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Management of Recalcitrant Cutaneous Warts: A Narrative Review of HPV Vaccination and Intralesional Therapies

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ABSTRACT:

Background: Cutaneous warts caused by human papillomavirus (HPV) are among the most prevalent dermatological conditions, with up to one third of non-genital lesions becoming recalcitrant to conventional destructive therapies. The limited efficacy of treatment and high recurrence rates associated with first-line modalities have driven growing interest in immunotherapeutic approaches.

Methods: This narrative review was conducted following a structured literature search of PubMed database, covering publications from January 2016 to March 2026, with the aim of synthesizing current evidence on intralesional immunotherapy and HPV vaccination in the management of recalcitrant extragenital cutaneous warts.

Results: Among intralesional agents, the MMR vaccine demonstrates the most consistent efficacy, with pooled complete response rates of 63.2% and distant wart clearance in 62.0% of patients. Intralesional HPV vaccination achieved the highest complete response rate in a placebo-controlled trial (75%), with a favorable safety. The evidence for intralesional vitamin D3 is heterogeneous; the sole double-blind, placebo-controlled trial showed no significant benefit over placebo. Therapeutic intramuscular HPV vaccination achieved complete resolution in 61.2% of patients across available studies, while routine prophylactic vaccination status did not influence wart resolution in standard treatment settings.

Conclusions: Intralesional MMR and HPV vaccines represent the most promising therapeutic modalities for recalcitrant cutaneous warts. Standardization of treatment protocols and large multicentre randomized controlled trials are required to establish definitive evidence-based recommendations.

Keywords: cutaneous warts, recalcitrant warts, intralesional immunotherapy, HPV vaccine, MMR vaccine, vitamin D3

HIGHLIGHTS

- Intralesional MMR vaccine demonstrates consistent efficacy with pooled complete response rates of 63.2% and distant wart clearance in 62.0% of patients.
- Intralesional HPV vaccination achieved the highest complete response rate (75%) in a placebo-controlled trial with a favorable safety profile.
- Evidence for intralesional vitamin D3 is heterogeneous; the sole double-blind RCT showed no significant benefit over placebo, unlike unblinded studies from other regions.
- Systemic immunostimulatory effects leading to distant wart resolution are characteristic of MMR and Candida antigen but largely absent with vitamin D3.
- Therapeutic intramuscular HPV vaccination shows promise (61.2% resolution), whereas routine prophylactic vaccination status does not influence existing wart resolution.
- Standardization of treatment protocols and large multicentre RCTs are urgently required to establish definitive evidence-based recommendations.

1. Introduction

Cutaneous warts are benign proliferations of epidermal keratinocytes caused by infection with the human papillomavirus (HPV), a small, non-enveloped double-stranded DNA virus with tropism for squamous epithelium, both keratinizing and non-keratinizing. To date more than 450 types of HPV have been identified and phylogenetically classified to five genera: *alpha, beta, gamma, nu, and mu;* based on genotyping of the L1 capsid gene. (1–3). The heterogeneity of clinical manifestations associated with HPV infection - ranging from benign cutaneous and anogenital lesions to premalignant intraepithelial neoplasia and invasive malignancies at both genital and extragenital sites - has led to the classification of HPV types according to their oncogenic potential. High-risk types, including HPV-16 and HPV-18, are implicated in the vast majority of cervical cancers, as well as in squamous cell carcinomas and precancerous lesions of the anal canal, vulva, vagina, penis and oropharynx. Low-risk types, such as HPV-6 and HPV-11, are more commonly associated with benign lesions, although malignant transformation has been reported (3). Depending on localization and morphology, cutaneous manifestations include common warts (verruca vulgaris), plantar warts (verruca plantaris), and

flat warts (verruca plana), predominantly caused by HPV types 1, 2, 4, 27, 57, and 63 (3–5) - and constitute the primary focus of the present review.

HPV is a highly transmissible pathogen, with transmission occurring mostly through direct skin-to-skin contact, including sexual activity. As a consequence, cutaneous warts represent one of the most prevalent dermatological disorders encountered in clinical practice, with prevalence peaking in the pediatric population. A cross-sectional study conducted in the Netherlands found warts in approximately 33% of children aged 4 to 12 years (1,5), while Australian data report prevalence rates of 12% in the same age group and 24% in 16-18 year-old children (5). Another study estimated that up to 40% of school-age children are affected (3), with prevalence in the general population ranging from 7% to 12% (6). The annual incidence of plantar warts has been reported at approximately 14% (7). Immunocompromised patients - including solid-organ transplant recipients, people living with HIV, and those with primary immunodeficiency disorders - are at particular risk of developing persistent, extensive, and treatment-resistant lesions (3,5).

Although spontaneous regression occurs in the majority of children within 1 to 4 years, the clinical course in adults and in patients with immune system dysfunction tends to be considerably more prolonged (1,5,8). The probability of resolution is further influenced by the HPV subtype: warts caused by HPV-1 demonstrate a substantially higher rate of spontaneous clearance compared with those attributable to types 2, 27, and 57 (58% vs. 7%) (1). Warts that persist despite three or more treatment attempts are commonly defined as recalcitrant, representing a clinically challenging subset associated with significant patient discomfort, psychological distress, and substantial burden on healthcare resources (5,9).

First-line management of cutaneous warts relies on destructive modalities, including topical salicylic acid, cryotherapy with liquid nitrogen, carbon dioxide laser therapy, surgical excision and photodynamic therapy. Despite being the most extensively studied and widely used approaches, their efficacy remains limited-response rates for both salicylic acid and cryotherapy in plantar warts barely exceed 30% (1). Up to one third of non-genital warts become recalcitrant to destructive therapies (5,8,10). Furthermore, these modalities carry risks of scarring, dyspigmentation, procedural pain, and recurrence rates of up to 30% (5,11). However, most importantly, their action is confined to the treated lesion - they exert no systemic effect and do not prevent the emergence of new warts at distant sites.

A key factor behind wart persistence and treatment resistance is the virus's capacity to evade host immune surveillance. HPV suppresses antigen presentation, downregulates major histocompatibility complex (MHC) class I expression, disrupts interferon signaling pathways through its E5, E6, and E7 proteins, and actively inhibits local immune responses within the skin (5). As a consequence, infected keratinocytes evade recognition by cytotoxic T lymphocytes, allowing chronic lesion persistence. Spontaneous wart clearance is contingent upon intact cell-mediated immunity (1,5). This biological rationale underpins immunotherapeutic strategies, which aim to restore the immune system's capacity to recognize and eliminate HPV-infected cells rather than physically destroying the lesion (12,13).

Prophylactic HPV vaccines, including the currently most comprehensive nonavalent formulation (Gardasil-9; HPV-6/11/16/18/31/33/45/52/58) were developed to prevent infection with oncogenic HPV types and are based on virus-like particles (VLPs) assembled from the major capsid protein L1 (3,5,14). The preventive effectiveness of HPV vaccination has been robustly demonstrated (15). Within the English HPV immunization program, initiated in 2008 using the bivalent vaccine, a marked reduction in cervical cancer incidence was observed, reaching 87% among women vaccinated at 12-13 years of age. In the same cohort, the incidence of CIN3 decreased by 97%, supporting projections of near-elimination of cervical cancer in women born after 1 September 1995 (16). In recent years, growing interest has emerged in the therapeutic application of these vaccines, both administered intramuscularly and delivered directly into the wart tissue, for the management of recalcitrant cutaneous warts (1,9). The structural homology between vaccine-targeted L1 proteins and those expressed by HPV types responsible for common cutaneous warts may induce cross-reactive immunity extending beyond the types directly covered by the vaccine. A distinct but related strategy is intralesional immunotherapy using other antigenic agents - including the measles-mumps-rubella (MMR) vaccine, vitamin D3, Candida antigen, purified protein derivative (PPD), and Bacillus Calmette-Guérin (BCG). This approach involves the direct injection of an immunostimulatory agent into the wart, triggering a type IV delayed-type hypersensitivity reaction and activating a Th1-polarised immune response characterized by the release of interferon-gamma (IFN-γ), interleukin-2 (IL-2), and tumor necrosis factor alpha (TNF-α), with subsequent activation of cytotoxic T lymphocytes and natural killer cells. A notable advantage of this strategy is its systemic effect - immune activation extends beyond the injected lesion and may lead to resolution of distant, untreated warts (5,17,18).

This narrative review examines the current evidence on the management of recalcitrant extragenital cutaneous warts, with particular emphasis on intralesional immunotherapy, especially the MMR vaccine and vitamin D, as well as on the therapeutic role of HPV vaccines administered both systemically and intralesionally. The aim is to critically appraise the available data on the efficacy and safety of individual modalities and to identify areas in which further research is warranted.

2. Methods

This narrative review was conducted to synthesize current evidence on the management of recalcitrant extragenital cutaneous warts, with particular emphasis on intralesional immunotherapy and the therapeutic application of HPV vaccination. A structured literature search was performed in the PubMed database, covering publications from January 2016 to March 2026. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to the following concepts: "cutaneous warts", "common warts", "verruca vulgaris", "plantar warts", "recalcitrant warts", "human papillomavirus", "HPV vaccination", "intralesional immunotherapy", "measles-mumps-rubella vaccine", and "vitamin D". Boolean operators (AND, OR) were used to combine search terms across concept domains. Reference lists of retrieved articles, including systematic reviews and meta-analyses, were additionally screened to identify relevant publications not captured by the primary database search.

Inclusion criteria encompassed original clinical studies, randomized controlled trials (RCTs), systematic reviews, meta-analyses, retrospective studies, and case series reporting on the efficacy, safety, or comparative effectiveness of intralesional immunotherapeutic agents or HPV vaccination in the treatment of extragenital cutaneous warts in human subjects of any age. Studies reporting exclusively on anogenital warts were excluded, as the causative HPV types and conventional therapeutic approaches differ substantially from those applicable to extragenital cutaneous lesions. Non-English-language publications were excluded. No restrictions were applied with respect to patient age or geographic origin of study populations.

Given the narrative design of this review, no formal quality scoring or meta-analytic pooling was performed. Study selection and data extraction were carried out by the authors, with emphasis placed on methodological rigor, sample size, and relevance to the clinical questions addressed. Where available, results from randomized controlled trials (RCTs) and registered systematic reviews and meta-analyses were prioritized in the synthesis of evidence.

3. Results

3.1. HPV Vaccination as a Therapeutic Modality: Systemic and Intralesional Administration

Two routes of HPV vaccine administration have been investigated therapeutically: systemic intramuscular injection and direct intralesional delivery.

Systemic (intramuscular) administration

A systematic review and individual patient data meta-analysis by Leeyaphan et al. (2025), registered in PROSPERO (CRD420251051106), identified 27 studies encompassing 183 patients in total with recalcitrant warts of various locations, including cutaneous extragenital sites, treated with at least one dose of intramuscular HPV vaccine. Complete resolution was achieved in 61.2% of cases (112/183), with a median time to clearance of 24 weeks (95% confidence interval (CI): 20.3-27.7 weeks). Cumulative cure rates were 22.8% at three months, 52.4% at six months, 61.4% at nine months, and 64.2% at twelve months. Younger age was significantly associated with better outcomes, with patients achieving complete cure being younger on average than non-responders (29.1 vs 37.5 years; $p = 0.003$). No significant difference in treatment outcomes was observed according to vaccine type, number of doses, or sex. Among immunocompromised patients with documented outcomes ($n = 14$), a clinical response was achieved in 92.9% of cases (13/14). The majority of included studies consisted of case reports and small case series, with only three of the 27 studies incorporating a comparator group (19).

Intralesional administration

Bar-Ilan et al. (2023) conducted a retrospective case series evaluating intralesional 9-valent HPV vaccine in 20 patients with recalcitrant cutaneous warts of predominantly palmar and plantar distribution, with a mean duration of 5 years in adults and 2.7 years in children. Patients received 0.1 mL injections into the largest wart at two-week intervals for a maximum of six sessions. Complete response was achieved in 60% of patients (12/20), with an additional 25% demonstrating an excellent response, defined as 75%-99% improvement. No systemic adverse effects were documented beyond transient injection-site pain, and no recurrences were reported during a mean follow-up period of 7.1 months. Older age was independently associated with a

better treatment outcome in multivariate analysis ($p < 0.05$), while a history of prior laser therapy was associated with a worse prognosis ($p < 0.01$) (9).

Fouda et al. (2024) conducted a three-arm RCT enrolling 60 patients with multiple recalcitrant non-genital warts, defined as warts persisting for more than one year and resistant to at least two prior therapeutic modalities. Patients were randomly assigned to receive intralesional injections of 0.3 mL of quadrivalent HPV vaccine (n = 20), 0.3 mL of Candida antigen at 1/1000 dilution (n = 20), or 0.3 mL of normal saline as a control (n = 20), administered at three-week intervals for a maximum of four sessions. Complete response was achieved in 75% of patients receiving intralesional quadrivalent HPV vaccine, 40% in the Candida antigen group, and 0% in the saline control group ($p < 0.001$). Regarding distant, uninjected warts, complete response was documented in 72.7% of patients in the HPV vaccine group compared with 33.3% in the Candida antigen group. No recurrences were reported during six months of follow-up in either active treatment group. The safety profile of intralesional HPV vaccination was favorable - fever as a distant adverse effect was significantly less frequent in the HPV vaccine group (10%) than in the Candida antigen group (55%) (18).

Next-Generation HPV Vaccines: L2-Based Approaches

Current prophylactic HPV vaccines are based on VLPs assembled from the major capsid protein L1, which elicit high-titer neutralizing antibodies that are largely type-restricted (20,21). This limitation has prompted growing interest in vaccines targeting the minor capsid protein L2, whose amino-terminal region contains broadly cross-neutralizing epitopes highly conserved across diverse HPV types, including cutaneous genotypes. Because this region has been subject to little evolutionary pressure for antigenic variation, antibodies raised against it can neutralize heterologous HPV types beyond those directly targeted by the vaccine. To overcome the inherently lower immunogenicity of L2 compared with L1-VLPs, L2 epitopes have been displayed on multivalent platforms that present the antigen in dense, repetitive arrays strongly stimulatory to B cells (21).

Two next-generation L2-based vaccine candidates - HPV16 RG1-VLP and CUT-PANHPVAX - were evaluated in a preclinical study by Ahmels et al. (2022) using the African multimammate rodent *Mastomys coucha*, a natural infection model in which the cutaneous *Mastomys natalensis* papillomavirus (MnPV) drives skin tumor development closely recapitulating the human scenario. Both vaccines induced cross-reactive antibodies against MnPV L2 and

conferred measurable in vivo protection, with significantly lower viral loads in vaccinated animals compared with mock-vaccinated controls. Regarding tumor prevention, 5 of 6 unvaccinated animals developed visible skin tumors within 75 weeks of experimental infection, whereas only 1 of 6 CUT-PANHPVAX-vaccinated and 2 of 6 HPV16 RG1-VLP-vaccinated animals developed tumors - both of them were classified as vaccine non-responders. These findings constitute the first proof-of-principle demonstration of L2-based vaccine efficacy against cutaneous papillomavirus infection and skin tumour development across different papillomavirus genera. Translation to clinical practice will, however, require confirmation in human subjects; at the time of writing, the mucosal predecessor of CUT-PANHPVAX - PANHPVAX - has entered phase I clinical evaluation (NCT05208710) (20).

3.2. Intralesional MMR Vaccine

The MMR vaccine has emerged as one of the most extensively studied intralesional immunotherapeutic agents in the management of recalcitrant extragenital cutaneous warts. The rationale underlying this approach rests on the induction of a delayed-type hypersensitivity reaction at the wart site, which stimulates a Th1-polarised cell-mediated immune response directed not only against the injected antigens, but also against HPV-infected keratinocytes. The presence of three synergistic viral antigens within the MMR preparation is considered to confer an immunogenic advantage over single-antigen preparations through mutual adjuvant effects (11).

Two randomized, placebo-controlled trials provide the most rigorous evidence for the efficacy of intralesional MMR in this indication. Awal and Kaur (2018) conducted a single-blind RCT enrolling 150 patients with extragenital cutaneous warts, of whom 72 completed the MMR arm and 50 the normal saline arm. Injections of 0.5 mL MMR vaccine were administered into the largest wart at two-week intervals for a maximum of five sessions. A complete response - defined as total clearance of all lesions - was achieved in 68% of patients in the MMR group compared with 10% in the saline control group, a difference that was highly statistically significant ($p < 0.00001$). Palmoplantar warts demonstrated the highest rate of complete clearance at 70.9%, followed by verruca vulgaris at 68.7% (22). Agrawal et al. (2018) conducted a double-blind RCT enrolling 100 patients with extragenital warts of more than one year's duration, with 30 patients completing each arm. Intralesional MMR (0.3 mL at three-

week intervals, maximum three injections) achieved complete response in 60% of patients in the interventional group versus 23.3% in the saline control group ($p = 0.01$) (11).

A clinically significant and therapeutically distinctive feature of intralesional MMR immunotherapy is its capacity to induce resolution of distant, anatomically separate warts that receive no direct injection. In the trial by Awal and Kaur (2018), complete response in distant warts was documented in 48% of patients in the MMR group compared with 24% in the control group. Agrawal et al. (2018) reported an even higher rate of distant wart clearance, with 69.5% of patients in the MMR group achieving complete resolution of distant lesions, compared with 0% in the saline group. This systemic effect is attributed to the induction of a widespread HPV-targeted cell-mediated immunity, involving activation of cytotoxic T lymphocytes and natural killer cells, which extends beyond the site of injection (11).

These findings are further contextualized by a systematic review and meta-analysis by Ju et al. (2022), which pooled data from 13 studies comprising 747 patients treated with intralesional MMR. The pooled complete response rate for the MMR group was 63.2% (95% CI: 53.1-73.4%), and the distant complete response rate was 62.0% (95% CI: 31.1-93.0%) (Ju et al., 2022). The pooled recurrence rate across all intralesional immunotherapy modalities was 2.0% (95% CI: 1.1-2.9%), markedly lower than the recurrence rates of up to 30% associated with conventional destructive therapies (23). In the RCT by Awal and Kaur (2018), recurrence at 16 weeks following the last injection was observed in only 2.7% of MMR-treated patients compared with 6% in the control group; Agrawal et al. (2018) reported recurrence in 16.6% of complete responders in the MMR group versus 57.1% in the saline group at six-month follow-up.

The safety profile of intralesional MMR is consistently favorable across the available evidence. In the trial by Awal and Kaur (2018), injection-site pain was the most frequently reported adverse effect, occurring in 90% of MMR-treated patients, though it was similarly common in the control group (88%), indicating that pain is largely attributable to the injection procedure itself rather than the vaccine. Flu-like symptoms including rhinitis and headache were reported in 6% of MMR-treated patients and resolved with paracetamol and antihistamines; mild local erythema and oedema occurred in 4% (22). In the trial by Agrawal et al. (2018), injection-site pain was reported in 60% and erythema in 13.3% of MMR-treated patients. No cases of infection, scarring, or serious adverse events were documented in either trial. Across the 54

studies included in the meta-analysis by Ju et al. (2022), all reported adverse events were characterized as mild and transient.

3.3. Intralesional Vitamin D3

The rationale for intralesional vitamin D3 in the treatment of cutaneous warts rests on its dual immunomodulatory and antiproliferative properties. Activation of toll-like receptors on keratinocytes and macrophages by 1,25-dihydroxyvitamin D upregulates the vitamin D receptor (VDR) and vitamin D-1-hydroxylase genes, leading to induction of antimicrobial peptides such as cathelicidin LL-37 and human β-defensin 2, which may augment local immune recognition of HPV-infected cells. Through VDR-dependent signaling, vitamin D3 additionally suppresses key pro-inflammatory cytokines including IL-6, IL-8, TNF-α, and IFN-γ, while simultaneously inhibiting abnormal keratinocyte proliferation and inducing terminal differentiation (7,24,25).

The clinical evidence for intralesional vitamin D3 is markedly heterogeneous. The systematic review and meta-analysis by Ju et al. (2022), encompassing nine studies with 311 patients, reported a pooled complete response rate of 54.2% (95% CI: 32.7-76.0%). Of particular importance, the pooled distant complete response rate was 17.6% (95% CI: -0.5-35.8%), which did not differ significantly from the saline control group (14.2%; 95% CI: -1.9-30.2%), indicating that the systemic immunostimulatory effect characteristic of other intralesional agents is largely absent with this modality (23). The systematic review by Mullen et al. (2024), encompassing 62 RCTs, reported complete response rates ranging from 40% to 96% across vitamin D3 studies, reflecting substantial variability in dosing protocols, injection volumes, and treatment intervals. (26)

The most methodologically rigorous assessment of intralesional vitamin D3 to date is the randomised, double-blind, placebo-controlled trial conducted by Merry et al. (2025) at Mayo Clinic. Seventy-seven adults with cutaneous warts - predominantly plantar (64%) and recalcitrant (69%) - were randomized to receive 12,000 IU (0.3 mL) of intralesional vitamin D3 or matched vehicle placebo every four weeks for up to three sessions. At 24 weeks, complete resolution was achieved in 30% of vitamin D3 recipients and 31% of placebo recipients. In a multivariable model adjusting for baseline wart size, number of warts, and vehicle, vitamin D3 demonstrated no significant effect on wart resolution (OR 0.31; 95% CI: 0.01-10.3; $p = 0.51$) or surface area reduction ($p = 0.98$) (8). The authors noted that the dose employed was substantially lower than those used in studies reporting high clearance rates (30,000 to

1,200,000 IU), and that geographic and demographic differences between study populations may account for divergent results.

The safety profile of intralesional vitamin D3 is generally characterized by injection-site pain, reported at higher rates than with MMR vaccine in comparative trials, likely attributable to the oily vehicle of commercially available preparations (25,27). Localized swelling and erythema are also frequently described, and rare injection-site pruritus - possibly related to the arachis oil base - has been noted (28). Across the 54 studies included in the meta-analysis by Ju et al. (2022), all adverse events were characterized as mild and transient. One study monitoring biochemical parameters noted subclinical hypervitaminosis D in a small number of patients receiving high-dose preparations, though symptomatic hypercalcaemia was not observed (7).

3.4. Intralesional MMR Vaccine versus Vitamin D3

The direct comparison of intralesional MMR vaccine and vitamin D3 has been the subject of multiple RCTs, reflecting the clinical relevance of establishing the relative merits of these two widely available and cost-effective immunotherapeutic agents.

Mohta et al. (2021) conducted a three-arm, placebo-controlled RCT enrolling 88 immunocompetent adults with recalcitrant extragenital warts resistant to at least two prior treatment modalities. Patients received intralesional MMR vaccine (0.2-0.3 mL, TRESIVAC), intralesional vitamin D3 (0.2-0.3 mL, 600,000 IU; 15 mg/mL), or normal saline every two weeks for a maximum of four sessions. Complete response in injected warts was achieved in 87.8% of MMR recipients and 77.4% of vitamin D3 recipients, a difference that did not reach statistical significance. Distant wart clearance was documented in 75.7% of the MMR group and 64.5% of the vitamin D3 group, again without significant intergroup difference. A statistically significant superiority of MMR over vitamin D3 was, however, demonstrated specifically for verruca plana ($p = 0.049$). No recurrences were observed in the MMR group at six-month follow-up, whereas two patients (6.5%) in the vitamin D3 group experienced recurrence among those who had previously achieved only partial clearance (28).

A RCT by Sallam et al. (2026) included 112 patients with multiple common, plantar, or flat warts, who were allocated to receive either 0.3 mL of intralesional MMR vaccine or 0.3 mL of intralesional vitamin D3 (15,000 IU of cholecalciferol) at two-week intervals for up to five treatment sessions. Complete response was achieved in 80.4% of the MMR group compared

with 66.1% in the vitamin D3 group, a statistically significant difference. Both groups required a mean of four sessions to achieve complete clearance, with no significant difference in the number of injections needed. Recurrence rates at six-month follow-up were low and comparable between groups, at 3.6% in the MMR group and 5.4% in the vitamin D3 group. Regarding adverse effects, the MMR group demonstrated a significantly higher incidence of mild pain and injection-site pruritus compared with the vitamin D3 group, whereas vitamin D3 recipients reported no injection-site reactions (29).

Sushantika and Singh (2025) conducted a randomized prospective comparative study enrolling 150 patients, of whom 70 completed the MMR arm and 80 the vitamin D3 arm, receiving injections every three weeks for up to six sessions. At 18 weeks, complete clearance was achieved in 60% of MMR-treated patients compared with 32.5% of vitamin D3-treated patients, a statistically significant difference ($p = 0.001$). Early response assessment at 12 weeks also favored MMR, with complete clearance in 14.3% versus 5% of vitamin D3 recipients. Pain was the most frequently reported adverse effect in both groups, occurring in approximately 60% of MMR patients and 95% of vitamin D3 patients; erythema and swelling were slightly more pronounced in the vitamin D3 group (25).

Singh et al. (2025) conducted a single-blind RCT enrolling 36 patients randomized to intralesional MMR (0.5 mL, TRESIVAC) or intralesional vitamin D3 (0.5 mL, 600,000 IU) every three weeks for a maximum of three sessions. Complete response was achieved in 64.7% of the MMR group and 36.8% of the vitamin D3 group, though the difference did not reach statistical significance given the limited sample size ($p = 0.14$). Both groups demonstrated significant within-group reduction in wart size throughout the treatment period. Side effects were mild and self-limiting; pain and swelling were reported in only three MMR patients compared with ten vitamin D3 patients (27).

These individual trial findings are synthesized in the systematic review and meta-analysis by Balach et al. (2026), registered in PROSPERO (ID: 1128443), which pooled data from nine RCTs comprising 742 patients. The meta-analysis demonstrated that vitamin D3 achieved significantly lower complete clearance than MMR, with a risk ratio of 0.85 (95% CI: 0.75-0.96; $p = 0.01$; $I^2 = 35\%$), and was associated with a significantly higher risk of non-response (RR 2.40; 95% CI: 1.40-4.13; $p = 0.002$; $I^2 = 0\%$). No statistically significant differences were identified for partial response, recurrence, or pain incidence. Vitamin D3 was associated with a significantly higher risk of injection-site swelling (RR 2.79; 95% CI: 1.15-6.75; $p = 0.02$),

while MMR was associated with a higher rate of erythema (RR 0.60; 95% CI: 0.42-0.86; p = 0.006) (7).

3.5. Other Intralesional Agents

Beyond MMR vaccine and vitamin D3, several additional immunotherapeutic agents have been evaluated for the treatment of recalcitrant extragenital cutaneous warts, including PPD, Candida antigen, and BCG vaccine. The breadth of available evidence for these modalities is captured in two major systematic reviews. Ju et al. (2022), pooling data from 54 prospective studies encompassing 3,446 patients, reported an overall complete response rate of 60.6% (95% CI: 54.8-66.5%) across all intralesional immunotherapeutic agents, with a pooled recurrence rate of 2.0% (95% CI: 1.1-2.9%) - markedly lower than the recurrence rates of up to 30% associated with conventional destructive therapies. Adverse events were reported in 51 of 54 studies and were uniformly characterized as mild and transient, with pain and flu-like symptoms being the most common (23). The systematic review by Mullen et al. (2024), encompassing 62 RCTs and 4,789 patients treated with 21 distinct intralesional agents or combinations, identified PPD and Candida antigen as the second and third most frequently studied modalities after MMR, with complete response rates of 48-87% and 25-84%, respectively (26).

Direct head-to-head comparisons of multiple agents within single trials provide more actionable comparative data. Chaudhary et al. (2023) conducted a four-arm, open-label RCT enrolling 100 patients with more than five cutaneous warts, randomized to receive intralesional MMR, PPD, Candida antigen, or vitamin D3 at three-weekly intervals for a maximum of three sessions. At three months following the last injection, complete clearance at the local site was highest with vitamin D3 (100%), followed by PPD and Candida antigen (both 84%), and lowest with MMR (68%). However, the pattern was reversed for distant wart clearance: Candida antigen achieved the highest distant complete response rate (80%), followed by PPD (72%) and MMR (60%), whereas vitamin D3 produced no clearance of distant warts whatsoever (0%). Pairwise comparisons revealed statistically significant differences between vitamin D3 and each of the other three agents for overall response (p = 0.001 for all), while no significant differences were observed between MMR, PPD, and Candida antigen (30).

Kabra et al. (2026) conducted a double-blind, three-arm RCT enrolling 60 patients with extragenital cutaneous warts, randomized to intralesional MMR (0.5 mL), BCG (0.1 mL), or vitamin D3 (0.5 mL, 600,000 IU) at three-weekly intervals for a maximum of five sessions. At

the final follow-up at 15 weeks, complete clearance at the injected site was achieved in 90% of MMR patients, 60% of BCG patients, and 25% of vitamin D3 patients, with statistically significant superiority of MMR over vitamin D3 ($p = 0.002$). Distant wart clearance followed a similar pattern: 80% for MMR, 40% for BCG, and 20% for vitamin D3 ($p = 0.016$). Kaplan-Meier analysis confirmed that MMR achieved the fastest time to complete clearance, with a mean of 5.3 ± 0.92 weeks, compared with 8.9 ± 1.86 weeks for BCG and 13.35 ± 2.54 weeks for vitamin D3 ($p < 0.001$). Cox proportional hazards analysis, using MMR as the reference group, demonstrated that BCG and vitamin D3 recipients had a 95% and 99% lower probability of achieving wart clearance at any given time point, respectively. Pain was the most common adverse effect, occurring at a significantly higher rate in the vitamin D3 group (80%) than in the BCG (35%) and MMR (20%) groups ($p < 0.001$) (31).

4. Discussion

This narrative review synthesizes the available evidence on intralesional immunotherapy and HPV vaccination as therapeutic strategies for recalcitrant extragenital cutaneous warts. The findings collectively support the superiority of immune-based approaches over conventional destructive modalities in selected patient populations, while also highlighting significant heterogeneity in efficacy across agents, unresolved questions regarding the role of HPV vaccination, and critical gaps in the standardization of treatment protocols.

The limitations of conventional destructive modalities in the management of recalcitrant extragenital cutaneous warts provide the fundamental rationale for immunotherapeutic approaches. Response rates for both salicylic acid and cryotherapy in plantar warts barely exceed 30%, recurrence rates reach up to 30%, and these modalities exert no systemic effect and do not prevent the emergence of new warts at distant sites. Intralesional immunotherapy addresses this limitation by triggering a Th1-polarised delayed-type hypersensitivity reaction that activates cytotoxic T lymphocytes and natural killer cells, restoring the host's capacity to recognize and eliminate HPV-infected keratinocytes both at the treated site and beyond. The pooled recurrence rate across all intralesional immunotherapy modalities in the meta-analysis by Ju et al. (2022) was 2.0% (95% CI: 1.1-2.9%) - markedly lower than the recurrence rates associated with conventional destructive therapies - underscoring the immunological rather than merely mechanical nature of the therapeutic effect (5,23).

Among the intralesional agents reviewed, the MMR vaccine emerges as the most extensively studied and consistently effective modality. Pooled data from the meta-analysis by Ju et al. (2022), encompassing 13 studies and 747 patients, demonstrated a complete response rate of 63.2% (95% CI: 53.1-73.4%) for intralesional MMR. The three-arm RCT by Kabra et al. (2026) demonstrated that MMR achieved 90% complete clearance at the injected site within 15 weeks, significantly outperforming both BCG (60%) and vitamin D3 (25%), with a mean time to clearance of 5.3 weeks - the shortest among the three agents. A particularly pronounced advantage for MMR was observed for verruca plana, which responded significantly better to MMR than to vitamin D3 in the placebo-controlled RCT by Mohta et al. (2021) ($p = 0.049$). The presence of three synergistic viral antigens within the MMR preparation is considered to confer an immunogenic advantage through mutual adjuvant effects, promoting a stronger Th1-biased response reflected in greater IL-12 elevation compared with other agents, as described by Kucharczyk et al. (2025). Across all head-to-head studies reviewed, MMR consistently demonstrated either superiority or non-inferiority compared with other agents, and the systematic review by Mullen et al. (2024), encompassing 62 RCTs, identified MMR as the most frequently studied intralesional agent with complete response rates ranging from 27% to 90% (5,23,26,28,31).

The capacity to induce resolution of distant, anatomically separate warts constitutes the most clinically meaningful advantage of intralesional immunotherapy over destructive modalities. The pooled distant complete response rate across all intralesional agents was 51.6% (95% CI: 37.9-65.3%) in the meta-analysis by Ju et al. (2022), with MMR and Candida antigen demonstrating the most pronounced systemic effects - distant complete response rates of 62.0% and 42.0%, respectively. The four-arm RCT by Chaudhary et al. (2023) demonstrated that Candida antigen achieved 80% distant clearance and PPD 72%, compared with 60% for MMR and 0% for vitamin D3, reinforcing the view that agents acting through non-specific antigenic stimulation generate a more robust systemic immune response than locally acting modalities. This systemic effect is mechanistically explained by the spread of immune activation beyond the injection site, allowing HPV-directed cell-mediated immunity to target infected keratinocytes throughout the body - a property with obvious clinical relevance in patients presenting with multiple or widely distributed lesions (5,23,30).

The evidence for intralesional vitamin D3 is characterized by a marked discrepancy between the results of unblinded comparative trials and the sole rigorous placebo-controlled, double-

blind trial. Numerous studies conducted predominantly in South Asian and Middle Eastern populations have reported complete response rates of 40-96%; however, the randomized, double-blind, placebo-controlled trial by Merry et al. (2025) at Mayo Clinic in a predominantly White North American population demonstrated no significant benefit over vehicle placebo at 24 weeks (30% vs 31% resolution; OR 0.31; $p = 0.51$). Several factors may contribute to this divergence, including the substantially lower dose employed by Merry et al. (12,000 IU vs 30,000-1,200,000 IU in other studies), differences in baseline vitamin D status between geographically distinct populations, and the absence of blinding and placebo controls in most positive studies. Furthermore, the pooled distant complete response rate for vitamin D3 in the meta-analysis by Ju et al. (2022) was 17.6% (95% CI: -0.5-35.8%), statistically indistinguishable from the saline control group, indicating that the systemic immunostimulatory effect characteristic of other intralesional agents is largely absent with this modality. Until adequately powered, double-blind, placebo-controlled trials using higher doses are conducted in diverse populations, firm conclusions regarding the efficacy of intralesional vitamin D3 cannot be drawn (8,23,26).

Intralesional HPV vaccination represents a mechanistically distinct and clinically promising strategy. Unlike non-specific immunostimulants, HPV vaccines contain VLPs assembled from the L1 capsid protein, which shares structural homology with L1 proteins expressed by cutaneous HPV types, potentially eliciting cross-reactive, HPV-directed immunity augmented by the vaccine's adjuvants. The three-arm RCT by Fouda et al. (2024) demonstrated a complete response rate of 75% with intralesional quadrivalent HPV vaccine - the highest reported for any single intralesional agent in a placebo-controlled trial - with distant wart clearance in 72.7% of patients and a favorable safety profile. The retrospective case series by Bar-Ilan et al. (2023) reported a 60% complete response with intralesional 9-valent HPV vaccine, with no recurrences over a mean follow-up of 7.1 months. Notably, intralesional HPV vaccination may offer a particular advantage in immunocompromised patients - including solid-organ transplant recipients and people living with HIV - who cannot safely receive live-attenuated vaccines such as MMR or BCG, yet remain at heightened risk of persistent and recalcitrant warts. The evidence base, however, remains limited to a small number of studies with modest sample sizes, and prospective RCTs with standardised outcomes are required to confirm these findings (5,9,18).

A conceptually related but empirically distinct question concerns the therapeutic and prophylactic role of systemically administered HPV vaccination in the context of existing cutaneous warts. The systematic review by Leeyaphan et al. (2025) demonstrated complete resolution in 61.2% of patients treated with intramuscular HPV vaccine, with a median time to clearance of 24 weeks and particularly favorable outcomes in immunocompromised individuals (92.9% clinical response. However, the evidence base consisted predominantly of case reports and small case series, with only three of the 27 included studies incorporating a comparator group, which substantially limits the strength of these conclusions. In contrast, the retrospective chart review by Burli et al. (2021), conducted in 151 pediatric patients, found no significant association between routine prophylactic HPV vaccination status and wart resolution following standard therapies including cryotherapy and Candida antigen injection ($p = 0.797$). Paradoxically, vaccinated patients required a significantly greater number of treatment visits ($p = 0.024$), a finding the authors attributed to confounding by healthcare-seeking behavior rather than a detrimental vaccine effect. Taken together, these findings suggest that while purposeful therapeutic intramuscular HPV vaccination may offer clinical benefit, routine prophylactic vaccination does not meaningfully augment the host immune response to existing warts - a distinction consistent with the different immunological mechanisms underlying these two approaches (19,32).

A fundamental limitation of the entire field is the absence of standardized treatment protocols. Across the studies reviewed, the dose of MMR vaccine ranged from 0.1 to 0.5 mL, the interval between sessions from two to four weeks, and the maximum number of injections from two to eight, with comparable variability observed for all other agents. As noted by Kucharczyk et al. (2025) and Mullen et al. (2024), this heterogeneity severely limits the comparability of results across studies and precludes definitive conclusions regarding optimal regimens. Pre-sensitization testing prior to MMR injection - advocated by some authors to enhance immunological responsiveness - has not been uniformly adopted, further complicating protocol standardization. Furthermore, the geographical concentration of published evidence - with the meta-analysis by Balach et al. (2026) noting that seven out of nine included RCTs were conducted in India and two in Egypt - limits the generalizability of findings to other populations and healthcare settings. Even the most extensively studied agent, MMR, had fewer than 1,000 patients across all published trials as of the systematic review by Mullen et al. (2024). Large, multicentre, RCTs with standardised dosing, blinded outcome assessment, and follow-up durations of at least 12 months are therefore urgently needed (5,7,26).

Beyond currently available agents, the development of next-generation HPV vaccines targeting the minor capsid protein L2 represents a conceptually significant advance. Unlike L1-based VLPs, which elicit type-restricted neutralising antibodies, L2-targeted vaccines are designed to generate broadly cross-reactive immunity against diverse HPV genotypes, including cutaneous types not covered by current prophylactic formulations. The preclinical study by Ahmels et al. (2022), conducted in the Mastomys coucha animal model, demonstrated proof-of-principle efficacy of two L2-based vaccine candidates - HPV16 RG1-VLP and CUT-PANHPVAX - against cutaneous papillomavirus infection and skin tumour development. If confirmed in human clinical trials - for which the mucosal predecessor PANHPVAX has entered phase I evaluation - L2-based vaccines may ultimately offer both broader prophylactic coverage and enhanced therapeutic potential for recalcitrant cutaneous warts (20).

5. Conclusions

Recalcitrant extragenital cutaneous warts represent a clinically significant therapeutic challenge, and the evidence reviewed in this paper supports intralesional immunotherapy as an effective and well-tolerated alternative to conventional destructive modalities, offering the distinctive advantage of systemic wart clearance through immune activation rather than localized tissue destruction.

Among the available intralesional agents, the MMR vaccine currently represents the most extensively studied and consistently effective option, with pooled complete response rates exceeding 60% and a demonstrated capacity to resolve distant, uninjected lesions - an effect largely absent with vitamin D3. The evidence for intralesional vitamin D3 remains conflicting: while numerous uncontrolled comparative studies from South Asian and Middle Eastern populations have reported substantial clearance rates, the only adequately blinded, placebo-controlled trial failed to demonstrate benefit beyond spontaneous resolution, and its systemic immunostimulatory capacity appears to be minimal. Intralesional HPV vaccination constitutes an emerging and mechanistically distinct approach, with the highest complete response rate reported in a placebo-controlled trial among all reviewed agents, and a potentially important role in immunocompromised patients who cannot receive live-attenuated vaccines. Purposeful therapeutic administration of HPV vaccine intramuscularly has also shown promise, whereas

routine prophylactic vaccination status does not appear to augment the response to standard wart therapies.

Despite these encouraging findings, the field is constrained by the absence of standardized treatment protocols, the predominantly single-centre and geographically concentrated nature of existing trials, and the limited sample sizes that characterize even the most extensively studied modalities. The development of next-generation L2-based HPV vaccines may in the future offer broader cross-genotype coverage and enhanced therapeutic potential.

Large, multicentre, randomized controlled trials with standardized dosing regimens, blinded outcome assessment, and long-term follow-up are required to establish definitive evidence-based recommendations and to translate the promising results of intralesional immunotherapy into routine clinical practice.

DISCLOSURE

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In preparing this work, the authors used Claude (Anthropic) for the purpose of language editing and improving readability. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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