An Investigation of Vaccine Candidates For the Treatment of Leprosy and Their Efficacy and Accessibility

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Abstract:
Leprosy is a disease caused by the immune system's response to the bacteria *Mycobacterium leprae*. Infection with *M. leprae* can severely damage peripheral nerves, leading to the loss of smell, sight, limbs and even paralysis. The majority of individuals impacted by this disease live in poor socioeconomic conditions. While over 120 countries report around 200,000 cases of leprosy per year, 52% of these cases were found in India alone in 2022. While treatments such as multi-drug therapy (MDT) are available to treat leprosy, there is still a chance of relapse. In addition, MDT requires long-term treatments that are not readily accessible to patients with few means. On the other hand, if vaccines were an option for leprosy, they might have a farther reach and prevent infections in high incidence regions Thus, this paper focuses on evaluating the efficacy and accessibility of the three vaccines currently being developed or that are approved by the FDA to treat leprosy: BCG, MIP, and LepVax. This review will also investigate current limitations that need to be overcome, such as lack of clinical trials and adverse side effects after administration of a vaccine. While vaccines on the market do provide some relief for those with leprosy, further work needs to be done to develop a vaccine that is both effective and accessible to those populations affected.

Introduction:

Leprosy is caused by the immune system's response to infection with the bacterium *Mycobacterium leprae* (termed *M. leprae)*, which can severely damage nerve cells[1]. It mainly affects the skin, eyes, nose and peripheral nerves. Symptoms include varying sizes of light colored or red skin patches with reduced sensation, numbness and weakness in hands and feet. Leprosy is rarely fatal; rather, it causes many impairments to the body and can result in loss of sight, smell, limbs, and paralysis over the course of years[2]. Historically, due to lack of medical understanding relating to leprosy, the disease was seen as a "curse" related to "sin," those affected were considered outcasts and forced to live in segregated communities. This stigma associated with leprosy is still present in countries such as India and has stopped many doctors and nurses from providing care. Infection with *M. leprae* may occur when a person with leprosy coughs or sneezes and a healthy person breathes in the droplets that contain the bacteria[3]. However, prolonged, close contact over many months with someone with untreated leprosy is needed to become infected with *M. leprae*. Simply shaking someone's hand who has leprosy will not pass the disease to a healthy individual. While over 120 countries report around 200,000 new cases of leprosy per year[4], the countries with the highest number of new leprosy cases diagnosed every year are India, Brazil, Indonesia and Bangladesh (Fig. 1; Fig. 2). More than half of all new cases of leprosy are diagnosed in India alone[4] - in 2022, 52% of the world's new leprosy cases were found in India[5].

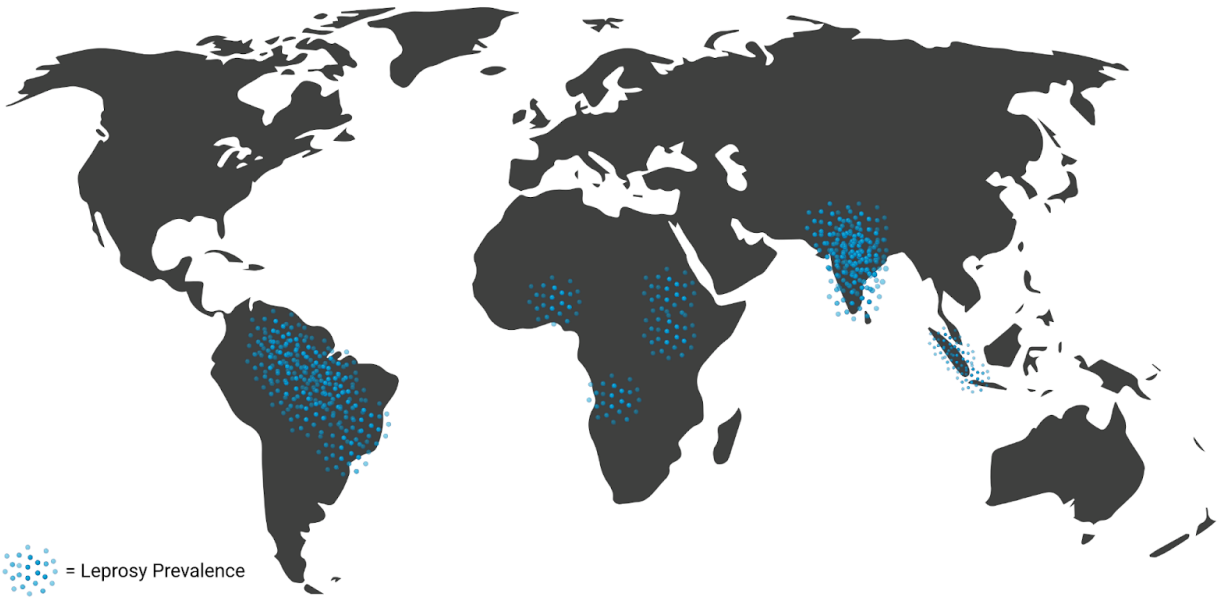

Figure 1: Prevalence of leprosy. *Countries with more cases of leprosy are denoted with blue dots. The thicker the dots, the more leprosy in the country, as seen in India and Brazil.*

Leprosy is distinguished by bacterial replication inside macrophages, Schwann cells, and endothelial cells[6]. Macrophages are cells that respond to an infection or accumulate damaged or dead cells and endothelial cells form the barrier between vessels and tissues in our bodies. Schwann cells are a type of glial cell that surrounds neurons, keeping them alive and sometimes covering them with a myelin sheath, and are the major glial cell type in the peripheral nervous system[7]. When *M. leprae* can find a host (commonly Schwann cells), it replicates very slowly, taking up to 13 days to complete a replication cycle[8]. First, the bacteria binds to receptors on the host cell surface, mainly on the extracellular matrix receptors including Fibronectin and Integrins of neural Schwann cells within the skin or lining of the nose[8]. Researchers have observed that *M. leprae* has high tropism, meaning it can use multiple binding sites to bind to various cell types such as endothelial cells and macrophages. This indicates that if one receptor on a cell is absent, another can work just as well[8]. Once the bacteria has attached to a receptor on the cell surface, it is phagocytosed by the cell, a process in which the cell consumes another particle and digests it.. If the bacterium infects the cell and survives the phagosome-lysosome fusion, it then begins to replicate, usually within macrophages. Throughout this survival process, *M. leprae* is able to create a region of safety directly surrounding itself, called the “electron transparent zone”, because of its transparency when viewed under electron imaging[6]. This allows the bacteria to survive the phagosome-lysosome fusion, but further research needs to be done to understand the bacterium’s mechanism behind their survival.

The currently recommended treatment for leprosy is multi-drug therapy (MDT). Multi-drug therapy is when multiple different types of antibiotics are given to treat a single disease in some person's body. Most commonly, this type of treatment is used for leprosy because it's easy for the bacteria to develop antibiotic resistance if only one type of drug is being used to treat the disease. There are three types of drugs used in this multidrug therapy: daily Clofazimine is added to Rifampicin and Dapsone, which were the previous drugs used before *M. leprae* started developing resistance[9]. This treatment goes on for about two years. Two key objectives of MDT are to minimize the rate of evolution of multidrug-resistant bacteria and to limit the total amount of antibiotics used in hospitals[10]. A study performed by Perron *et al.*, from 2009 to 2015 studied leprosy cases in 19 countries and looked for incidence of resistant strains to the aforementioned MDT[10]. The results showed that among the 1,932 (1,143 relapse and 789 new) cases studied, 8.0% of *M. leprae* strains were found with mutations conferring resistance. Twenty cases showed Rifampicin and Dapsone resistance, four showed Ofloxacin and Dapsone resistance, but no cases were resistant to both Rifampicin and Ofloxacin. However, among relapse cases, Rifampicin resistance was observed in 12 countries[10]. Resistance to Ofloxacin was developed, because even though this antibiotic is not part of MDT, resistance was probably developed in relation to the general intake of antibiotics in MDT.

Selected comparison of 2019 and 2020 world data

World data	2019	2020	Percentage change
Number of registered cases at the end of the year	178,371	129,192	▼ -27.6%
Number of new cases detected	202,488	127,396	▼ -37.1%
Number of new child cases	14,981	8,629	▼ -42.4%
Number of new cases with G2D	10,816	7,198	▼ -33.5%
Number of multibacillary (MB) cases	130,058	85,686	▼ -34.1%

Figure 2: Cases of leprosy between 2019-2020 from the Sasakawa Leprosy Initiative[11]. *While this image shows that there was a slight decrease in cases during this time period, this is likely due to lockdown conditions of the pandemic. Specifically, the lockdown isolated those with the disease, preventing long, prolonged contact thus leading to lower transmission rates. However, this does not negate the need for a treatment, as people still suffer from this disease. In addition, now that the lockdown is no longer in place, cases may likely start to rise again.*

The Bacille Calmette-Guérin (BCG) vaccine (used for Tuberculosis caused by the *Mycobacterium tuberculosis* bacteria related to *M. leprae*) is also being used to treat leprosy. A

single dose of this vaccine gives about 26% - 41% or higher protection for those who have not been infected with leprosy[12]. By comparison, the polio vaccine (given in the first six years of life) has a protection rate of 99 -100% against polio[13]. However, while BCG does have beneficial outcomes regarding childhood tuberculosis, the BCG vaccination may cause adverse events, particularly regarding the skin, including a small ulcer or blister. However, this reaction cannot be predicted before vaccination, nor is its association with protection against leprosy known[14]. Skin complications after BCG vaccination can also indicate a higher risk of developing tuberculoid leprosy - a milder form of leprosy with relatively few bacteria in the patient's skin or nerves[14].

There are individuals in the world who are suffering from this disease that don't have access to expensive or long-term treatments for leprosy, so it is imperative that alternate treatments are generated so that these people may also have a chance to cure their leprosy or be protected against it in the first place. The World Health Organization (WHO) has made MDT free worldwide, but people still have to pay around 24 pounds, 2,500 rupees, or approximately 30 US dollars in order to get the treatment. This covers the costs of staying in the hospital, transportation and many other things. People who are often affected by leprosy live in extreme poverty without access to employment, exacerbating the effect that socioeconomic conditions have on those who are more at risk for leprosy[15]. Vaccines are a good prevention option because they do not require an individual to undergo long-term treatment, and they may not cause as many adverse effects as MDT. The purpose of this paper will be to address potential vaccine candidates that might be effective in protecting against leprosy beyond the standard BCG vaccine.

Vaccines for the Treatment of Leprosy:

Vaccines are generally a useful prevention option for society as they protect communities by allowing them to remain healthy while letting their immune system build up the proper protection against a certain harmful organism. Vaccination can even prevent up to three million deaths every year[16]. Vaccination campaigns rely on the idea of herd immunity, where if enough people are vaccinated against a certain pathogen, outbreaks can be prevented, protecting those who cannot or have chosen not to take the specific vaccine [16]. Vaccines are a good prevention option for leprosy because they do not require an individual to undergo long-term treatment and deal with drugs that may cause ill effects later on in life. While they are not necessarily universally accessible, vaccines can be more accessible than MDT, the current treatment for leprosy. As explained previously, there is a cost for MDT but the treatment can also be prohibited by itself due to the side effects of the drugs given, as some patients might be extremely sensitive to the reactions elicited by the drugs. Rifampicin, one of the drugs used in MDT, can lead to lack of coordination, temporary discoloration of one's skin, teeth, and secretions, bleeding gums, nausea and more[17]. However, this may provoke a question: why is there no fully effective vaccine for leprosy? Researchers are still trying to understand the immune response behind leprosy and why one's body responds the way it does to leprosy. In fact, 35-70% of infections with *M. leprae* resolve naturally without the person developing leprosy[18]. In addition, vaccine development is made harder by a lack of reliable tests to detect infection, predict treatment response, and vaccine efficacy[19]. These limitations also make it difficult to select the study population to be vaccinated. Efficacy trials for vaccines are slowed by factors associated with the slow growing nature of *M. leprae*. Specifically, vaccine production relies on cultivation of M leprae and the long incubation period required results in slower overall

production. Although 37 °C is the standard incubation temperature used for most pathogens, *M. leprae* requires a low temperature for growth. Therefore, in humans it tends to prefer and parasitize cooler areas such as the skin, nasal mucosa and ears, which can be difficult environments to imitate *in vitro*[20]. Current culturing practices include propagation in a mouse footpad and the nine-banded armadillo[21] .

Before discussing the different types of vaccines used to treat leprosy, one must understand what a vaccine target is. A vaccine target is a part of a pathogen that performs functions essential for productive infection[21]. A proper vaccine target is determined by whether it's an unique component of the microorganism and it is capable of inducing a protective immune response. The general characteristics that are preferable for a vaccine target candidate are: 1. Highly conserved; 2. Pathogen-specific; 3. Important for structure/function; 4. Immune-relevant; and 5. Antigenically (substances that cause the body's immune system to react and produce antibodies) similar to circulating strains[22]. These characteristics are preferable because, for example, highly conserved targets are less likely to mutate and escape recognition by the immune system, which increases the effectiveness of the vaccine. Theoretically, a vaccine that targets most strains of a bacterial species is usually expected to eliminate many strains including those that are resistant to antibiotics[23]. This is not always effective, but researchers are constantly looking for potential vaccine targets.

The first vaccine that is being used to protect against leprosy is the BCG vaccine. The vaccine was developed by French scientists Albert Calmette and Camille Guérin between 1908 to 1921 to protect against tuberculosis of the lungs, which was a leading cause of death in the early 1900s[24]. This vaccine is being used to treat leprosy because both *M. tuberculosis* and *M. leprae* are from the same family, and physically and chemically, they exhibit similar characteristics[25]. For this reason, researchers have believed that the BCG vaccine would be the most effective way to combat leprosy. The mechanism of action for the BCG vaccine is to induce an innate immune training by activating the innate immune cells through gene modification [26]. Some variants for this vaccine to prevent leprosy include adding killed *M. leprae* to the BCG vaccine. This would potentially increase the effectiveness of the vaccine, which is currently between 26% - 41%, by nearly double, but the protection rate is not increased for patients younger than 15 years[27]. Other possible improvements for this vaccine might be using recombinant antigens in appropriate adjuvants, or recombinant BCG strains. This could increase the immunogenicity - the ability of a foreign substance, like an antigen, to provoke an immune response - of the vaccine and duration of protection[27]. However, as mentioned above, the reason why BCG is not widely used to treat or prevent leprosy is for a few reasons. For example, there is a lack of high quality trials to gain proper evidence on the efficacy of this vaccine for preventing *M. leprae* infection, there are environmental effects on the strain of bacteria as it requires the proper temperature for cultivation, and even the person themselves can affect the efficacy of the vaccine[27]. While the BCG vaccination is given once in a person's life, its protection only lasts for 15 years and then people are susceptible to leprosy again[28]. There are some uncomfortable side effects with this vaccine, for instance it is possible to develop an abscess at the injection site or at the lymph node near the site. People might also have lymphadenitis - infection of the lymph nodes - because the bacteria in the BCG vaccine may sometimes cause a slowly developing infection and enlarge the lymph node near the injection site[29]. Currently, storage requirements as given by the FDA state that the intact vials of the BCG vaccine should be

stored refrigerated at 2–8°C (36–46°F)[30]. Since the agent contains live bacteria, it should be protected from direct sunlight as well[30]. If stored at this temperature properly, the vaccine's shelf life can be up to three years. For countries with access to these conditions, they can utilize this vaccine over a long period of time, whereas countries that don't have massive storage refrigerators will have to find some other way to store the vaccine or administer them quickly.

The second vaccine that is being used to treat leprosy is the LepVax vaccine. In 2002, the charity American Leprosy Missions (ALM) began a partnership with the Infectious Disease Research Institute in Seattle, Washington to develop a vaccine for leprosy. After investing 17 years and more than six million dollars, the result was LepVax - a defined subunit vaccine that works by stimulating the immune response to the *M. leprae* antigen to form immune memory, thus preventing extensive nerve damage should the patient eventually become infected with leprosy[31]. Because LepVax is a subunit vaccine, it does not target the whole bacteria; rather, it uses a specific part of the germ and generates a strong immune response. While this vaccine is not widespread in usage yet as it is still in Phase 2a of clinical trials, many researchers believe it has the potential to treat, and even prevent, leprosy[32]. Vaccine immunogenicity studies done in 2018 show the vaccine's ability to induce immunity is based on the vaccine's ability to interact with CD4+ T helper cells - a type of adaptive immune cell [12]. This interaction can release T helper 1 cell-type cytokines category of small proteins important in cell signaling - that play an important role in controlling mycobacterial infections[12]. The presence of an immunological response from the presence of cytokines in Schwann cells means pathogenic infections can be localized. Induction of cytokines can improve nerve function when infected by *M. leprae* and prevent damage to Schwann cells due to infection[33]. A paper published by Duthie *et al.*showed that prophylactic immunization of mice with LepVax significantly inhibited *M. leprae* growth in subsequently challenged mice 4 weeks post vaccination[34]. In addition, the use of LepVax in the experimental post-exposure setting involving *M. leprae*-infected armadillos demonstrated not only its safe usage, but efficacy against motor nerve damage[34]. However, at present, there is still a need for further clinical trials in humans and the determination of dosage needed for LepVax to prevent leprosy infections in the future[31]. This is because in 2019, once the FDA approved human clinical trials for LepVax, the Phase 1a clinical trial for LepVax with healthy adults was completed, showing the vaccine to be safe and eliciting a strong immune response (Fig. 3)[32]. The next step in the trials is to study LepVax in people living in a leprosy-endemic area, such as Brazil. For the Phase 1b/2a clinical trials, they will enroll healthy participants and patients with tuberculoid leprosy (Fig. 3)[32]. However, in 2021, the ALM filed regulatory paperwork with the Brazilian National Health Surveillance Agency, ANVISA, an analogous organization to the FDA. They anticipated ANVISA approval by late 2022, with results from the two-and-a-half-year study expected in 2025, but due to COVID-19, that might be delayed further[32].

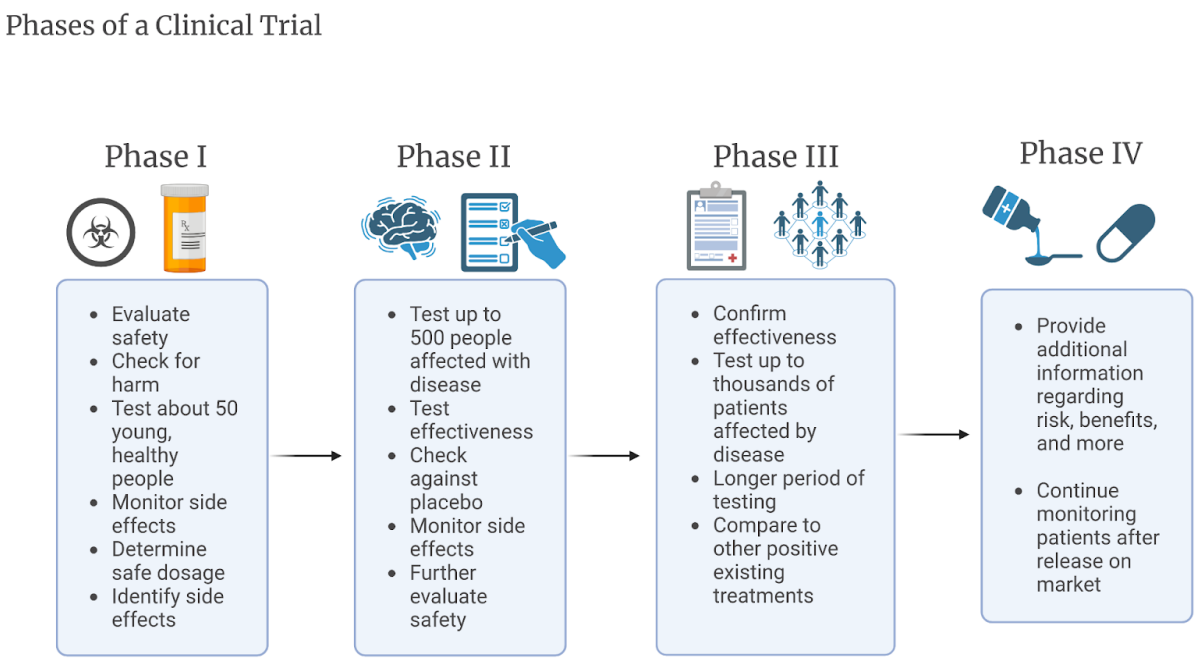

Figure 3: Four phases of Clinical Trials for US Based Approval of a Drug or Vaccine. *The figure shows from left to right the process of clinical trials and what is done in each step. Overall, the process takes about six to nine years to complete, which is why putting new antibiotics on the market takes a while.*

The final vaccine this paper discusses is the *Mycobacterium Indicus Pranii* (MIP) vaccine. *Mycobacterium Indicus Pranii* is a non-pathogenic, genetically modified, and rapidly growing atypical mycobacterium developed by Talwar *et al.* in New Delhi in the 1970s[35]. Scientists specifically chose to use this bacterium because it was found to be a close cousin of *M. leprae* and could be successfully cultivated in a lab, unlike *M. leprae*[35]. This vaccine was developed in India and is used to treat leprosy due to its relatively high protection rate. In a study done in 2021 by Muniyandi *et al.*, it was observed that the protective efficacy by administration of MIP (including boosters) to contacts of newly diagnosed leprosy cases was 68% three years post-vaccination, 60% at the end of five to six years post-vaccination, and 28% at the end of nine to ten years post-vaccination[36]. However, as shown by these results, immunity from MIP wanes with time[36]. In an analysis of several clinical trials conducted at urban leprosy centers in two hospitals in Delhi, Sharma *et al.* concluded that the results obtained with MDT alone in four to five years could be achieved within two to three years following the addition of the MIP vaccine to standard MDT, in lepromatous leprosy[37]. MDT with the MIP vaccine once every three months led to faster bacillary clearance, expedited clinical recovery, and shortened the duration of drug treatment in highly bacillated leprosy[37-38]. In addition, the patients, family members, and contacts received two doses of autoclaved (inactivated pathogens due to steam sterilization) MIP at six-month intervals along with being treated using MDT because they are all in proximity to the patient who is being treated[39]. Therefore, there is still a need to refine this vaccine before it can be completely effective in treating leprosy, due to decreasing protection rate over the years and long-term treatment it currently requires.

Conclusion:
In conclusion, leprosy is a debilitating disease that can lead to permanent damage of nerve cells and paralysis. Most countries that report cases of leprosy tend to be those with people living in poor socioeconomic conditions, meaning that it's also harder for affected people to get proper treatment. The currently recommended treatment for leprosy is MDT. Most commonly, this type of treatment is used for leprosy because it's easy for the bacteria to develop antibiotic resistance if only one type of drug is being used to treat the disease. Currently, many individuals in the world have leprosy but cannot access MDT. They do not have the means to reach the hospital where it is administered or they do not have the money to pay for some of the additional fees their treatment might incur. Thus, it is imperative that alternate treatments are created, so that these people may also have a chance to cure their leprosy or be protected against it in the first place.

The BCG vaccine has finished its clinical trials and is currently being administered to both adults and children in the hopes of preventing leprosy. While originally intended to treat tuberculosis, because of the similarities between the bacteria that cause tuberculosis and leprosy, scientists have repurposed this vaccine to treat leprosy. Currently, this is the most effective vaccine that is on the market to treat leprosy; however, a single dose of this vaccine gives about 26% - 41% percent protection against the disease, which is very low[12]. Skin complications after BCG vaccination can also indicate a higher risk of developing tuberculoid leprosy[14]. While the BCG vaccination is given once in a lifetime, its protection only lasts for 15 years and then people are susceptible to the disease once more. Unfortunately, after the vaccine is given, it is possible to develop an abscess at the injection site or at the lymph node near the site. People might also develop lymphadenitis. Storage requirements as given by the FDA state that the intact vials of the BCG vaccine should be stored refrigerated at 2–8°C (36–46°F)[30]. Since the agent contains live bacteria, it should be protected from direct sunlight as well and if stored properly, the vaccine's shelf life can be up to three years[30]. If stored at this temperature properly, the vaccine's shelf life can be up to three years.

The LepVax vaccine is currently in Phase 1b/2a of its clinical trials and so far, it has shown promising results (Fig 3). Those injected with the vaccine show stronger immune responses when exposed to *M. leprae* compared to those who are not injected with the vaccine. The vaccine causes the release of T helper 1 cell-type cytokines that play an important role in controlling mycobacterial infections[12]. However, despite all the progress and positives that the LepVax vaccine is showing, there is still a need for more clinical trials, The ALM hopes that LepVax will be an exciting new way to stop the transmission of leprosy and the *only* way to protect people long term. They also believe that the vaccine may protect against nerve damage among those already diagnosed with leprosy[40]. Currently, the data expected from the next clinical trial will be in 2025, so LepVax may not be used commercially until proper approval from the FDA. Storage information for LepVax is not available to the public right now as the vaccine is not being used commercially.

The MIP vaccine is the final vaccine that is currently on the market and may have some efficacy in treating leprosy. This vaccine is specifically used because it is targeted against a close cousin of *M. leprae* and *M. leprae* that can be cultivated in a lab[35]. The MIP vaccine has been approved to test on humans, as it has been assessed in three recent large-scale phase III

clinical trials in the US. The results from these trials evaluated this vaccine as an adjunct to first-line MDT in treating leprosy[41]. This vaccine does have a very high protection rate, but after 10 years, post vaccination, there is a drop of about 40% in protection against leprosy. However, this vaccine must be used along with MDT in order to successfully cure leprosy and it requires for other people, including the patient, to be treated because of close contact. Storage information for this vaccine is also not publicly available, possibly because its usage has not spread to the U.S. yet.

As of right now, the best vaccine candidate to treat leprosy would be the LepVax vaccine. This is due to the formulation of the vaccine: directly using antigens from *M. leprae*. This makes the vaccine extremely specific, whereas the BCG vaccine and MIP vaccine have varied targets. While this vaccine is not yet available on the market, it would generate a large-scale impact on those who do receive it because the vaccine would not require long-term treatment and results from the clinical trials have shown that the vaccine elicits a strong immune response.

However, with developments in vaccines, it's important to consider whether accessibility will also increase as a result. In order to increase accessibility, one could set up clinics in rural areas of the world. Because clinical trials involve testing on a human population, the clinics would serve the purpose of both testing and provision of vaccines. This would increase the accessibility that people in rural or tribal areas have to not only the vaccine, but also basic healthcare. This benefit would increase their way of living much more, and they may not be as susceptible to diseases as they were before without healthcare. However, this can incur a large cost, so other alternatives may need to be considered. Another way to increase accessibility might be to engineer the vaccines in such a way that they can be stored in room temperature conditions, rather than in conditions that require refrigerators. This means that countries who don't have access to refrigeration can still utilize these vaccines to the fullest extent.

In the future, research could benefit from the development of culturing techniques for *M. leprae*. Right now, all the vaccines that show some sort of efficacy share common roots in the *Mycobacterium* genus. This methodology seems to be working, however, utilizing specific *M. leprae* antigens might prove to be more successful. Considerations that need to be made are the protection rate and the effectiveness of these vaccines. Something else that scientists will need to focus on will be the length of protectiveness from the vaccines. For BCG, the length of protection is 15 years, but it has a low protection rate (26 - 41%), while MIP has a high protection rate (68%) that lasts for a short amount of time (eight to ten years). Some methods that have worked in other vaccines include using different adjuvants and or boosters. In addition, according to Barros-Martins, J. *et al.*, protective durability could be increased by combining vaccine platforms; some studies have suggested that this approach can significantly boost the vaccine immunity, and provide potential benefits for long-term protection[42]

Overall, this paper demonstrates the significant need for a vaccine against *M. leprae*. Currently, the three vaccines on the market - BCG, LepVax, and MIP - all show some initial effectiveness against leprosy. The protection length for leprosy vaccines is quite long compared to vaccines such as influenza and typhoid that require frequent boosters. However, because of the need for life-long protection, the length of effectiveness for leprosy vaccines is relatively short. In the future, the author hopes that researchers will be able to use this information to aid in their

discovery of new vaccines or vaccine targets in order to effectively treat those with leprosy or prevent it in the first place.

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