

# Managing Recalcitrant Warts: Facts about *Bacillus Calmette-Guerin* (BCG), *Mycobacterium Indicus Pranii* (Mw Vaccine), and Purified Protein Derivative (PPD) as Immunotherapy

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## Abstract

Recalcitrant warts can accurately be defined as warts that persist after six months of conventional therapy. Up to one-third of non-genital warts, especially periungual and plantar warts, become recalcitrant. Traditional treatment options for warts include topical salicylic acid, cryotherapy, and electrocautery; however, patients with recalcitrant warts remain a major therapeutic challenge. There is evidence that immunotherapy can clear recalcitrant warts if traditional treatment fails. Given this, clinical studies published in PubMed and Google Scholar that used *Bacillus Calmette-Guerin* (BCG), *Mycobacterium Indicus Pranii* (Mw vaccine), and purified protein derivative (PPD) as immunotherapy for wart, were reviewed in this study. Neither of these treatments has been subjected to a randomized controlled trial, thus to date, there are no standardized protocols to use them. Our review highlights the scientific facts in the clinical applications of the previous options to treat recalcitrant warts and investigate the differences among them, concerning efficacy, adverse effects, dosage, and route of administration.

## Keywords

Recalcitrant Warts, BCG Vaccine, *Mycobacterium W Vaccine*, PPD (Purified Protein Derivative)

## 1. Introduction

Warts are benign epidermal growths caused by human papillomaviruses (HPVs).

Today, more than 120 genotypes of distantly related HPVs have been identified. HPVs infect the epithelial cells of the skin and mucous membranes of the mouth, esophagus, larynx, trachea, cervix, and conjunctiva and cause both benign and malignant lesions [1]. Warts affect 7 to 10 percent of the general population. The spread of the virus is related to the patient's immune status, with more advanced lesions occurring in children and immunocompromised adults [2]. Moreover, verrucae can spread by autoinoculation to develop at sites adjacent to the viral infection. The conventional treatment of warts includes topical salicylic acid, cryotherapy, duct tape, and electrocautery. Topical management is usually dependent on patient compliance and requires long application periods, which should not continue for more than six months to eradicate the lesions [3].

The present study reviews the management of recalcitrant warts and sheds light on the latest developments in the clinical uses of the Bacille Calmette-Guerin (BCG) vaccine, the *Mycobacterium w* vaccine (MWV), and a purified protein derivative (PPD) as immunotherapeutic options. The study also identifies the differences among them regarding efficacy, adverse effects, dosage, route of administration, and clearance and recurrence rates.

### 1.1. Recalcitrant Warts

Recalcitrant warts can accurately be defined as warts that remain after six months of conventional treatment (Figures 1-4). Up to one-third of non-genital warts, especially plantar and periungual warts, become recalcitrant. Given that malignant skin disorders, such as squamous cell carcinoma and verrucous carcinoma, can present with characteristics similar to warts, the dermatologist should do a punch biopsy to confirm the diagnosis of any lesions that fail to respond to treatment regimens [4].



**Figure 1.** Periungual wart aged two years and persist six months after to traditional treatment.



**Figure 2.** Plantar warts with poor response to treatment.



**Figure 3.** A-12-year-old boy with verruca plana persists six months after treatment.



**Figure 4.** A young adult with recalcitrant interdigital and plantar warts. Note: The photos were taken to patients attending the outpatient dermatology clinic at Diwaniyah Teaching Hospital, Diwaniyah, Iraq.

Treatment modalities available for recalcitrant warts include topical treatments like imiquimod, topical 5FU, topical formic acid, intralesional immunotherapy (bleomycin, candida antigen, interferon alfa), and oral therapies like oral retinoids and zinc sulfate. Laser treatments such as the CO<sub>2</sub> laser, pulsed dye laser, and Nd: YAG, were used as a last resort of treatment [5]-[11] (Table 1).

## 1.2. Intralesional Immunotherapy

Intralesional immunotherapy stimulates the immune system to grow a delayed-type hypersensitivity response to various antigens and the wart tissue. This modality is associated with the production of Th1 cytokines, which activate cytotoxic and natural killer cells to eradicate HPV infection. This option clears not only local warts but also distant warts, unlike traditional wart therapies [12].

Different immunotherapeutic agents have been used for intralesional injection. These include autogenous vaccine, Candida antigen, mumps antigen, trichophyton skin test antigen, MMR vaccine, BCG vaccine, *Mycobacterium w* vaccine, tuberculin and interferon alpha, and gamma injection. This procedure utilizes the fact that there is a high prevalence of immunity to these antigens in the general population. Most children well tolerated the dose of the antigen [12]. Intralesional immunotherapy can give significant results with few sessions. It can also eradicate distant warts with mild or insignificant adverse events at the site of injection.

## 1.3. BCG Vaccine

BCG stands for Bacille Calmette Guerin. BCG is a weakened (attenuated) version of bacteria called *Mycobacterium bovis*, which is closely related to *Mycobacterium tuberculosis*, the agent responsible for tuberculosis.

Several BCG vaccines, based on different strains, are available worldwide. BCG vaccines are usually administered by intradermal injection on the deltoid area. The correct administration technique by a well-trained health worker is essential to ensure proper dosage and optimal BCG efficacy and safety. A scar usually develops at the site of BCG injection due to local inflammatory

**Table 1.** Treatment considerations for warts.

Type of wart	First line	Second line	Third line
Common	Salicylic acid, cryotherapy, Electrocautery	Cantharidin	Intralesional immunotherapy, Bleomycin, Laser therapy
Plane	Salicylic acid, topical retinoic acid	Imiquimod, 5 fluorouracil, Cryotherapy	Intralesional immunotherapy, laser therapy
Periungual	Salicylic acid, lactic acid, cryotherapy	Cantharidin	Intralesional immunotherapy
Plantar	Salicylic acid, Trichloroacetic acid	Cryotherapy,	Bleomycin, surgical removal intralesional immunotherapy, laser therapy

processes. However, scar formation is not a marker for protection, and approximately 10% of vaccine recipients do not develop a scar. BCG vaccine has been standardized in a dose of 0.05 mL for infants and 0.1 mL for children and older, and it is not available in combination with other vaccines [13]. The protective immunity after primary infant BCG vaccination could last for up to 15 years in some populations [13].

Who should have the BCG vaccine?

1) BCG is recommended when immunization with it has not previously been carried out, and they are negative for tuberculo protein hypersensitivity.

2) Neonates with a family history of tuberculosis in the last five years.

3) Neonates, infants, and children below 16 years old were born or whose parents were born in a country with an incidence of TB higher than 40 per 100,000 [13].

4) New immigrants aged 16 - 35 years from Sub-Saharan Africa or a country with an incidence of tuberculosis greater than 500 per 100,000 [13].

5) Contacts under 36 years old with active respiratory tuberculosis (for healthcare or laboratory workers who have a history of contact with clinical materials or patients with a disease, age limit does not apply).

6) Healthcare workers and laboratory staff (irrespective of age) who are likely to have contact with patients, clinical materials, or derived isolates. (There is inadequate evidence of protection by the BCG vaccine in adults aged over 35 years; however, vaccination is recommended for healthcare workers irrespective of age because of the increased risk to them or their patients) [13] [14] (Table 2).

Who should not have the BCG vaccination?

The BCG vaccine is not recommended for:

1) People who have already had a BCG vaccination and those with a history of TB.

**Table 2.** Indications and contraindications of BCG.

Who should have BCG	Who should not have BCG
*Neonates who have a family history of Tuberculosis in the las five years.	*People who have been vaccinated with BCG, and people with a history of TB.
*Neonates, infants, and children below 16 years who born or whom their parent born in a country with an incidence of T.B > 40 per 100,000.	*People with a positive TST (Mantoux)
*Contacts aged under 36 years of those with active respiratory TB.	*People who have had a history of anaphylactic reaction to any of the substances used in the vaccine.
*Healthcare workers and laboratory staff (irrespective of age) who have contact with patients.	*Neonates in a household where a case of TB is suspected or confirmed.
*New immigrants aged 16 - 35 years from Sub-Saharan Africa or a country with an incidence of TB > 500 per 100,000.	*People who are seriously unwell or have a septic condition at the site of injection.
	*Immunocompromised people.
	*Pregnant women

- 2) People with a positive tuberculin skin test (Mantoux).
- 3) People who have had a previous anaphylactic reaction (severe allergic reaction) to any of the substances used in the vaccine.
- 4) Newborn babies in a household where a case of TB is suspected or confirmed.
- 5) Immunocompromised people, either as a result of health conditions such as HIV, leukemia, and lymphoma or treatments such as chemotherapy and systemic steroids.
- 6) People who are seriously unwell (vaccination should be delayed until they recover) or have a septic skin condition at the site of injection.
- 7) Pregnant women.

Because the vaccine doesn't work well for adults, BCG vaccinations are not usually given to people over 16 years old and never over the age of 35, with exception to people who have an occupational risk for TB [15] (Table 2).

### 1.3.1. Adverse Effects of BCG

The efficacy of the BCG vaccine was believed to mainly prevent severe forms of tuberculosis (TB) in children. In comparison, BCG seems to be more protective against leprosy [16] [17]. The BCG vaccine is safe; however, some adverse effects may occur, including abscesses at the site of injection and adenitis, disseminated disease due to impaired immunity such as chronic granulomatous disease, and impaired IL12- and IFN $\gamma$ -mediated immunity [18]. In Iraq, the BCG that was used to revaccinate young people and adults were given without a pre-existing tuberculin test, so any adverse effects that occurred due to the immunosuppression were recorded after giving the vaccine.

### 1.3.2. Can BCG Be Repeated?

The WHO recommended that primary BCG does not appear to prevent primary infection with *M. tuberculosis* but can provide protection against meningitis and miliary TB in children with a rate from 46% to 100%. Moreover, there is no evidence that revaccination with BCG can afford any additional protection, therefore this use remains controversial. BCG induced epigenetic reprogramming of innate immunity and trained the T cells toward beneficial nonspecific protection [19] [20].

The decision to revaccinate people with BCG for any cause should not be adopted without doing a prior tuberculin test to assess the protective immunity. Tuberculin testing is carried out at regular intervals, and revaccination is given when the reaction is considered negative. This practice of revaccinating from a single negative tuberculin test, and of withholding revaccination from persons who still react to tuberculin, has no scientific basis [21] [22].

The evidence from randomized controlled trials and retrospective cohort and case-control studies demonstrate the limited effects of revaccination in adolescents and adults after primary infant BCG vaccination for protection against *M. tuberculosis* infection and TB disease [23] [24].

Apart from children under 6 years, any person considered for BCG immunization must first be screened for hypersensitivity to tuberculo protein. A skin test is not necessary for a child under 6 years provided that the child has not stayed for longer than three months in a country with an incidence of tuberculosis greater than 40 per 100,000. The child has not had contact with a person with tuberculosis, and there is no family history of the disease within the last five years [14].

### **1.3.3. Is Revaccination with BCG Safe?**

Several studies indicate that the immune response conferred by the BCG vaccination declines with age and proposed revaccination with two or more doses to boost immunity. Routine revaccination is practiced in some TB endemic countries for individuals who are tuberculin negative or for those without a visible BCG scar after the first dose [24] [25]. BCG revaccination of MTB infected adults is safe, well tolerated, and reactogenicity is similar to that of primary BCG vaccination [26]. A study (Rio de Janeiro sub-strain) in 71,000 Brazilian school-children showed that adverse reactions to BCG revaccination were rare, and no significant difference in the rate of adverse reactions was observed between primary BCG vaccination and BCG revaccination [27].

### **1.3.4. BCG as Immunotherapy for Recalcitrant Warts**

We conducted a review of the research into how to inject BCG vaccines, dosage, the number of doses, and the scientific reasons for use. We also investigated the side effects, cure rate, and recurrences of warts after receiving the vaccine. We found that there was a difference in views between the different researchers. Most of them used intra-lesional injections of the BCG vaccine to treat recalcitrant warts, and a few of them used the intradermal route. The doses are given, and the number of treatments were varied and ranged from 3 to 10 doses. Two studies used intra-lesional BCG in 2 to 5 sessions with a two-week interval, one for a single huge common wart and the other for periungual warts [28] [29]. Local and systemic adverse effects following injection were investigated. Erythema and edema with or without pustules were reported at the site of injection. A flu-like illness that rapidly subsided within three days was also observed with each injection. Ashish Jagati *et al.* used a session of intra-lesional BCG to treat different types of warts, excluding genital warts [30]. One study tried intradermal injections in 1 to 3 courses to manage common, plantar, and plane warts [31]. With this modality of treatment, no local or systemic adverse reactions were observed apart from the natural appearance of a tender papule or a pustule at the site of injection. Metaweia *et al.* used the topical application of BCG for the treatment of condylomataacuminata, by weekly application, for six consecutive sessions [32]. The clinical responses to the treatments in all the previous studies were analyzed, and the results were uneven. The cure rate after treatment in the study that used intralesional injection was 86% and 39% in the study that used the intradermal vaccine (**Table 3**).



**Table 3.** Comparison between different studies used BCG as immunotherapy for warts, in term of the type of wart, dose, route of injection, no. of sessions, response and recurrence [28] [29] [30] [31] [32].

BCG study	Nofal A <i>et al.</i> [28]	Piyush Kumar <i>et al.</i> [29]	Ashish Jagati <i>et al.</i> [30]	Sharquie <i>et al.</i> [31]	Metawea <i>et al.</i> [32]
Type of wart	Huge common war	Periungual Wart	Different types of warts excluding genital and plane warts	Common, plantar and plane warts	Condylomataacuminata
Dose and route	Intralesional	0.1 mL Intralesional	0.1 mL Intralesional	Intradermal 0.1 ml	Topica
Interval	2 weeks	2 weeks	Single dose	1 month	Weekly
No. of sessions	5	3	Once	1 - 3	6 consecutive weeks
Complete response in a time	5 sessions	Not reported	86.66% of palmoplantar 100% of periungual	39.7%	80%
Recurrence	No recurrence after 6 month follow-up	Not reported	2.1% of the common wart	No recurrence after 3 months follow up	No recurrence

#### 1.4. *Mycobacterium w Vaccine*

*Mycobacterium indicuspranii* (MIP), earlier known as Mw, is a non-pathogenic, rapidly growing, atypical *mycobacterium*. It shares many common Band T cell determinants with *Mycobacterium leprae* and *Mycobacterium tuberculosis*, [33] based on its growth characteristics and metabolic properties [34] [35]. It is validly classified as a member of the *Mycobacterium avium* complex [35]. The new concept of this bacterium is due to its translational application as an immunotherapeutic. The origin of this nomenclature is the combination of isolating bacterial species from India (indicus) and the name of the discoverer PranTalwar (pranii) and studied at the National Institute of Immunology, India [36]. Mw vaccine consists of  $0.5 \times 10^9$  heat-killed bacilli per 0.1 ml that used as an adjunct in patients with multibacillary leprosy. The vaccine induces strong cytokine responses including IL-2, IL-4, IL-5, and interferon gamma [37].

Mw vaccination by both the parenteral route and aerosol administration gives greater immunity than BCG administered parenterally in the mouse model of tuberculosis [38]. The vaccine is primarily used as adjuvant immunotherapy for multibacillary leprosy. Its immunomodulatory effects have also been shown in other disorders such as pulmonary TB, HIV infection, and malignant neoplasms of the head, bladder, and lung [39].

#### *Mycobacterium w Vaccine as Immunotherapy for Recalcitrant Warts*

As an adjunct to chemotherapy, the vaccine accelerates bacterial elimination and hastens clinical improvement. A significant number of patients vaccinated with MWv showed histopathological upgrading and, eventually, attainment of a state of nonspecific infiltration without dermal granulomas [40]. Published studies used Mw vaccine for multiple warts, anogenital warts, extensive extragenital cutaneous warts, and periungual or subungual warts with no prior history of treatment for the same. The mean dose of Mw vaccine used to clear one wart is equal to that required to remove >10 warts.

The route of administration was intralesional to 3 - 5 lesions at a time, intrale-



sional injections in <3 warts, intralesional in a single wart, or the largest in case of multiple warts. A maximum of 10 injections (12 weeks) was given, whichever was earlier, until either complete clearance of wart [41] [42] [43].

The side effects of Mwv include tender erythematous papules healed with a scar, erythema at the site of warts in (70%) of patients, swelling in (16%), and superficial ulceration in one patient. Two patients had a low-grade fever, and two patients had tenderness and swelling of the submandibular lymph node.

The recurrence rate varied from zero in some studies to 14.28% in one study (Table 4).

### 1.5. Purified Protein Derivative (PPD)

A skin test composed of a purified protein derivative (PPD) of *Mycobacterium* antigens which elicit immune response in the classic example of delayed hypersensitivity reaction. T lymphocytes that are sensitized due to a previous infection are recruited to the site of injection, where they release lymphokines. Lymphokines cause the induration through vasodilatation, edema, fibrin deposition, and attraction of other inflammatory cells to the site. The Mantoux method is the only technique that has been standardized and extensively validated to do TST testing. PPD-S (0.1 mL = 5 tuberculin units) (TU) is injected into the volar aspect of the forearm using a 27-gauge needle. PPD-RT23 of 2(TU) is alternative to PPD-S. The diameter of the induration is measured after 48 - 72 h. The tuberculin skin test (TST) has a sensitivity ranging between 33% and 96% and specificity of 62.5%. QuantiFERon and Elispot are FDA-approved tests that assess sensitizations to MTB by measuring the amount of interferon-gamma release (IGRA) secreted from lymphocytes. QuantiFERon has 89% and 99% sensitivity and specificity, respectively, while Elispot has 98.8% and 100% sensitivity and specificity. Thus, these tests can determine TB even in patients who have received previous BCG and active disease, too [44] [45] [46] [47] [48].

**Table 4.** Mw vaccine in different studies; the frequency of use, sensitization, dosage, route of injection, success and recurrence rates [39] [41] [42] [43].

MWV study	Mean <i>et al.</i> [39]	Gupta <i>et al.</i> [41]	Singh S. <i>et al.</i> [42]	Shilpa Garg. <i>et al.</i> [43]
Use	Multiple warts	Anogenital warts	Extensive extra genital cutaneous warts	single or multiple warts
Sensitization with 0.1 ml	Done and then after two weeks subsequent injections were given	Done sensitization, subsequent	Done, and 2 weeks after doses given	Not done
Dosing interval	1 week	1 week	2 weeks	4 weeks
Dose	0.1 mL	0.1 mL	<0.1 mL	0.1 mL
Route	Intralesional to 3 - 5 lesions at a time	Intralesional injections in <3 warts	Intralesional to 2-4 warts	Intralesional in a single wart or the largest in case of multiple
Maximum doses	10	10	10	10
Success rate	83% clearance	88.9% clearance	54.5%	93.3%
Recurrence	In (3 out of 37)	No recurrence after 5 months	No recurrences during 3 - 9 months	In 14.28% of patients at new site

The proportion of BCG-vaccinated people who had a positive TST has been reported to vary from 0% to 90% [45]. Apart from children under six years, any person considered for BCG immunization must first be given a skin test for hypersensitivity to tuberculo protein. The skin test is not necessary for a child under 6 years provided the child has not stayed for longer than three months in a country with an incidence of tuberculosis greater than 40 per 100,000, the child has not had contact with a person with tuberculosis, and there is no family history of tuberculosis during the last five years [14].

A positive test can result from clinical or latent infection due to *M. tuberculosis*, from BCG vaccination, and from environmental mycobacteria [47] [49].

Rare cases of anaphylactic reactions and foreign body reactions involving a Mantoux test site have been reported. There is no chance of TB development from this test, as live bacteria are not used in it. Rare occurrences of local reactions, such as regional lymphangitis and adenitis, were also reported [46].

Inactive cases of TB, immunosuppression, and old age are considered to be a contraindication to PPD. It should be used with caution in pregnant women as it is pregnancy category C.

#### **1.5.1. What Are the Drawbacks of TST?**

The lack of specificity is a significant drawback in populations vaccinated with BCG. As the TST depends on a lymphocyte-induced delayed hypersensitivity reaction, it is of low sensitivity in immunosuppressed patients. Individuals with severe illness, including those with some forms of active tuberculosis, with HIV infection, and on immunosuppressant drugs, including corticosteroids, may have false negative reactions [50] [51].

#### **1.5.2. PPD as Immunotherapy for Recalcitrant Warts**

Several studies have reported that purified protein derivative (PPD) is effective and safe in the treatment of recalcitrant warts (palmoplantar, multiple common, periungual, and genital types) by intralesional route [52] [53] [54] [55] [56]. PPD was given to 40 pregnant women by intradermal route in their forearms and appears to be effective with insignificant side effects [57]. The previous study contravenes the documented reports that recommended PPD during pregnancy only for screening and diagnosis of women at high risk for TB [58]. An evidence based on randomized clinical trials has required to confirm the safety of PPD in pregnancy. BCG vaccine may be more effective than PPD, though it had more adverse effects [59].

PPD was also studied in comparison to other modalities like cryotherapy [54]. Measles mumps rubella (MMR) seems to be of equal effect [60]. Eman M. K. Yousif *et al.* noticed that IL PPD is more effective than IL zinc sulfate 2% in multiple resistant palmar and plantar warts, and it results in the clearance of distant warts when given into the largest one [61]. Saoji V. *et al.* had used PPD 2.5TU by IL route for two weekly intervals of four sessions to treat verruca vulgaris, plane, and plantar warts with a 76% clearance rate [62]. No significant ad-

verse events from IL PPD for single and multiple warts was reported by Nimbalkar A. *et al.* [63].

The frequent PPD injections can induce an exaggerated response that creates difficulty in the interpretation of TST and IGRA when used to diagnose latent TB in a patient who has received PPD immunotherapy [64].

**Table 5** and **Table 6** demonstrate the differences between BCG, MWV, and PPD.

## 2. Discussion

In this study, we have reviewed the latest developments that concern the use of BCG, MWV, and PPD vaccines in the treatment of recalcitrant warts. The data was collected from articles that were retrieved from PubMed and ResearchGate, published between 2000 and 2018, using BCG, MWV, PPD, and recalcitrant warts as search terms. Recalcitrant warts can be defined as warts that persist after six months of conventional therapy. The aims of treatment of warts are; a. to remove wart without recurrence b. not to produce scarring c. to induce life-long

**Table 5.** The differences among BCG, MWV, and PPD concerning type of bacteria, uses, formulary, route of administration, and their safety in pregnancy.

Variance	BCG	MWV	PPD
Type of bacteria	Live attenuated <i>mycobacteriumbovis</i>	Heat killed bacilli in a buffer solution	Purified protein derivative of <i>Mycobacterium</i> antigen
Uses	Routine vaccination against TB and leprosy (by WHO) in addition to researches	Immunotherapeutic adjunct to multidrug therapy of multibacillary leprosy in India.	Use to determine if someone has developed immune response to <i>mycobacterium</i> TB
Formula	0.05mL for infants, 0.1 mL for Children & adults	Multi-dose vial of 0.5 ml containing 500 million heat-killed bacilli in a buffer solution	5 TU/0.1 ml solution
Tuberculin test	Mandatory before injection	Not necessary	Not necessary
Route of administration	Intradermal, percutaneous by multipuncture	Intralesional	Intradermal route in the volar aspect of the forearm
Safety in pregnancy	Category B	Category B	Category C

**Table 6.** The differences in nature of adverse reactions among BCG, Mw vaccine, and PPD.

Nature of reaction	BCG	MWV	PPD
Mild	Papule at the injected site (2 - 4 weeks) Ulceration (1 - 2 months) Scar (2 - 5 months)	Papule at the injected site, Induration, ulceration, scar formation.	Redness, Induration 48 - 72 hr Local;
Severe	Local; abscess, keloid, suppuration 2 - 6 months.  Systemic; Cutaneous lesions, osteitis, disseminated BCG, immune reconstitution syndrome	Local; abscess, adenitis  Systemic; fever 2 days after intradermal injection, Pain and paraesthesia distal to the injected site lasting for one week	lymphadenitis Systemic; anaphylactic reaction, foreign body reaction

immunity. The indications for treatment include pain, interference with function, the risk of malignancy, and cosmetic embarrassment [65]. The causes of resistance to treatment are multifactorial, including the strength of the medicine used, the lack of patient commitment, the strains of the virus causing the wart, and not necessarily because of a defect in the immune status. Several factors determine the choice of the appropriate method of treatment, including age, sex, pregnancy, previous treatment, and immunocompetence. After the despair of traditional therapy with all its available options, for six months, we can resort to other methods, such as vaccination. Several vaccines are available and used by researchers for immunotherapy. Through our review of research on these vaccines, we concluded that the practice of its use is based on the number of warts and the site of the lesion. These vaccines can be given through various routes, including topical, intralesional injections, and intradermal administration. Topical application is preferable for resistant plane warts of the face and some time for genital lesions, while the intralesional mode is more suitable for single lesions or a number less than five located on the hand or foot. If there are more than five lesions as in a plane, and common warts of the face or extremities, or presence of disseminated warts, we have to select the largest three and inject them by intralesional route. If the injected warts respond to treatment, distant warts disappeared spontaneously. The intradermal model of treatment has limited uses in case of resistant common or plane warts; however, PPD was tried with considerable success in some studies, and it is superior to BCG as it does not have a specific age group [45] [52] [53] [55]. In countries where TB is endemic, tuberculin testing, is mandatory before revaccination with BCG to assess the immune status of the patient. A short term of follow up is not adequate after BCG revaccination, as the incidence of BCG complications such as lupus vulgaris and scrofulodermais challenging to predict and may need months to years to develop. The national management guideline of TB control program did not recommend the use of BCG revaccination, because there is no evidence that it gives additional protection (Table 7).

### 3. Conclusion

Before we decide to use immunotherapy, we must have abundant information about the BCG vaccine and the PPD, including the reasons for the use, the immunological effects, and the adverse reactions. However, the use of the previous option for treatment of recalcitrant warts remains dependent on the exhaustion of all conventional therapies for six months. We have considered that Mw vaccine has more opportunities for use than BCG and PPD as immunotherapy, to manage recalcitrant warts, especially in countries where TB is endemic. As Mw vaccine consists of heat-killed bacilli in a buffer solution, and its use neither needs a prior tuberculin test nor has a specific age group. Further randomized controlled studies are required to obtain more information to construct a therapeutic protocol.

**Table 7.** The key points highlighted in this review.

Highlights
Before starting immunotherapy, it is necessary to determine whether it is an adjuvant or alternative for conventional treatment.
BCG vaccination policy depends on the prevalence of tuberculosis in the country, and there is no evidence that BCG revaccination affords additional protection.
In countries where TB is endemic, tuberculin testing, is mandatory before revaccination with BCG to assess the immune status of the patient.
A short term of follow up is not adequate after BCG revaccination, as the incidence of BCG complications such as lupus vulgaris and scrofuloderma is challenging to predict and may need months to years to develop.
The interpretation of TST is required to rule out the presence of latent TB (LTBI), taking into consideration the false positive and negative possibilities.
The frequent injection of PPD as immunotherapy for warts may result in an overstated response. The first dose can boost the subsequent treatments and will lead to difficulty in the interpretation of TST and IGRA when used to diagnose latent TB in a patient receiving PPD immunotherapy.
MWV consists of heat-killed bacilli in a buffer solution, and its use neither needs a prior tuberculin test nor has a specific age group.
In the case of multiple recalcitrant warts, it is preferable to do intralesional injection for the largest one to limit the adverse events due to numerous local injections. Distant lesions will disappear spontaneously after the eradication of the large wart.

## Conflicts of Interest

The authors declare no conflict of interest.

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### **Abbreviations**

BCG: Bacilli Calmette Guerin,  
TST: Tuberculin test,  
LTBI: Latent tuberculosis infection,  
IGRA: Interferon gamma release assay,  
PPD: Purified protein derivative,  
IL: Intralesional.