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Should The Tuberculosis Vaccine be Included in the NHS Regular Vaccination Schedule?

An analysis of current healthcare developments regarding the tuberculosis infection, socio-geographical data, and the age demographic of the United Kingdom – Ece Aslan | Toni Bennett | Chloe Warbey | 2022

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Abstract

Tuberculosis (TB) is the second leading infectious killer worldwide and remains a global health threat. Currently, the NHS regular vaccination schedule does not include a TB vaccine to be given to the population of the UK. This research debates the necessity of including a tuberculosis vaccine in the NHS regular vaccination schedule in the near future; and whether or not the current measures will remain enough to combat the tuberculosis infection in the UK.

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Introduction

Tuberculosis (TB) is an infectious disease caused by bacteria, with the lungs as its main site of infection. It is the second leading infectious killer worldwide (preceded only by COVID-19) (World Health Organisation, 2021). Dr Ibrahim Abubakar, head of tuberculosis surveillance at the Health Protection Agency, has emphasised this condition: "*We are concerned. TB is a preventable and treatable condition, but if left untreated can be life-threatening*." (BBC, 2010).

As it currently stands, the TB vaccine is not included in the NHS routine vaccination schedule. In light of its dangers to the population, it is important to establish why that decision might have been made, along with how much longer it will continue to be in the public's best interest. With rapid changes in factors like population density and immigration, the aging population, and healthcare development taken into consideration, the authors of this paper anticipate that a change in mind regarding this decision will be likely in the near future. Therefore, the aim of this paper to answer the following: question

***'Should the tuberculosis vaccine be included in the NHS regular vaccination schedule?'*.**

The ever-developing concern of the tuberculosis disease is complex and is affected by numerous other factors, so it was decided that it would be beyond the reach of this paper to try and include every single aspect of this complicated matter.

Therefore, this paper will limit its scope to three key areas. These three sections will cover a different factor and elaborate on its relationship with the tuberculosis cases in the UK. In relation to the rationale behind deciding what three key areas to look at, the authors chose contrasting factors to one another as a means of gaining a more diverse understanding of the spread of the infection, and therefore, what could and/or should be done to minimize the impact.

Section one studies the current developments regarding the TB vaccine and debates how likely it is that it would be beneficial to the public if included in the NHS vaccination schedule.

Section two looks at the impact of immigration from low-income countries with a high TB burden on the cases in the UK and investigates the TB data from a socio-geographical viewpoint.

Section three studies the relationship between age and the spread and severity of the TB infection and applies this knowledge to the general age demographic of the UK.

Section 1 – The current affairs regarding the development of the tuberculosis vaccine

The benefits and drawbacks of the current vaccine against TB need to be considered because the extent to which it is effective, has wide ranging implications. For example, if the vaccine is not as effective as it could be, should we be spending money on manufacturing and delivering it, or could that money be better spent elsewhere? In addition, the growing rates of vaccine hesitancy, particularly in high income countries (Kennedy, 2020), means that vaccines are under more scrutiny than ever by

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the public. If there are strong reasons for doubt regarding the vaccine, then it should be scrutinised at the highest level to ensure that any decrease in the overall rate of vaccination is fully justified and is not the result of public reaction to unsubstantiated concerns and avoid it causing a decrease in the overall rate of vaccination.

The current vaccine for TB is commonly known as the BCG vaccine, which stands for bacillus Calmette-Guérin, is the only TB vaccine licenced for use in humans (Zhu, et al., 2018). This vaccine was originally introduced for use against infant TB in 1921 (Kaufmann, et al., 2017) and is also now widely used to prevent severe forms of extrapulmonary TB (Kaufmann, et al., 2017). However, this vaccine only provides limited protection against the most common form of TB, which is pulmonary TB (Kaufmann, et al., 2017). Not effectively preventing the most common form of TB is a major drawback of the vaccine as it means that even people who have been vaccinated are not protected against the form of TB that they are most likely to encounter meaning that TB could still be deadly. It is also not recommended for HIV-exposed neonates in several countries (Kaufmann, et al., 2017) but this will be expanded upon later. In addition, the current NHS guidelines state that it should only be offered to babies, children, and adults under the age of 35 (NHS, 2019). There are also additional guidelines including how babies should get the vaccine if, for example, they live in an area with high TB rates or have parents or grandparents from a high-risk TB country (NHS, 2019). These guidelines imply that there are many risks and drawbacks associated with the BCG vaccine, some of which have already been acknowledged by medical professionals, meaning that it may not be the most effective way to combat TB in the 21st century.

The biggest incentive to include the BCG vaccine in the NHS schedule is that it is the only TB vaccine currently licenced for use in humans (Zhu, et al., 2018). That, combined with the fact that TB has killed one billion people over the last 200 years and is still one of the most infectious diseases worldwide (Kaufmann, et al., 2017), means that the BCG vaccine is the only weapon we have in the fight against(Sable , et al., 2019) meaning that the BCG vaccine would be more effective in the UK than in many other countries, thus providing a higher incentive for the NHS to introduce the BCG vaccine into the regular vaccine schedule does not recommend the BCG vaccine for most of its population (Australian Government Department of Health, 2013), however, Australia has an average yearly temperature that is 13.06°C higher than the UK's (Domensino, 2022; UK Met Office, 2022) and is around 8.7 degrees closer to the Equator meaning that the vaccine is less effective there (Polis, 2022). Further in its favour, this vaccine has saved tens of millions of lives in the past 100 years (Lange, et al., 2022) with the majority of these lives belonging to children as the vaccine provides strong and long-lasting protection against miliary and meningeal TB in children (Lange, et al., 2022). Miliary TB occurs when the TB has left the lungs and spread through the bloodstream, infecting other organs (Tierney & Nardell, 2020) and is most common in children under four(Tierney & Nardell, 2020) and can be fatal (Vohra & Dhaliwal, 2022). However, it also only accounts for 1-2% of all cases of TB (Vohra & Dhaliwal, 2022), showing that in the wider picture, the BCG vaccine may not have a significant impact in the fight against TB. The other form of TB that the BCG vaccine is particularly effective against is meningeal TB (Lange, et al., 2022) which is a form of TB that affects the central nervous system. The strong levels of protection that the BCG vaccine provides against these two strains is an example of how the vaccine is saving people's lives in the UK and there should be no reason why people should not have access to this protection. Combined with the fact that it is the only licensed vaccine for use in humans, means that the BCG vaccine arguably still has a significant role to play in the fight against TB.

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The BCG vaccine has many different strains and there is evidence that proves that these different strains have various levels of effectiveness against TB as well as differing resistance to anti-TB drugs (Ritz & Curtis, 2009). An investigation proved that more virulent strains of the vaccine demonstrated a higher level of protection than less virulent strains (Zhang, et al., 2016) (BCG-Phipps was more protective than BCG-Sweden, for example (Zhang, et al., 2016)) and even within the most virulent group of vaccine strains, during this study, there were differences with BCG-Japan being less protective than BCG-Russia (Zhang, et al., 2016). Another case proving the differing levels of protection was seen in an analysis of a Kazakhstan cohort where BCG-Japan reduced the risk of TB by 69%, BCG-Serbia reduced the risk by 43% and BCG-Russia only reduced the risk by 22% (Favorov, et al., 2012) further demonstrating how the differing strains of the vaccine offer widely different protection levels against TB. In 2009, 83 out of 188 countries used more than one strain of the BCG vaccine (Ritz & Curtis, 2009) meaning that different people within the same population would unknowingly have diverse levels of protection and therefore differing chances of surviving a TB infection. Furthermore, as previously mentioned the efficacy of the BCG vaccine increases as the latitude increases. This is one of the reasons why results from clinical trials vary hugely depending on where they were performed (Andersen & Doherty, 2005). This means that although the BCG vaccine was a major part of the large decrease in TB rates in Europe, it is struggling to have that same impact in lower latitudes (Dara, et al., 2014). These are the reasons why the variable efficacy of the vaccine should be considered in this debate.

Pulmonary TB is TB that has not spread from the lungs, and it is the most common form of TB worldwide (National Jewish Health, 2013) meaning that it is the type that needs to be treated most. It is also the type that often occurs before the TB has spread to other parts of the body, therefore if this type is prevented then you are also preventing the other types of TB from taking hold. Vaccination against pulmonary TB using the BCG vaccine is also extremely difficult because it is the form of TB against which the vaccine has the widest range in efficacy at different latitudes (Mangtani, et al., 2014). In the UK in 2021 48.6% of people diagnosed with TB were diagnosed with pulmonary TB, making it the most prominent type in the UK (UK Health Security Agency, 2022) meaning when we are analysing whether the TB vaccine should be included in the vaccine schedule its effectiveness against this specific type of TB should be carefully considered. There has been debate about this topic on several grounds for a long time with many professionals, for instance, believing that protection given by the BCG vaccine only lasts 10 years, however, new evidence may be suggesting otherwise (Mangtani, et al., 2017).

The previous conclusions about the length of time for which the vaccine provided protection for, may have been wrong due to limitations in technology and testing (Katelaris, et al., 2020). There have been newer studies which suggest that there was protection against infection in both infants and adults for a longer period (Katelaris, et al., 2020). However, such studies also found that there were still significant amounts of variation depending on factors such as age, race, distance from the Equator and time since vaccination meaning that efficacy can still vary widely between different communities (Katelaris, et al., 2020). Another case study in 2008 also concluded that BCG had a positive effect against TB infection in the UK - although this was a small study it suggested that 21 out of 32 of the infections studied could have been prevented by BCG vaccination (Eriksen, et al., 2010). All this evidence shows that there are conflicting views on the efficacy of BCG vaccination against pulmonary TB and with more testing with modern technology a more concrete conclusion could be reached.

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Another factor to consider is the coinfection of TB and HIV as when there is such a coinfection with them the vaccine is far less effective. This causes TB to become more deadly with each disease speeding up the progress of the others (World Health Organisation, 2021) is a problem as the number of TB cases worldwide is growing and that growth is attributed to the growing number of people who are HIV positive, particularly in Africa (Andersen, 2007). HIV makes everything to do with diagnosing and treating TB patients harder as it means that symptoms may be masked, and typical drug treatment plans often cannot be used because of the patients' current medication (Narendran & Swaminathan, 2016). The fact that the BCG vaccine is not recommended for neonates exposed to HIV means that there is a significant difference in its effectiveness among different populations (United Nations, 2020). The rates of HIV in the UK are estimated to be around 1.6 per 1,000 people (Public Health England, 2016) which is well below the UNAIDs 90-90-90 target for 2020 (National AIDS Trust, 2022). These statistics show that although HIV and TB are a deadly combination the HIV rates in the UK are so low that it may not be a big enough factor to impact the decision about whether the BCG vaccine should be included in the NHS vaccine schedule. However, there may still be cause for concern in this regard as over 30% of people infected with HIV in the UK are black (National AIDS Trust, 2022) and this population group is therefore are at a higher risk from contracting TB, in addition, around 1 in 16 people in the UK do not know that they have HIV (National AIDS Trust, 2022) meaning that they will also be more at risk of contracting TB without knowing of their increased susceptibility. The presence of these distinctly higher-risk groups raises the question of whether the BCG vaccine should be provided to everyone as a preventative measure as there is no way to predict with any degree of certainty who will contract either TB or HIV in their lifetime, but this point may be invalid due to the exceptionally low rates of TB and HIV in the UK.

It has been proven that age influences the efficacy of the BCG vaccine and that its effectiveness decreases during puberty and then maintains that decreased effectiveness from then on (Sable , et al., 2019). This conclusion was reached by looking at how there is a peak in the number of people infected in the young adult age category (20-30) (Iqbal, et al., 2018). This study also showed that there was a peak in decreased efficacy in the 0-5 age category perhaps because of the previously mentioned difficulties in administering the BCG vaccine to neonates with HIV as well as the growing vaccine hesitancy among adults around the world (Kennedy, 2020). This means that adults will have lower rates of protection because of the decreased efficacy and the fact that the NHS does not recommend the BCG vaccine for people who have already had it (NHS, 2019). Additionally, another drawback related to the previous point is the fact that the BCG vaccine is estimated to only protect people for only around 10 years as many studies investigating the BCG vaccine did not continue to follow their participants for more than 15 years (Abubakar, et al., 2013). This review also showed that the rate of the decline was variable among different populations (Abubakar, et al., 2013) showing that it is extremely hard to predict whether someone will continue to be protected against TB into their adult years. All these points will be expanded upon later in the report and there will be more detailed analysis of the impact that age has on the vaccine's efficacy.

However, all this research may become redundant in the final decision as there are currently new TB vaccines in development that hope to offer more protection as well as longer lasting protection (Kaufmann, et al., 2017). This new research and development is occurring on a large scale as there are over a dozen TB vaccine candidates under active evaluation and in the last 20 years over 20 vaccine candidates have progressed through clinical studies and 14 are currently undergoing clinical trials (Sable , et al., 2019). Currently, the most advanced vaccine candidate is the recombinant BCG vaccine which has shown a better safety and efficacy profile than the standard BCG vaccine and is in the

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testing stages (Kaufmann, et al., 2017). All these new developments may mean that in five or ten years there is cause for the NHS to fully revaluate which vaccine it recommends but as none of these vaccines have been licenced yet, the BCG vaccine remains the primary focus of this discussion. In the meantime, it is people from developing countries that are suffering most from this slow rate of research into the BCG vaccine or alternative vaccines and the lack of funding provided to these projects. They also are not receiving the investment that they require to meet WHO targets regarding worldwide levels of infection with spending in developing countries in 2020 amounting to less than half of the global target (World Health Organisation, 2021). Therefore, although there are newer vaccines in development, the BCG vaccine needs to remain at the forefront of the conversation as development is occurring slowly and it is possible that results may not be seen for decades.

Section 2 – The impact of immigration on tuberculosis cases in the UK

TB remains a '*global health emergency*' and causes significant mortality and morbidity across the globe. Much of the burden of severe infectious cases is concentrated in Asia and Africa, with cases in Asia making up 58% and Africa 28% of all cases (M Pareek, 2016). However, TB remains significant for high-income nations. Just like in Asia and Africa, TB is a major disease affecting a high density of people in the UK. Urban areas, like London, tend to be the most affected. According to the BBC, London is responsible for nearly half of England's total cases (BBC, 2010). Bearing in mind that London is one of the most multicultural parts of the UK, there appears to be a correlation between urbanization and an increased burden of TB infections, as illustrated in Figure 1. (UK Health Security Agency , 2021).

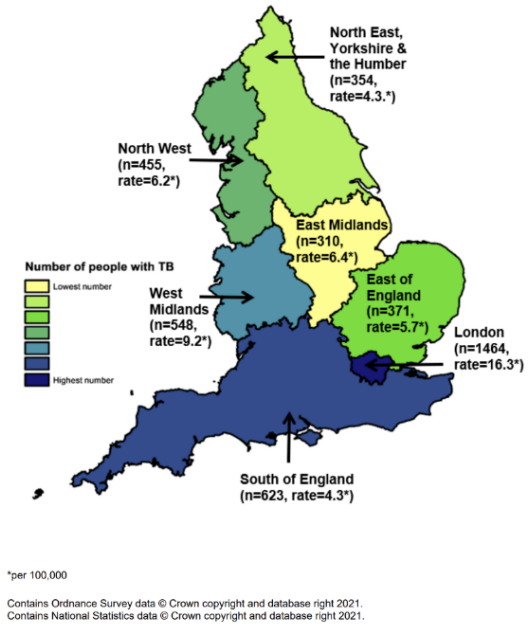

Figure 1: Number of people with TB

In high-income countries, TB causes significant mortality and morbidity, and the burden of which the majority of the infected and/or infectious cases across the country is disproportionately borne by foreign-born nationals (M Pareek, 2016). In a literature review done by Pareek (2016), the cause of this is stated as such: due to globalization, conflict, and financial reasons, more permanent migrants are moving from low/medium income countries with higher TB burden to high-income, developed countries with lower TB burden. This in turn may result in the increased development of TB in the high-income country in several ways, such as a) due to the migrants carrying active TB, b) migrants carrying latent TB which gets reactivated post-arrival and c) TB infection upon local transmission of the disease.

Latent TB and reactivation upon arrival to low TB burden, high-income countries

Latent TB is when an individual is infected with the TB bacteria but is asymptomatic because the body can fight the bacteria to stop them from growing (Centers for Disease Control and Prevention, 2020). A patient with a latent TB infection still needs treatment to prevent the infection from reactivating and turning into TB disease. One of the biggest problems with latent TB is that, because the individual shows no symptoms, it is difficult to diagnose, and therefore, take measures against the chance of the TB disease developing and spreading to other healthy individuals. Although latent TB is not contagious, upon its reactivation it develops into the TB disease, which is infectious.

Latent TB does not show on pre-arrival screening procedures done on migrants coming from high-burden countries. Upon arrival, migrants that have acquired a latent TB infection in their country of origin shortly before migration are more likely to develop active TB, contributing to the TB cases of the low TB burden country of arrival. (M Pareek, 2016)

Current measures taken for tuberculosis control on migrants from high-risk areas

In a literature review covering the impact of migration on the TB epidemiology, Pareek notes that "[The global TB control policies] do not fully address the potential source of reactivation of remotely acquired latent TB infection (LTBI) progressing to active TB disease – such as that seen in migrants" (M Pareek, 2016).

Currently in the UK, there is a pre-entry TB screening policy for migrants applying for a UK visa for over six months, from countries with a TB incidence of over 40 per 100,000 population. But the pre-entry TB screening does not test for latent TB infection (LTBI) (Office for Health Improvement and Disparities, 2021).

Between 2015-2020, the UK undertook the Joint PHE and NHSE England strategy for dealing with TB (Public Health England, 2021). This strategy included screening for LTBI for new entrants from countries with a high incidence of TB. This strategy resulted in a 29% decline in TB incidence in England since its launch in 2015, however, TB cases rose by 2.5% in 2019. A new national TB Action Plan (2021 to 2026) is taking place now to maintain the net decrease in TB cases in England. (UK Health Security Agency, 2021).

In a study that evaluated the impact of migration on TB rates in the United Kingdom compared with other European countries in 2008, it was concluded that "*The increase in the rate of TB in the UK, which contrasts with most other European countries, may, at least in part, be due to the fact that a high proportion of UK cases occur in the foreign-born, coupled with a comparatively large number of foreign nationals from countries with a very high incidence of TB*" (R. L. Gilbert, 2008). To support this finding, in another piece of research published in 2016, it was calculated that in the UK, the percentage of TB notifications in the foreign-born is roughly 70% (M Pareek, 2016).

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Immigration into the UK

Immigration into the UK has been rising considerably since 2004. About 70% of the population increase between 2001-2011 was due to foreign-born immigration (The Migration Observatory, 2020). A net increase in immigration throughout the years can be seen in Figure 2. (ONS, December 2016)

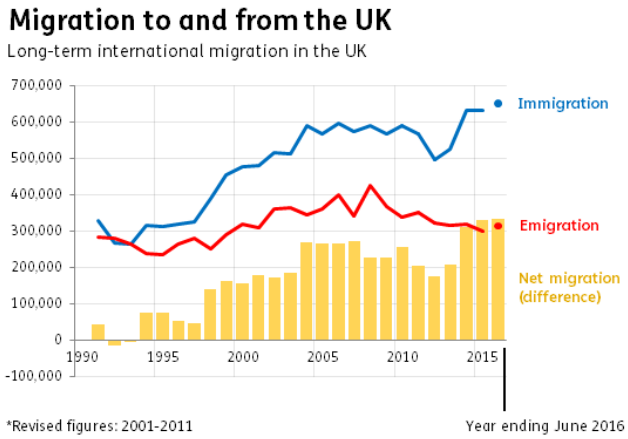

Figure 2: Migration to and from the UK

Therefore, when taking the above factors into account, it can be concluded that with the ever-increasing rate of immigration to low TB burden, high-income countries, it is likely that the cases of LTBI-born TB disease will continue to increase.

Section 3 – The relationship between age and severity of the tuberculosis infection

Age can impact the severity of TB in addition to how susceptible you are to catching TB. A report by Muzyamba, et al. (2021) concluded that the largest number of people who were diagnosed with TB in 2020 were over the age of 65, however, with cases of individuals who were not born in the UK, the highest number of cases occurred in the 25-44 age group.

However, the overall trend in data showed that as age increased the percentage of cases also increased with less than 8% of the TB cases occurring in children under the age of four (Muzyamba, et al., 2021). This would suggest that as age increases the risk of contracting TB also increases. In terms of severity, the report by Muzyamba, et al. (2021) also shows that the age group with the largest proportion of deaths in the first twelve months of the disease, was over 65 with the fewest number of people successfully completing treatment as patients either died or terminated treatment. The age group with the largest proportion of treatments completed was age 0-14 and as the age of patients increased, the proportion of deaths in each age group also increased whilst the proportion of patients who completed treatment decreased (Muzyamba, et al., 2021). However, this could be as children (aged under 16) are recommended to have the vaccine (Oxford Vaccine Group, 2022) as this is when the TB vaccine is most effective (NHS, 2019) and therefore TB rates are reduced in the groups which are vaccinated.

In the UK, the age group with the largest proportion of the population was in the 24-44 age group with 25.6% of the UK population falling in this age group which does not align with the proportion of people who are most affected by TB (Office for National Statistics, 2021). People over 65 accounted for 16.4% of the population in 2011 and whilst this is not the majority age group, it is still over 10 million people who are affected. To reduce the number of cases, the vaccine could be used to help prevent the spread of TB to these age groups.

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A study in the US investigated hospitalizations depending on whether the patient has PTB (Pulmonary TB) or EPTB (Extra-pulmonary TB) and found that EPTB is more commonly hospitalized and often more expensive to treat (Banta, et al., 2020) which suggests that if you are indisposed to EPTB you are at higher risk of being hospitalized.

A study in Denmark, designed to compare the effect that TB had on diverse groups of people and identify any risk factors, composed of 5,684 TB patients with 871 (15.3%) in the 15-24 age category, 2,657 (46.7%) in the 25-44 age category, 1,336 (23.5%) in the 45-64 age category and 820 (14.4%) above the age of 64 (Zhang, et al., 2011). This data showed that the type EPTB is more common in the age category of 25-44 and suggests that this age group is more likely to contract this type of TB (Zhang, et al., 2011). Therefore, as this age group makes up most of the UK population, it is reasonable to suggest that the vaccine should be used to prevent this. Furthermore, the vaccine is 70-80% effective against types of TB such as EPTB (Oxford Vaccine Group, 2022) so it can be used to prevent the spread of this strain.

In conclusion, considering that the vaccine is highly effective at protecting against EPTB it would be beneficial to vaccinate children early to prevent them from developing EPTB when they are aged 25-44, which could result in profoundly serious cases of TB. Furthermore, as over 65s are most susceptible to TB and have the highest risk of death due to TB it would also be valuable to vaccinate early, as with the NHS's guidelines you can only vaccinate once and the vaccine is the most effective in young children, to ensure that the risk is reduced.

It is also important to note that the current BCG vaccine was only available in 1953 (Oxford Vaccine Group, 2022) and therefore a considerable proportion of the over 65 category was unable to receive the vaccine initially.

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Conclusion

The tuberculosis infection remains to be of global concern. Looking at the current developments in healthcare regarding TB, the socio-geographical data of immigration into the UK from low-income, high TB burden countries, and the age demographic of the UK,the authors of this paper anticipate that it will be in the best interest of the UK to include a tuberculosis vaccine in the regular NHS vaccination schedule in order to combat the TB infection effectively.

There are many drawbacks to the BCG vaccine including the decreased efficacy with increasing latitude, age, and the bias against certain races. However, for the UK and the NHS, the BCG vaccine specifically offers more protection and has a higher efficacy meaning that people in the UK are better protected against TB as a result. There is also a lot of newer data regarding the BCG vaccine which is being discovered with the advancement of technology, which suggests that the BCG vaccine may offer more protection than was previously thought.

As a high-income country, the UK receives immigration from low-income, high TB burden countries. Although the measures taken to prevent the increase of TB cases across the UK due to migration-related reasons have been successful in the last seven years, looking at the increased migration rate, it is likely that these measures will be in need of assistance from a TB vaccine to further ensure the control of the infectious disease.

To protect the older proportion of the UK's population, it would be crucial to vaccinate our children, not only to prevent the spread of TB but to decrease the risk of TB in these children as they get older. This would disrupt the current trend in TB cases and hopefully reduce the number of people who develop EPTB and who die as a result of catching TB late in life.

The overall sentiment of these conclusions is the fact that the current TB vaccine should be a part of the NHS vaccine schedule due to its ability to save lives and prevent infection. This becomes increasingly important with the increasing multiculturalism and immigration into the UK, along with the vulnerable age group in the UK, meaning that a vaccine can be used to help reduce rates of TB in these vulnerable communities.

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