence OR and the corresponding 95% CI are calculated by

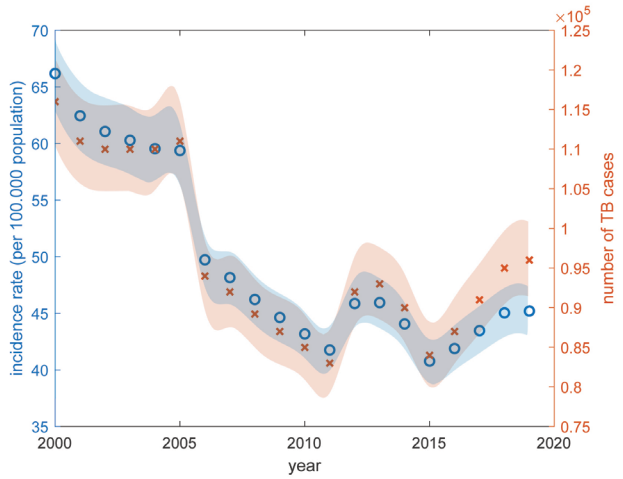

Figure 1. Incidence rate (blue) and total number of TB cases (red) in Brazil in 2000–2019.

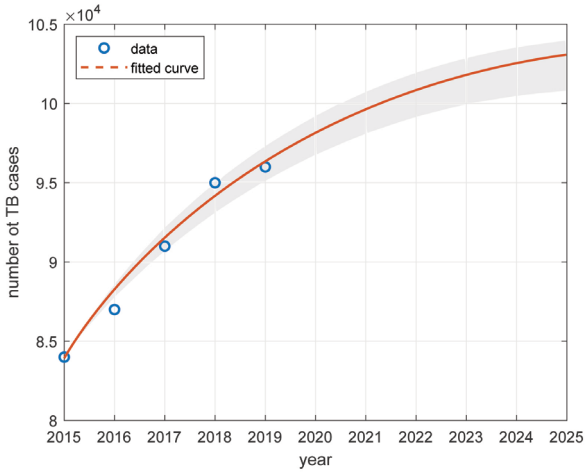

Figure 2. Actual data and best-fitted curve: predictions for the next few years of TB incidence trends in Brazil.

logistic regression in order to measure the strength of association for each characteristic. All statistical analysis are performed using R software.

Differential equations are solved using Matlab software and standard solver *ode45*, which is based on 4th order Runge–Kutta algorithm with variable step. The tolerance is 10^{-6}. We use Matlab *lsqcurvefit* function, which is a nonlinear curve-fitting procedure in least-squares sense, which provides a convenient interface for data-fitting problems. As the fitting procedure is based on gradient methods, it can lead to local minimum of the objective functional. In order to avoid this problem, the fitting algorithm is used 100,000 times with different initial values.

4. RESULTS

Based on actual data from 2015–2019 we can see that the disease spreads and the incidence increases. This confirms the need to improve the current spread control strategy. In order to propose a best way to control the disease, we apply the idea from Romaszko et al.[19], Choiński et al.[20] and Bodzioch et al.[21,27] Dividing the population into two subpopulations: non-homeless and homeless people, we are able to obtain deeper insight into the TB dynamics in the Brazilian population. Using the best-fitted parameter values, we can estimate the disease spread within both subpopulations and between them. We use the best-fit procedure to estimate disease transmission parameters and recovery rates. All parameters are listed in Table 2. For the estimated parameters we can calculate that the basic reproduction rate R_0 is 1.24 (1.19–1.32).

TB incidences for the population and the fitted curve are depicted in Figure 2. The grey region depicts the uncertainty ranges of the predictions, based on the best-fitted procedure. Based on the considered model and estimated parameters, we can make prediction about the future disease dynamics in the considered population.

In Figure 3 the basic reproduction number is plotted against the recruitment rates. The black point depicts the rate values estimated for the population. Figure 4 shows the dependence of the predicted incidence decline for different

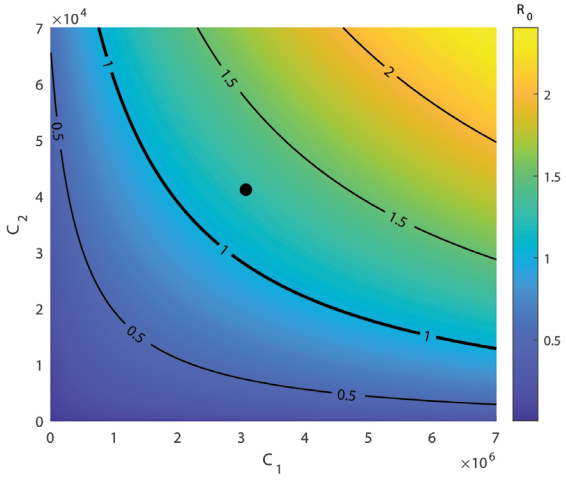

Figure 3. Dependence of the basic reproduction number on the recruitment rates. Black point depicts point (C_1,C_2) taken from Table 2.

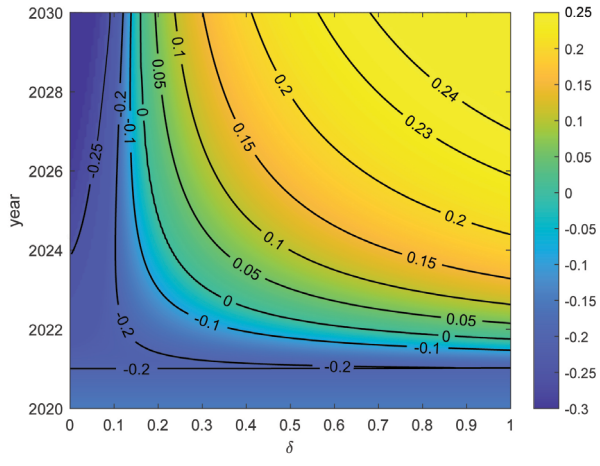

Figure 4. Dependence of the incidence decline in years 2020–2030 compared with 2015 on the detection rate, assuming that the detection will apply from 2021.

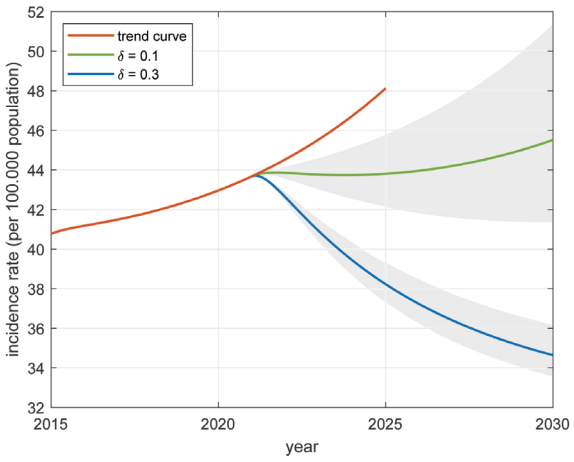

Figure 5. Incidence rates under three control strategies. Red curve depicts current trends, while green and blue ones represent ACF among homeless with detection rates 0.1 and 0.3, respectively. Grey regions represents future predictions for the rate of (0.05,0.15) and (0.25,0.35).

detection rates. Colors represent the total decline in incidence in the following years compared to 2015. Note that it is assumed that the detection will be used from 2021.

Figure 5 shows results for three control strategies applied in the population of homeless people. The first part, depicted by red solid line, represents actual trends in the general population without any additional protocols (see also Figure 2). Then, we assume that active detection will be used among homeless from 2021 and we estimate the disease spread in the 2021–2030 period. Green and blue curves represent the results when detection rates are 0.1 and 0.3, and the grey regions depict the predicted trends for $\delta \in (0.05, 0.15)$ and $\delta \in (0.25, 0.35)$, respectively.

5. DISCUSSION

In this paper we adapt the concept presented by Romaszko et al.[19] We investigate the impact of ACF among the high-risk subpopulation of homeless on the incidence decline. Using the actual data we are able to fit the model parameters and then predict the future trends of the disease spread in the population. Figure 2 shows the estimation of new cases in the next few years under the current control strategy. Simulations show that the disease is spreading in the population and if the upward trend from 2015–2019 is not stopped, the incidence in the next few years will increase by 5%–7% per year.

Control of the basic reproduction number is the most common method of limiting the spread of disease. As we have mentioned, the value of this rate is greater than one and the disease can spread in the population. Typically, most epidemic parameters are strictly dependent on the disease and the population. It is extremely difficult to change the disease transmission and mortality rate, thus we examine how the value of this rate depends on the recruitment rates (see Figure 3). Note that, when the rate C_2 is below the solid line, the value of the reproduction number is less than one and the epidemic dies out. Various types of humanitarian and social organizations aim to lower the recruitment rate, but it is difficult to achieve.

In our study we aim to investigate the dependence of the incidence in the population on the active detection among homeless people. By δ we denote the detection rate. It is expected that the larger the rate δ is, the smaller the value of R_0 should become. Figure 4 shows the dependence of the incidence decline in years 2022–2030 compared with 2015 on the value of the detection rate. Here, we assume that ACF campaigns start in 2021 and then we show their impact on the incidence decline in the following years. It is predicted that in 2021 the incidence rate will increase by 20% compared to 2015 and if an appropriate control started will be applied, it may start decreasing. In general, the larger the detection rate, the larger the decline of the reported incidence. However, increasing values of the detection rate are more and more difficult to achieve. Additionally, as the detection rate increases, so does the cost of active screening. Usually, prevalence of new active cases in screening is 7%–10% decreases as the number of tested people increases. It means that in general one new infection is diagnosed per 10–15 tested people. It is clearly visible that the dependence in Figure 4 is not linear and in a long horizon of time the same results can be obtained for a smaller detection rate. The most effectiveness of the ACF can be observed for detection rate of 0.3. For larger values of the rate, the expected decline in incidence increases slightly. It is very important from the economical point of view as the financial support for preventative actions is highly limited. Following the results by Romaszko et al.,[19] each identified homeless person may reduce the incidence of 3–4 individuals within 1 year and up to 20 individuals within 5 years, while carrying out similar screening in the general population gives much worse results, as the disease transmission is less intense there. One should also notice that if the detection rate stays below approximately 0.17 for the next few years, the incidence increases (the decline is negative), compared to 2015.

Figure 5 shows that for protocol with $\delta = 0.1$, even if at the beginning the increase in incidence slows down, after 3–4 years it rises again. Increasing the rate to approx. 0.17 only reduces the incidence to the level of 2015. In the following years, the incidence will increase again. This behavior is due to the reproduction number in the population is greater than one. A clear decrease in incidence is noticeable when the rate exceeds the value of 0.2. However, the effectiveness of the ACF campaign decreases as the detection rate increases above 0.3. Note that, the detection rate of 0.3 means identifying 800 TB-positive (i.e. less than 1% of the total TB cases) and testing 8,000–12,000 homeless people annually.

Our study shows a possible way to limit the disease spread in a population with an incidence of TB infection. It is expected that protocols should be changed when the disease spread is slowed down. We are aware of certain limitations related to access to data and parameters. Nevertheless, our results are qualitative and indicate future trends and directions. We believe that they will help to design more ef-

fective and less costly ACF campaigns and will contribute to better control of the spread of TB. It should be pointed out that our result can be applied not only for subpopulation of non-homeless and homeless people, but for each heterogeneous population that differ in disease spread, as well as for other infectious diseases which do not confer immunity.[28] It should be pointed out that ACF may not only reduce the disease spread in the general population, but it may also prolong the average life span of people from high-risk populations, e.g. homeless people. As the average life span of a homeless person is shorter by almost 20 years[29] and in this population TB is the leading cause of death by an infectious disease, any reduction of disease spread may have important role in extending the expected life span.

6. CONCLUSIONS

TB may be intensively transmitted from the homeless to the general population. The larger the detection rate is, the higher incidence decline is observed. An increase in the detection rate is associated with an increase in the costs of active screening. In a long horizon of time, similar results can be achieved for a smaller detection rate. Reduction of the disease transmission in one subpopulation may reduce the incidence of the disease and help to control the disease spread.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors. All data is fully available and anonymized.

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