

# Updates on the use of vaccines in dermatological conditions

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## Abstract

Numerous vaccines are being actively developed for use in dermatologic diseases. Advances in the fields of immunotherapy, genetics and molecular medicine have allowed for the design of prophylactic and therapeutic vaccines with immense potential in managing infections and malignancies of the skin. This review addresses the different vaccines available for use in dermatological diseases and those under development for future potential use. The major limitation of our review is its complete reliance on published data. Our review is strictly limited to the availability of published research online through available databases. We do not cite any of the authors' previous publications nor have we conducted previous original research studies regarding vaccines in dermatology. Strength would have been added to our paper had we conducted original studies by our research team regarding the candidate vaccines delineated in the paper.

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## Introduction

Vaccines are among medicine's greatest achievements and most successful strategies to prevent diseases. Not only have they helped eradicate smallpox, but they also prevent around 2–3 million deaths every year from diphtheria, tetanus, pertussis and measles.<sup>1</sup> The concept of vaccination entails improving immunity to a specific disease. This is accomplished by introducing a weak form of the disease-causing agent, an antigen, which induces a specific immune response to produce specific types of antibodies. When the actual disease antigens are introduced to the body of a vaccinated individual, the pre-formed antibodies produced in response to the vaccine are already present and they either prevent the disease from happening or help in diminishing the severity of the disease presentation.

The World Health Organization recommended, through its Expanded Program on Immunization in 1961, inclusion of vaccines for preventable diseases in the national health programs of countries. Since then, there was increasing worldwide recognition

of the role of vaccines in limiting the spread of infectious diseases in the community. India, for example, has expanded its immunization efforts and has strategically introduced several new vaccines in its adopted Universal Immunization Program, with 42% of spending on routine vaccination being made by the Indian government itself.<sup>2,3</sup> As a result, the under-five mortality rate has dropped from 233 to 63 per 1000 over the last 5 decades.

Due to the recent developments in the medical field, immunotherapy has not only played a pivotal role as a cost-effective public health intervention for prevention of infectious diseases but also has surged as an attractive method aimed at treating and preventing other types of diseases, including malignancy, autoimmune disorders and allergies. In fact, the identification of specific antigens and immunological epitopes has allowed the creation of vaccines derived from multiple types of antigen sources including glycolipids, tumor-associated antigens, dendritic cells, autologous and allogeneic peptide antigens.<sup>4</sup> Such vaccines are actively being

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developed and tested in multiple ongoing clinical trials to target a wide variety of diseases. This review aims at summarizing the use of vaccines in dermatological diseases.

### Vaccines for Viral Infections Affecting the Skin

Skin infections are very common. Some are primary, such as herpes simplex virus, human papillomavirus, varicella/zoster or leishmanial infections. Other infections can have secondary skin manifestations such as measles, rubella, human immunodeficiency virus, cutaneous tuberculosis and Lyme disease.

Interestingly, the first vaccine (vaccinia-cowpox) for immunization was developed to prevent smallpox, a highly contagious and fatal blister-forming infection. The vaccine was introduced by Edward Jenner in 1798 and allowed the worldwide eradication of this deadly disease in 1980.<sup>5</sup> The great success of this global immunization campaign led by the World Health Organization in 1967 urged researchers to develop further vaccines for both prophylaxis and treatment of certain diseases.

#### Human papillomavirus infection

Infection with high-risk human papillomaviruses, particularly human papillomavirus types 16 and 18, promotes the development of genital warts and cervical, anal and oral cancers.<sup>6</sup> This represents a substantial public health burden. Indeed, cervical cancer is a major cause of cancer deaths in women.<sup>7</sup> Men are also at a risk of human papillomavirus-associated verrucae and cancers, especially anal and penile cancer. The incidence of human papillomavirus-associated genital cancers is particularly high in men who have sex with men, suggesting an acute need for prevention in this population.<sup>8</sup>

Three human papillomavirus vaccines are currently available. The bivalent/2vHPV vaccine (Cervarix) by GlaxoSmithKline protects against human papillomaviruses 16 and 18. The quadrivalent/4vHPV vaccine (Gardasil) by Merck covers strains 6, 11, 16 and 18. Finally, the 9-valent/9vHPV vaccine (Gardasil 9) by Merck produces immunity against human papillomavirus types 6, 11, 16, 18, 31, 33, 45, 52 and 58. Any of these vaccines can be used in females.<sup>8-10</sup> According to the Advisory Committee on Immunization Practices, it is recommended that females between ages 11 and 12 are vaccinated with three doses of the human papillomavirus vaccine. These can be given to females as young as 9 years and to those whose ages range between 13 and 26 as well who have not been previously vaccinated. There is no need to test by pap smear or human papillomavirus DNA or antibodies prior to vaccination. On the other hand, the American Cancer Society does not recommend routine vaccination for women older than 18 years because they are more likely to have been already exposed to human papillomavirus. Therefore, according to the American Cancer Society, this decision should be made on an individual basis. In addition, vaccination is also recommended below 26 years of age for men who have sex with men and immunocompromised individuals, including those with HIV infection, if they have not received the vaccine previously. At a population level, use of the 9vHPV vaccine was found to be more cost-effective compared with 4vHPV for both men and women.<sup>8-11</sup> The human papillomavirus vaccines are generally well-tolerated with the most common side effects, reported in up to 50% of patients, being injection site pain, mild fever and injection site reaction.<sup>12</sup> Table 1 includes the recommended immunization schedule for human papillomavirus vaccine with possible adverse

events, and Table 2 shows the available human papillomavirus vaccines and their price.

Despite the benefits of the available human papillomavirus vaccines, controversy remains regarding whether their benefits outweigh the risks. This has led to resistance to implementation of these vaccines by some communities. Concerns about human papillomavirus vaccines have been led not only by people but also by some physicians and healthcare professionals. The most common reason lies in some studies that suggest mild documented adverse events with a positive risk-benefit assessment against human papillomavirus vaccines.<sup>13-15</sup> For example, a large systematic review, that included a total of 29,540 individuals, showed that pain, swelling and fever were the most frequently reported events, in addition to mild headache, fatigue and gastrointestinal symptoms.<sup>13</sup> Interestingly, association between these vaccines and autoimmune manifestations has also been reported in some studies. However, recent reports have emphasized the importance of genetic background and previous history of adverse events to other vaccinations in developing autoimmune disease post human papillomavirus vaccination. Therefore, despite all the controversy, human papillomavirus vaccination remains the most effective way to prevent cervical cancer.<sup>13,14</sup>

In addition to such controversies, there are several limitations that limit the successful implementation of human papillomavirus vaccines, especially in developing countries. Such limitations include high vaccine costs, lack of public awareness about cervical cancer and about early screening and detection and most importantly the nature of human papillomavirus transmission, which carries the stigma of unacceptable sexual behavior. In many communities, not only is human papillomavirus vaccine expensive but promotion of human papillomavirus vaccines may be perceived by some as promotion of promiscuity. In India, for example, the introduction of human papillomavirus vaccine clinical trials was met with strong resistance from civil society organizations who expressed their worries to the Indian Government.<sup>16</sup> Two important factors highly associated with increased acceptance of the human papillomavirus vaccine were community awareness of its benefits and understanding that all children are at risk regardless of religious or moral values. This emphasizes the importance of continuous efforts to break these barriers and to spread awareness of the importance of human papillomavirus vaccine in the prevention and control of communicable human papillomavirus infections and malignancies.<sup>17,18</sup>

While human papillomavirus vaccines resulted in significant achievement in terms of prevention of human papillomavirus infections and its associated diseases, there remains a great human papillomavirus-associated disease burden worldwide. In fact, to date, it is estimated that 5 million women are infected with human papillomavirus worldwide that carry a risk for developing invasive cervical cancer. In India, for example, the annual incidence of cervical cancer is approximately 130,000 cases with 75–80,000 deaths, which makes about one-fourth of the global cervical cancer burden. As a result, there is a need to develop therapeutic human papillomavirus vaccines for better control and eradication of existing human papillomavirus-associated diseases.<sup>16-18</sup>

Multiple types of therapeutic human papillomavirus vaccine candidates have been developed and are being tested in pre-clinical studies and clinical trials. These include live vector, protein/peptide, nucleic acid and cell-based vaccines. The rationale behind designing

**Table 1: Recommended immunization schedule for persons aged 21 years or younger**

Vaccine	Birth	6 weeks	6 months	12-15 months	18 months-3 years	4-6 years	7-10 years	11-12 years	13-18 years	19-21 years	Adverse events (probability)
MMR (146-149)				1 <sup>st</sup> dose	Range of recommended ages for catch-up immunization*	2 <sup>nd</sup> dose**	Range of recommended ages for catch-up immunization*				Fever (2%) Acute arthralgia (25%) Injection site reaction (17-30%) Febrile seizure (1/2000)
VZV (120, 146-149)				1 <sup>st</sup> dose	Range of recommended ages for catch-up immunization*	2 <sup>nd</sup> dose	Range of recommended ages for catch-up immunization*				Fever (15%) Injection site reaction (7-30%) Generalized skin rash (3-5%) Febrile seizure (4/10,000)
HPV (34)	Immunocompromised children with SCID or HIV infection, should receive a 3-dose series at 0, 1-2, and 6 months 1 <sup>st</sup> dose	2 <sup>nd</sup> dose	3 <sup>rd</sup> dose				For children with history of sexual abuse or assault, administer HPV vaccine beginning at age 9 years	Range of recommended ages for all children	Range of recommended ages for catch-up immunization, if not previously vaccinated		Injection site pain (78%) Local erythema andswelling (25%) Headache (30%) Generalized skin rash (1%)
MIP (120-124)	All children and adults, especially those in close contact with leprosy patients and/or in endemic areas, at any age										Injection site reaction (pain, swelling, itching) (13%) Scar at injection site (0.7%)
BCG (146-149)	Administer to all newborns before hospital discharge										Local abscess, keloid (1/10,000-1000) Cutaneous <i>Mycobacterium bovis</i> (2 case reports only) Atypical papular tuberculoides (9 case reports)
Hepatitis B (146-149)	Administer to all newborns before hospital discharge 1 <sup>st</sup> dose	2 <sup>nd</sup> dose					The final (3 <sup>rd</sup> or 4 <sup>th</sup> ) dose in the HepB vaccine series should be administered no earlier than age 24 weeks and at least 16 weeks after the first dose				Headache (3%) Local erythema and swelling (3%) Low grade fever (1-6%)
Color code		Routine immunization	Catch-up immunization	Special population							

\*All children and adolescents should have had 2 doses of MMR vaccine; the minimum interval between the 2 doses is 4 weeks, \*\*The second dose may be administered before age 4 years at least 4 weeks after the first dose. \*All patients between 7 and 12 years of age without evidence of immunity should have 2 doses of varicella vaccine at least 3 months apart. For persons aged 13 years and older, the minimum interval between doses is 4 weeks. MMR: Measles-mumps-rubella, VZV: Varicella Zoster Virus, HPV: Human papillomavirus, MIP: *Mycobacterium indicus Pranii*, BCG: Bacillus Calmette-Guerin, SCID: Severe combined immunodeficiency, HIV: Human immunodeficiency virus

**Table 2: List of available vaccines, their trade names and price\***

Vaccine	Trade name	Manufacturer	Price per dose, in Indian rupees (₹)	Price in USD (\$)	References
MMR	Morupar	Sanofi Aventis	75	1.17	150-152
	Tresivac	Serum Institute of India Limited	96.25-140.75	1.5-2.198	
	Trimovax	Aventis Pasteur India Limited	72	1.12	
	Trimovax merieux	Serum International Limited	70.6	1.10	
Varicella	Biovac V	Wockhardt	1799	27.98	153
	Varivax	Merck and Co	1690	26.29	
	Varilrix	GlaxoSmithKline	1560	24.26	
HPV	Gardasil, quadrivalent (HPV types 6, 11, 16, and 18)	Merck and Co	2975	46.28	152,154
	Cervarix, bivalent (HPV types 16 and 18)	GlaxoSmithKline	2190	34.07	
	Gardasil 9 (9-valent) (HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58)	Merck and Co	Not yet licensed for import to India		
MIP	MIP	Cadila Pharmaceuticals India Limited	Free of charge (NLEP, Government of India Funds, in addition to support from the WHO)		91,148,155,156
BCG	Tubervac	Serum Institute of India Limited	6	0.09	152
	BCG	Aventis Pasteur India Limited	25	0.39	
Hepatitis B	Biovac B	Wockhardt	140	2.18	43
	Engerix B	GlaxoSmithKline	199	3.10	
	Enivac HB	Panacea Biotech Limited	170	2.64	

\*The Price of the drugs indicated above may not match the actual price at which they are actually sold. It can also change depending on factors, including taxes. These are only approximate indicative prices of the vaccines. NLEP: National Leprosy Elimination Program, MMR: Measles-mumps-rubella, HPV: Human papilloma virus, MIP: *Mycobacterium Indicus Pranii*, BCG: Bacillus Calmette-Guerin

these vaccines lies in targeting the E6 and E7 oncoproteins. These are constitutively expressed by human papillomavirus-associated tumors and are important for the introduction and maintenance of cellular transformation by human papillomavirus-infected cells and result in activation of cytotoxic T cells.<sup>19-35</sup> These vaccines have shown promising results in clinical trials involving patients with human papillomavirus-related infections and malignancies. The vaccine candidate HPV-16 SLP, for example, has been shown to be safe and highly immunogenic and resulted in significant enhancement of CD8 positive T cell response to E6 and E7 in patients with genital warts who were vaccinated as compared to placebo recipients.<sup>21,36</sup> In addition to genital warts, therapeutic human papillomavirus vaccine candidates have been tested with mild success in human papillomavirus-associated malignancies, including vulvar intraepithelial neoplasia and vaginal intraepithelial neoplasia. In a clinical trial by Baldwin *et al.*, vaccination with therapeutic HPV vaccine (TA-HPV) candidate resulted in 50% reduction in lesion diameter over a six-month period in 5 out of 12 patients, and one patient had complete response.<sup>21,36</sup> Details regarding therapeutic human papillomavirus vaccine candidates are listed in Table 3.

### Herpes simplex virus

Herpes simplex viral infections are some of the most ubiquitous of all infections, with prevalence in the United States ranging from 65% for herpes simplex virus-1 and 16% for herpes simplex virus-2.<sup>37,38</sup> Prevalence varies among different countries. India for example, has herpes simplex virus-2 infections ranging between 11.4 and 28.82% in retrospective data analysis studies.<sup>39</sup> Herpes

simplex virus-2 seroprevalence ranges between 43 and 83% among sexually transmitted diseases patients and between 7.9 and 14.6% in population-based cross-sectional studies. Herpes simplex virus-1 seroprevalence, on the other hand, ranges between 36.5 and 92.5% in cross-sectional studies.<sup>40,41</sup> Given that significant morbidity and mortality are associated with those viruses and that antiviral medication have a minimal impact on prevalence, numerous efforts have been made to develop an efficacious vaccine. Multiple strategies are being studied now for eventual development of a herpes simplex virus-2 vaccine, especially that reducing genital herpes would be expected to reduce HIV spread.<sup>42</sup>

While no effective vaccines against herpes simplex virus infection are available yet, multiple vaccine candidates have been tested in the preclinical phase on animals and are being studied in clinical trials.<sup>37,43</sup> Table 4 shows a list of herpes simplex virus vaccine candidates and their current developmental status.

To date, the largest clinical trial of a herpes simplex virus vaccine candidate was the Herpevac trial, which studied the efficacy of herpes simplex virus-2 gD vaccine against herpes simplex virus disease in herpes simplex virus-1 and herpes simplex virus-2 seronegative patients. Interestingly, the vaccine, which consisted of glycoprotein D from HSV-2 with 3-O-deacylated monophospholipid A (MPL) adjuvant, provided 35% efficacy against herpes simplex virus-1 disease and 58% efficacy against herpes simplex virus-1 genital disease, but was not efficacious against herpes simplex virus-2 acquisition.<sup>44</sup> Within the past 3 years, four additional herpes simplex virus vaccine candidates have entered into phase

**Table 3: List of therapeutic human papilloma viruses vaccine candidates**

Vaccine category	HPV vaccine candidate	Vaccine platform	Development status	References
Live vector based (bacterial)	Lm-LLo-E7	prfA (the transcriptional activator of virulence genes)-defective Lm strain transformed with plasmid encoding HPV-16 E7 antigen fused to a fragment of nonhemolytic LLO	Phase I clinical trials	19
Live vector based (viral)	TA-HPV	Recombinant vaccinia virus (large, complex, enveloped virus belonging to the poxvirus family); encodes oncoproteins E6 and E7 of both HPV 16 and HPV18	Phase II clinical trials	20,21
	TG4001	Recombinant modified vaccinia Ankara-expressing HPV-16 E6, E7, and IL-2	Phase I clinical trials	22
	MVA E2	Recombinant modified vaccinia Ankara encoding E2 from bovine papillomavirus	Phase III clinical trials	23
Protein/peptide based	HPV 16-SLP vaccine	Combination of nine HPV-16 E6 and four HPV-16 E7 synthetic peptides adjuvanted with Freund's adjuvant (solution emulsified in mineral oil)	Phase II clinical trials	24
	GL-0810	HPV-16 immunomodulatory peptide with adjuvant montanide and granulocyte macrophage colony stimulating factor	Phase I clinical trials	25
	Pepcan + candid	HPV16 E6 peptides combined with Candida skin testing reagent candid	Phase I clinical trials	26
	GTL001	Recombinant HPV16 and HPV18 E7 proteins fused to inactive <i>B. pertussis</i> adenylate CyaA expressed in <i>E. coli</i>	Phase I clinical trials	27
	TA-CIN	HPV16 E6/E7/L2 fusion protein	Phase II clinical trials	28
	TA-CIN+TA-HPV	HPV16 E6/E7/L2 fusion protein and vaccinia virus with HPV16/18 E6/E7	Phase II clinical trials	29
Nucleic acid-based	pNGVL4a-sig/E7 (detox)/HSP70 + TA-HPV	Plasmid encoding mutated form of HPV16-E7 linked to sig and heat shock protein HSP70 and vaccinia virus with HPV16/18 E6/E7	Phase I clinical trials	30
	pNGVL4a-CRT/E7 (detox)	Plasmid encoding mutated form of HPV16-E7 linked to calreticulin	Phase I clinical trials	31
	GX-188E	Plasmid encoding fusion protein of HPV 16/18 E6/E7 linked to FMS-like tyrosine kinase 3 ligand (Flt3L) and tpa	Phase I clinical trials	32
	VGX-3100	Mixture of two plasmids encoding optimized consensus of E6 and E7 antigen of HPV 16 and 18	Phase I and II clinical trials	33
	Cell based	DC + KLH	DC pulsed with HPV-16 and HPV-18 E7 and KLH	Phase I clinical trials
DC		DC pulsed with HPV + tumor lysate	Phase I clinical trials	35

HPV: Human papilloma virus LM: listeria monocytogenes, LLO: Listeriolysin O, SLP: Synthetic long peptide, IL: Interleukin, CIN: Cervical intraepithelial neoplasia, TA: Therapeutic antigen, KLH: Keyhole limpet hemocyanin, DC: Dendritic cells, MVA: Modified vaccinia virus, *B. pertussis*: *Bordetella pertussis*, *E. coli*: *Escherichia coli*, CyaA: Cyclase toxin, HSP: Heat shock protein

II trials as therapeutic vaccine candidates. These have novel adjuvants which stimulate T cell immunity. GEN-003, a subunit vaccine consisting of glycoprotein D2 and Infected Cell Protein 4 (GD2-ICP4) with Matrix M adjuvant, showed a 50% decrease in genital HSV-2 shedding rate after the therapeutic vaccine series.<sup>45-47</sup> Another candidate was HerpV, a 32 peptides vaccine linked to heat shock protein and QS-21 adjuvant. It showed a 15% decrease in viral shedding up to 6 months after the initial vaccine series.<sup>48</sup> VCL-HB01/HM01, a plasmid DNA vaccine encoding glycoprotein D2 and Unique Long (UL)-46 protein adjuvanted with Vaxfectin®, a lipid-based formulation, has also shown a statistically significant reduction in genital lesion rate compared to baseline. Interestingly, HSV529, a live attenuated herpes simplex virus-2 that is replication defective with deletion of UL-5 and UL-29 proteins, is currently in phase I trials and is being studied as both therapeutic and preventive vaccine candidate.<sup>49</sup>

On the other hand, several vaccine candidates are currently undergoing pre-clinical experiments on animals, mostly mice and guinea pigs. These include Glycoprotein D2/Glycoprotein C2/Glycoprotein E2, HSV-2 0 ΔNLS, HF10, ΔGlycoprotein

D2, AD472, CJ2-Gd2, Inactivated herpes simplex virus-2 in MPL, HSV-1 Glycoprotein B Lentiviral vector and Glycoprotein B1s-NISV.<sup>50-55</sup> Details regarding these vaccines are delineated in Table 3.

#### Varicella-zoster virus

Varicella-zoster virus causes both varicella, also known as chickenpox, and herpes zoster, also known as shingles. Not only did the introduction of the varicella vaccine in 1984 lead to a marked decrease in the incidence of chickenpox and shingles but it also resulted in a significant drop in varicella-related hospitalization to 14.5 per 100000 cases worldwide. In fact, the World Health Organization recommends that, in countries where varicella is an important public health burden, its vaccine should be introduced into their routine immunization programs. As a result, varicella vaccine was added to the immunization schedule by the Indian Academy of Pediatrics in 2011, and its incidence has dropped by almost 50%.<sup>56-58</sup>

Table 1 includes the recommended immunization schedule for varicella vaccine with possible adverse events, and Table 2 shows the available varicella vaccines and their price. The immunization

**Table 4: List of herpes simplex virus vaccine candidates**

Candidate	Vaccine platform	Target HSV	Development status	References
HSV-2 Glycoprotein D	Glycoprotein D from HSV-2 with alum and 3-O-deacylated MPL as an adjuvant	HSV-1 (no efficacy against HSV-2)	Phase III clinical trials, preventive	43,44
GEN-003	Subunit vaccine: Glycoprotein D2 and (glycoprotein D2-ICP4) with matrix M adjuvant	HSV-2	Phase II clinical trials, therapeutic	45-47
Herp V	Peptides complexed with HSP with QS-21 adjuvant	HSV-2	Phase II clinical trials, therapeutic	157
VCL-HB01/HM01	Plasmid DNA vaccine encoding glycoprotein D2 and UL-46 protein adjuvanted with Vaxfectin®, a lipid-based formulation	HSV-2	Phase II clinical trials, therapeutic	158
HSV529	Live, attenuated vaccine: HSV-2 that is replication defective, with deletion of UL-5 and UL-29 proteins	HSV2	Phase I clinical trials, preventive and therapeutic	159
Glycoprotein D2/glycoprotein C2/glycoprotein E2	Subunit vaccine: Glycoprotein D2, C2, and E2	HSV1 and HSV2	Preclinical (studies on mice)	160
HSV-2 0 ΔNLS	Live, attenuated replication-competent HSV-2 with deletion of ICP 0	HSV-2	Preclinical (studies on mice)	161
HF10	Live, attenuated replication-competent mutant herpes simplex virus HSV-1	HSV-1	Preclinical	162
ΔGlycoprotein D2	Live, attenuated mutant herpes simplex virus HSV-2 with deletion of glycoprotein D2	HSV-2	Preclinical	50
AD472	Live, attenuated recombinant herpes simplex virus HSV-2 with deletion of gamma 34.5 gene and UL-43.5, 55 and 56 gene, and US-10, 11 and 12 genes	HSV-2	Preclinical (studies on guinea pigs)	51
CJ2-Gd2	Live, attenuated recombinant herpes simplex virus HSV-2 capable of expressing target antigens of HSV-2 specific CD8 T-Cell response, including glycoprotein D2	HSV-2	Preclinical	52
Inactivated HSV-2 in MPL	Formalin-inactivated HSV-2	HSV-2	Preclinical (studies on mice)	53
HSV-1 glycoprotein B lentiviral vector	Lentiviral vector expressing glycoprotein B1	HSV-1 (with cross-protection against HSV-2)	Preclinical (studies on mice)	54
Glycoprotein B1s-NISV	Intranasal NISV containing recombinant HSV-1 glycoprotein B	HSV-1	Preclinical (studies on guinea pigs)	55

HSV: Herpes simplex virus, MPL: Monophosphoryl lipid A, ICP: Infected cell protein, HSP: Heat shock protein, UL: Unique Long, NISV: Nonionic surfactant vesicles, US: Unique short, QS: Adjuvant protein, CD: Cluster of differentiation

schedule consists of a first dose at 12–18 months followed by a second dose between 4 and 6 years of age. The second dose can be administered 3 or more months following the first dose in children below 4 years of age.<sup>59</sup> Breakthrough varicella is defined as chickenpox occurring more than 42 days after vaccination. It is manifested by atypical features with fewer and predominantly maculopapular lesions. This entity was initially reported in 2 to 4% of cases per year with a recently reported 14% cumulative incidence over 7 years. Interestingly, the time from varicella vaccination was the most important risk factor for breakthrough varicella.<sup>60</sup>

### Measles-mumps-rubella

Another pivotal vaccine that prevents two dermatologic entities is the measles-mumps-rubella vaccine, which was combined in 1971. Vaccination against measles led to a 75% decrease in deaths from 2000 to 2013 according to the World Health Organization. As the vaccination programs got incorporated globally, the number of reported rubella cases decreased from 135,947 in 1998 to less than 1,000 cases in 2003 according to the National Center for Infectious Diseases.<sup>61</sup> Despite it being no longer endemically transmitted in the United States, rubella continues to be endemic in several parts of the world, and only two World Health Organization regions – European and American regions – have established rubella elimination goals for the year 2010.<sup>62</sup> This emphasizes the need for accelerating

measles-mumps-rubella vaccination campaigns in other areas such as south Asia. For example, a study from Jammu in India showed that 32.7% of girls aged between 11 and 18 were not immune to rubella.<sup>63</sup>

The measles-mumps-rubella vaccine can be administered in combination with varicella as a tetravalent vaccine, the measles-mumps-rubella-varicella vaccine. Some reports showed an increased risk for febrile seizures with this combined vaccine, and thus preference was expressed for use of separate varicella vaccination only for the first dose.<sup>64</sup> Although varicella is considered to be a benign disease, the burden of varicella with its associated morbidity and mortality, has proven the vaccine to be cost-effective.<sup>65</sup> The live zoster vaccine, Zostavax®, was approved in 2006 for prevention of shingles and post-herpetic neuralgia in immunocompetent people aged more than 60 years.<sup>65</sup> This vaccine contains 14-fold more virions than the varicella vaccine.<sup>66</sup> However, the efficacy of this live attenuated zoster vaccine was shown to decrease within 5 years' post-vaccination, mandating the need for proper patient education regarding its safety and efficacy. In general, the zoster vaccine is well-tolerated causing minimal systemic side effects and mostly mild-to-moderate symptoms at the injection site. In addition, vaccinated individuals aged 60 to 69 years were shown to be more susceptible to such adverse events when compared to

those aged 70 years or above.<sup>66</sup> Table 1 includes the recommended immunization schedule for measles-mumps-rubella vaccine with possible adverse events, and Table 2 shows the available measles-mumps-rubella vaccines and their price.

Not only has measles-mumps-rubella vaccine proven to be efficacious in the prevention of measles, mumps and rubella, it also showed promising results when used for other diseases, namely recalcitrant warts and molluscum contagiosum. The hypothesis behind this was that it can result in induction of cellular immune response, which can accelerate the destruction of virus and virus-infected host cells. Being recurrent and often resistant to treatment, warts represent a frustrating challenge for both patients and physicians. Studies have shown that intralesional immunotherapy by measles-mumps-rubella vaccine is a promising, effective and safe treatment modality for warts.<sup>67</sup> Nofal *et al.* evaluated this vaccine in a randomized placebo-controlled trial and noted complete response in 81.4% of patients as compared to 27.5% in the placebo group.<sup>68</sup> Although we could not find clinical trials that study measles-mumps-rubella vaccine in molluscum contagiosum, we found two case reports in which successful treatment was reported.<sup>69</sup>

#### Human immunodeficiency virus

HIV had a prevalence of 0.8% in 2015 with 36.7 million people living with the virus worldwide.<sup>70</sup> Ever since its identification as the cause of acquired immunodeficiency syndrome (AIDS) in 1984, significant advancement has been made towards its prevention and treatment. Interestingly, India, which has the third largest HIV epidemic in the world after South Africa and Nigeria, had a 32% decline in new HIV infections between 2007 and 2015.<sup>71</sup> Despite this improvement, the quest for developing an HIV vaccine that can be therapeutic and preventive remains of significant importance to public health.

Although there is no Food and Drug Administration-approved vaccine to date, multiple candidates have been studied in pre-clinical experiments and clinical trials. The first HIV vaccine candidates consisted of recombinant subunit vaccines that mimic the viral envelope protein gp120 and its precursor gp160 in the hope that they would prevent HIV from entering human cells. These were the basis for the AIDSVAX vaccines. Two recombinant gp120 vaccine, bivalent subtype B/B and bivalent subtype B/E, could reach phase III clinical trials testing, but both failed to prove efficacious.<sup>72-78</sup> Following the failure of recombinant envelope vaccines, attempts at developing vaccines that can induce immune responses that would achieve cross-strains immunity began. These vaccines began with the replication-defective recombinant Ad5 vector with HIV-1 clade B gag/pol/nef inserts. It was designed to induce a CD8+ T-cell response to HIV-1 in the hope that immunity would be directed at conserved regions of HIV and would be effective against its different clades. While pre-clinical studies showed promising immunogenicity, two phase II clinical trials, STEP and Phambili, were stopped after interim efficacy analysis. The STEP study, conducted among men who have sex with men, showed that vaccine recipients had an increased risk of HIV-1 acquisition. Phambili, conducted in heterosexual adults, showed no vaccine effect on HIV acquisition during blinded follow-up but increased risk of HIV-1 acquisition during the unblinded follow-up.<sup>76,77</sup> Following the Adenovirus 5 (Ad5) vector vaccine was the prime-recombinant adenovirus type 5 boost (DNA/rAd5) vaccine. It was designed to elicit HIV-specific, multifunctional responses in CD4+ and CD8+ T-cells and antibodies to envelopes of the major circulating strains. The vaccine is a

6-plasmid mixture encoding HIV envelope glycoprotein (env) from subtypes A, B and C and subtype B gag, pol and nef proteins, and rAd5 vector expressing identical genes, with the exception of nef. The HIV Vaccine Trials Network conducted a phase II trial of this vaccine in men or transgender women who have sex with men and showed lack of efficacy in reducing the rate of acquiring HIV-1 infection (W).<sup>53</sup> Interestingly, Canarypox ALVAC-vCP1521 vaccine is the only vaccine to date that has proven efficacious in reduction of HIV-1 acquisition rates in both pre-clinical studies and phase III clinical trials that are still ongoing.<sup>73,74</sup> The RV144 trial, a multicenter, double-blind phase III trial, demonstrated 60% efficacy over the first year compared with placebo.<sup>79</sup> Although there is not yet a Food and Drug Administration-approved HIV vaccine, these results are encouraging for the future development of a successful HIV vaccine.<sup>80</sup>

In addition to preventive vaccines, vaccine developers have recently experimented therapeutic vaccine candidates that can be used as adjunctive treatment to highly active antiretroviral therapy. Tat vaccine, which consists of antibodies against HIV-1 transactivator of transcription (Tat) protein, have shown a statistically significant reduction of blood HIV-1 DNA load that persisted for up to 3 years post-vaccination.<sup>81</sup> Another therapeutic vaccine candidate was AGS-004, which is a personalized vaccine consisting of patient-derived dendritic cells and HIV antigens. It is currently being studied in phase II clinical trials.<sup>82</sup> Table 5 shows a list of HIV vaccine candidates and their current developmental status.

### Vaccines for Bacterial or Parasitic Infections Affecting the Skin

#### *Propionibacterium acnes* mediated acne vulgaris

The treatment of acne encompasses a wide variety of topical and oral agents ranging from antibiotics to retinoids. Interestingly, a research group from the University of California is currently investigating the use of vaccines for treating *Propionibacterium acnes*-associated diseases including acne vulgaris. This stems from the idea that cell wall-anchored sialidase of *P. acnes* or killed-whole organisms of *P. acnes* have been shown to induce *in-vivo* protective immunity against *P. acnes* along with downregulation of cytokine production.<sup>83</sup> Multiple other vaccines are currently being developed based on killed pathogens, cell wall-anchored sialidase, monoclonal antibodies to the Christie, Atkins, Munch-Peterson factor of *P. acnes*, anti-Toll-like receptors and antimicrobial peptides.<sup>83</sup>

#### *Mycobacterium leprae*

Caused by the bacterium *Mycobacterium leprae*, leprosy affects the skin, nervous system, respiratory tract and eyes and can result in disfigurement and disability in advanced stages. Interestingly, 58% of new annual leprosy cases in the world are from India. According to the latest published annual report of the National Leprosy Elimination Program, a total of 86,028 leprosy cases were reported up until April 1, 2016 for the year 2015–2016 in India.<sup>84</sup> While India has an ongoing national program for eradication of leprosy, the number of cases increased from 1,25,785 to 1,27,326 between 2014 and 2015.<sup>84,85</sup> Even though multidrug therapy is the gold standard for treating leprosy, the use of vaccines has been suggested as immune-prophylactic and immunotherapeutic. *M. leprae* expresses a varied amount of surface-associated and secretory proteins such as lipoproteins, outer membrane proteins and secretory proteins that may be utilized as antigenic targets in vaccine development. In fact, recent clinical trialists and vaccine developers have employed live

**Table 5: List of human immunodeficiency virus vaccine candidates**

HIV vaccine candidate	Vaccine platform	Development status	References
Recombinant gp 120 AIDS VAX Bivalent subtype B/B Bivalent subtype B/E	Two recombinant gp 120 surface proteins from different HIV-1 strains	Phase III clinical trials, preventive (mid 1990s)	75
Ad5 vector	Replication-defective rAd 5 vector with HIV-1 clade B gag/pol/nef inserts	Phase II clinical trials, preventive (step trial: 2004 and phambili trial: 2007)	76,77
DNA/rAd5 vaccine	6-plasmid mixture encoding HIV env from subtypes A, B and C and subtype B gag, pol and nef proteins, and rAd5 vector expressing identical genes, with the exception of nef	Phase II clinical trials, preventive (HVTN trials: 2010-present)	78,163
Pox virus vector-based vaccine: Canarypox ALVAC-vCP1521 vaccine	Live, attenuated nonreplicating poxvirus vector with genetically engineered genes encoding HIV1 env, gag, and pol proteins	Phase III clinical trials, preventive (RV144 trial: 2004-2009)	119-121
Tat vaccine	Antibodies against HIV-1 Tat protein	Phase II clinical trials, therapeutic (passive immunization) (2008-present)	81
AGS-004	Personalized vaccine utilizing patient-derived DC and HIV antigens	Phase II clinical trials, therapeutic (2012-present)	82

HIV: Human immunodeficiency virus, Tat: Transactivator of transcription, env: Envelope glycoprotein, Ad5: Adenovirus 5, rAd5: Recombinant Ad5, DNA/rAd5: Prime-rAd type 5 boost, HVTN: HIV Vaccine Trials Network

or killed whole mycobacteria, such as bacillus Calmette–Guérin, Indian Cancer Research Center bacilli and *Mycobacterium* w either alone or admixed with killed *M. leprae*.<sup>86</sup> Interestingly, an Indian research group recently identified a penicillin-binding protein, ML0018c, as a possible candidate which may elicit both cellular and humoral immune response in *M. leprae*-infected patients. This protein can be used for the development of a peptide-based vaccine conveying immunity against leprosy.<sup>87</sup>

A vaccine prepared from heat-killed *M. welchii* has shown very promising results in leprosy prevention and treatment. The vaccine was initially developed in 1990s and consisted of heated *M. welchii*, a cultivable, non-pathogenic and rapidly growing saprophyte. Clinical trials were initiated by the Indian Council for Medical Research institute in endemic areas in India, namely Madhya Pradesh, Orissa, Bihar, UP, West Bengal, Uttaranchal, Chhattisgarh and Jharkhand. Sharing a number of common B and T cell determinants with *M. leprae*, the vaccine significantly reduced the disease burden. Its efficacy was 70% tested over a 10-year period. The vaccine has gained approval as a therapeutic and preventive vaccine against leprosy from the Drug Controller General of India (DCGI), Central Drugs Standard Control Organization, the National Regulatory Body under the Ministry of Health and Family Welfare in India and the US Food and Drug Administration. Its inclusion in the treatment regimen not only accelerates bacterial clearance but also shortens the recovery period and is effective in patients who are slow responders to multidrug therapy.<sup>84,88-91</sup>

*M. welchii* vaccine was renamed *M. Indicus Pranii* (MIP). The new name was a combination of the site of isolation of the bacterial species from India (indicus), the founder of the National Institute of Immunology in India Professor Pran Talwar (*pranii*) and the National Institute of Immunology India (nii in pra-nii). Globally, new case detection rates for leprosy have remained fairly stable in the past decade, with India responsible for more than half of the cases reported annually. However, the Indian government aims at eliminating leprosy by 2020.<sup>92</sup> As a result, the National Leprosy Elimination Program initiated in August 2016 the Leprosy Case Detection Campaign aiming at detection of all leprosy cases in the community and their treatment. *M. indicus pranii* is being used to vaccinate contacts of leprosy patients, and, along with multidrug therapy, for the treatment of leprosy patients. This vaccine

may prove to be India's landmark step towards eradication of leprosy.<sup>87,93,94</sup> Table 1 includes the *M. indicus pranii* vaccine as part of the immunization schedule with adverse events reported to date.

#### Lyme disease

Despite adequate clinical results, the only Food and Drug Administration approved vaccine for prevention of Lyme disease, LYMERix™, was withdrawn from the market 3 years after its initiation. This was mainly due to significant local effects at the injection site, 26.8% vs 8.3% in controls, as well as systemic symptoms, 19.4% vs. 15.1% in controls.<sup>95</sup> In the absence of a Lyme vaccine, efforts are being tailored towards developing a reservoir targeted vaccine. Ongoing trials done over a period of 1 year and 5 years have shown a reduction in Lyme disease prevalence ranging from 24 to 76%, respectively.<sup>96</sup> In addition, adverse events to Lyme vaccines were mild and transient including local reactions such as swelling, redness and pain.<sup>96</sup>

#### Cutaneous leishmaniasis

Given that 90% of *Leishmania* infections present as a localized cutaneous reaction,<sup>97</sup> dermatologists have sought after different treatment strategies for this mucocutaneous disease, including pentavalent antimonials, second-line pentamidine, amphotericin B, allopurinol and ketoconazole. Studies in mice have highlighted the role of dendritic cells as important inducers of a T-helper (Th) 1/cytotoxic T (Tc) 1 protective immunity against leishmaniasis.<sup>97</sup> This fact has allowed the development of multiple experimental prophylactic vaccines, using dendritic cells pulsed with parasite lysate,<sup>98</sup> recombinant parasitic proteins<sup>99</sup> or even adjuvants such as CpG oligodeoxynucleotide motifs promoting IL-12 release.<sup>99</sup> One vaccine containing killed *Leishmania amazonensis* was shown to be safe in phase II clinical trials, however, did not demonstrate efficacy in phase III trials.<sup>100</sup> The use of bacillus Calmette–Guerin vaccine for the treatment of cutaneous leishmaniasis has shown promising results in murine, canine and hamster models but is still in pre-clinical studies.<sup>101</sup>

#### Cutaneous tuberculosis

Cutaneous tuberculosis is an infection caused by *M. tuberculosis* complex, *M. bovis* and bacillus Calmette–Guérin. It is characterized by numerous papulovesicular lesions, which can leave residual hypochromic scars upon healing. Bacillus Calmette–Guerin was

initially introduced as a prophylactic agent against tuberculosis. The World Health Organization currently recommends that bacillus Calmette–Guerin vaccine should be administered to all those living in areas of endemic tuberculosis. In India, for example, the vaccine is part of the national immunization schedule and is administered directly after birth. Table 1 includes bacillus Calmette–Guerin as part of the Indian Academy of Paediatrics immunization schedule with possible adverse events, and Table 2 shows the available vaccines, their trade names and their price. Interestingly, it was noticed that the incidence of leprosy decreased markedly after administration of bacillus Calmette–Guérin vaccine, especially when used as an adjuvant to multidrug therapy in the treatment regimen compared to multidrug therapy alone.<sup>102</sup>

Owing to its beneficial effect in cutaneous tuberculosis and leprosy, which was most likely related to cell-mediated immune response, interest rose in using bacillus Calmette–Guerin vaccine as a therapeutic agent in other skin conditions, including warts, cutaneous leishmaniasis and oral lichen planus.<sup>103</sup> A total of 122 patients have received intralesional bacillus Calmette–Guérin vaccine as a treatment of warts in all studies published to date. Only one study was a single-blind, placebo-controlled study conducted on 154 patients divided into a control and placebo groups. Intralesional bacillus Calmette–Guérin vaccine proved to be an effective and safe modality for the treatment of viral warts. Most studies showed complete clearance of the warts within 6 weeks to 2.5 months.<sup>104</sup> Topical and intralesional bacillus Calmette–Guérin vaccine has also proven efficacious and safe in oral lichen planus when compared to triamcinolone. This suggests a possible role as a promising therapeutic alternative for erosive oral lichen planus, especially for those resistant to glucocorticoids.<sup>105</sup>

### Vaccines for Treatment of Skin Malignancies Melanoma

According to the National Cancer Institute, the incidence of invasive melanoma in the United States was estimated to be about 73,870 cases in 2015, and one American dies of melanoma every hour. Melanoma treatment depends on the stage of the cancer. Early lesions (Stage 0 melanoma) are often cured by surgical excision alone. Stage II and stage III resectable melanoma are managed with surgery and lymph node resection. Stage III unresectable and stage IV are aggressively treated with chemotherapy, targeted therapy and recently immunotherapy.<sup>106</sup> The 10-year overall survival rate for advanced melanoma is improving but is still only 10–15%.<sup>107</sup>

The use of melanoma vaccines in the treatment of malignant melanoma is currently being intensely investigated. The use of such vaccines is reasonable given the antigenic differences between normal adult melanocytes and melanoma cells in addition to the resulting immune anti-melanoma response triggered by immunocompetent cells.<sup>108</sup> Melanoma vaccines have utilized many antigen sources such as peptide antigens, glycolipids, tumor-associated antigens and dendritic cells.<sup>4</sup> Table 6 summarizes the different vaccines used in melanoma.

Experimental clinical trials with “melanoma vaccines” are currently in progress and few have shown significant benefit as adjuvants in the setting of high-risk melanoma. However, ongoing trials have been more promising, especially with the advances in the immunology of melanoma. One recent study demonstrated higher response rates and longer progression-free survival in advanced melanoma patients when gp100 vaccine was combined with interleukin-2 (IL-2) immune activating agent.<sup>109</sup> The median overall

**Table 6: Vaccines used for melanoma treatment**

Vaccine	Response
Autologous/allogenic peptide antigens	Showed unfavorable results in Phase II clinical trial for Stage III unresected and Stage IV melanoma
DC	Clinical response only evident in a minority of metastatic melanoma patients
Tumor associated antigens	gp100 vaccine showed higher response rates and longer progression free survival when combined with IL-2
Cancer causing viruses	Increased response rate was evident in a Phase III melanoma trial
Glycolipids	GM2 vaccine shows no improved clinical response

IL: Interleukin, DC: Dendritic cells, GM: adjuvant Ganglioside

survival was also longer in the gp100+IL-2 group than in the IL-2 only group (17.8 months; 95% CI, 11.9 to 25.8 vs. 11.1 months; 95% CI, 8.7 to 16.3;  $P = 0.06$ ).<sup>109</sup>

Multiple types of antigen sources have been used in the production of melanoma vaccines including autologous/allogenic peptide antigens, glycolipids, tumor-associated antigens and dendritic cells.<sup>4</sup> Vaccines using tumor cell-derived antigens are divided into two categories – autologous and allogeneic vaccines. In autologous vaccines, the patient’s tumor cells are used, thus providing a narrow antigen spectrum specific to a particular patient. Limitations to its use include limited amount of tumor tissue accessible for vaccine preparation, especially after complete resection of clinically evident disease. In a recent phase II clinical trial for metastatic melanoma, an autologous vaccine composed of tumor-derived heat shock protein peptide complexes gp96 was shown to induce an anti-melanoma, class I HLA-restricted T-cell-mediated immune reaction in a proportion of treated patients. However, of the 28 patients enrolled, only two had a complete response and only three had stable disease at the end of follow-up.<sup>110</sup>

Allogeneic vaccines may be more representative as they are composed of melanoma cells from other patients selected for a variety of shared antigens. Even though they may not contain all the tumor-associated antigens on the treated patient’s tumor, they do allow for large-scale randomized trials. One studied allogeneic vaccine is Canvaxin polyvalent cancer vaccine. The cumulative data for Canvaxin therapeutic cancer vaccine represent the largest phase II clinical trial of any cancer vaccine. The vaccine exhibited prognostic significance for patients with stage III and IV melanoma. However, a phase III clinical trial for stage III unresected and stage IV melanoma showed unfavorable results.

Another category of vaccines is composed of cell surface glycolipids such as gangliosides GD3 and GM2.<sup>111</sup> In a phase III clinical trial for stage II resected melanoma, adjuvant ganglioside GM2 vaccine was not shown to improve clinical outcome.<sup>112</sup>

In addition to the use of tumor cell-derived antigens and gangliosides, tumor-associated antigens have been integrated into vaccines and often combined with adjuvants such as GM-CSF. Melanoma specific tumor-associated antigens include Melan-A/MART-1, gp100, tyrosinase, tyrosinase-related protein-1 (trp-1) and tyrosinase-related protein-2 (trp-2).<sup>113,114</sup>

Dendritic cells, being antigen-presenting cells specialized for the induction of a primary T-cell response, have also been explored for

manufacturing vaccines in advanced melanoma. Mouse studies have shown that dendritic cells do induce antitumor immunity, and thus multiple studies aimed at demonstrating the clinical effect of such vaccines on the survival of melanoma patients have been done.<sup>83</sup> However, one study showed that vaccinating with peptide-loaded dendritic cells can result in long-term clinical response in only a minority of metastatic melanoma patients (2 out of 15 patients).<sup>115</sup> In addition, a recent phase I/IIa clinical trial in stage IV melanoma using autologous tumor-dendritic cell fusion (dendritoma) vaccine with low-dose interleukin-2 showed that overall survival was significantly higher in the experimental group (23.8 versus 8.7 months,  $P = 0.004$ ).<sup>116</sup>

Another vaccine tested in melanoma is herpes simplex virus-1 oncolytic vaccine known as Talimogenelaherparepvec (T-VEC). T-VEC is designed to induce systemic antitumor immunity and was effective in increasing the response rate and survival ( $\geq 6$  months) vs GM-CSF in a phase 3 melanoma trial.<sup>117</sup> A phase 1 trial studied its toxicity and showed that combining T-VEC with Ipilimumab was tolerable and did not result in dose limiting toxicities (DLTs) but resulted in grade 3 or 4 adverse events in 32% of the patients. The adverse events included hypophysitis, adrenal insufficiency and diarrhea. Studies on T-VEC suggest T-VEC+ipilimumab is more effective than Ipilimumab alone.<sup>108</sup>

Advanced techniques using cDNA-expression cloning and autologous antibodies have allowed for the identification of a wide array of antigens and peptides utilized in manufacturing melanoma vaccines. Further trials are imperative at this point to establish the therapeutic benefit of those vaccines in advanced melanoma as evidence so far is lacking.

Even though treating melanoma using a cancer vaccine is an ingenious approach, several challenges are arising with this strategy. So far, vaccines have been developed based on tumor antigens that are commonly overexpressed and shared across many patients and tumors. One challenge is to develop vaccines that are personalized to each patient, i.e. vaccines based on the antigens the tumor expresses in a particular patient. This approach will add more cost and time but might be more beneficial compared with the general vaccines. In addition, another challenge is to develop vaccines composed of nucleic acids that encode antigens. Developing vaccines based on these nucleic acids might allow more specific immune responses towards the tumor rather than normal tissue. It also allows for vaccinating against several antigens rather than one because of the ability to administer several nucleic acid sequences encoding different antigens. For example, a recent vaccine was developed composed of a nanoparticle containing tetravalent RNA sequences, each encoding a separate antigen, for the treatment of patients with malignant melanoma. The approach allows more efficient targeting of antigen-presenting cells.<sup>118,119</sup> Despite the ambiguous clinical effectiveness of current melanoma vaccines, they are relatively safe in the management of malignant melanoma.<sup>120</sup>

### Cutaneous T-cell lymphoma

Primary cutaneous T-cell lymphomas are defined as clonal proliferation of skin-infiltrating T lymphocytes, which manifest initially in the skin. Cutaneous T-cell lymphomas are generally incurable and therapeutic options are limited, especially in advanced stages. This led to the development of various treatment strategies including attempts to vaccinate against the malignant tumor.<sup>121</sup>

Neoplastic T cells from cutaneous T-cell lymphomas patients express tumor specific antigens that serve as the targets of an immune response. Thus, one possible vaccination modality is using whole tumor cells or tumor cells fused with dendritic cells to improve delivery to antigen presenting cells.<sup>122</sup> Multiple investigated targets included cancer/testis antigens, anaplastic lymphoma kinase fusion proteins, and mimotopes.<sup>123</sup> Vaccinations of few individuals have shown short partial remissions, but studies have not been published yet and further research is required.

### Vaccines in Immunocompromised Individuals

The use of vaccines in immunocompromised individuals is relatively safe and effective. In fact, guidelines have recommended that HIV-infected patients older than 18 years of age receive one dose of the 13-valent pneumococcal conjugate vaccine (PCV13) followed by a booster vaccination with the pneumococcal polysaccharide vaccine (PPV23).<sup>124</sup> Multiple vaccines are currently encouraged and considered safe in the immunocompromised such as the inactivated influenza vaccine in young children,<sup>125</sup> the human papillomavirus vaccine,<sup>126</sup> the live attenuated Oka zoster vaccine,<sup>127</sup> whole-virus cell culture-derived H5N1 influenza vaccines<sup>128</sup> and the heat-treated zoster vaccine.<sup>129</sup>

However, there are a few exceptions that should be noted. First, the varicella vaccine is not recommended in immunocompromised individuals as such individuals may be unable to limit the replication of live attenuated vaccine viruses.<sup>130</sup> Second, the use of replicating smallpox vaccines such as the LC16m8, licensed in Japan, should not be promoted given the limited data on safety and efficacy in immunocompromised individuals.<sup>131</sup> If needed, the World Health Organization advisory group recommends use of a nonreplicating smallpox vaccine comprised modified vaccinia virus Ankara instead.

Currently studies are being designed to examine the potential role of a new vaccine against tuberculosis meningitis,<sup>132</sup> brucellosis,<sup>133</sup> *Candida albicans* infection<sup>134</sup> and Ebola virus<sup>135</sup> in the immunocompromised population.

### Vaccine-Induced Dermatological Adverse Effects

Vaccines have been established to be significant contributors in the prevention and treatment of some dermatologic entities. However, just like any modality, their use has been associated with multiple cutaneous adverse effects.

#### Hepatitis B vaccine

Hepatitis B vaccination has been found to trigger an intense lichenoid reaction in one patient.<sup>136</sup> In another case, lichen planus was induced by anti-hepatitis B vaccination and was successfully treated with prednisone 1 mg/kg/day for 2 weeks.<sup>137</sup> Infantile bullous pemphigoid has been reported in three infants following vaccination for diphtheria, pertussis, tetanus, poliomyelitis, hepatitis B, *Haemophilus influenzae* B and meningococcus C. However, the etiology remains uncertain. Systemic steroids when given led to resolution of lesions in 2–6 months for two infants, whereas high-potency topical steroids were required for the third infant.<sup>138</sup> Table 1 includes hepatitis B vaccine as part of the Indian Academy of Paediatrics immunization schedule with possible adverse events, and Table 2 shows available vaccines, their trade names and their prices.

#### Smallpox vaccine

A characteristic smooth scar develops following administration of the smallpox vaccine. Based on previous published reports, exaggerated

scarring, dermatofibroma and nevus sebaceous (Jadassohn tumor) have been described at the scar site.<sup>139</sup>

### Bacillus Calmette–Guérin vaccine

Two case reports describe cutaneous *M. bovis* infection in two infants with immune disorders following the bacillus Calmette–Guérin vaccination.<sup>140</sup> Another nine case reports published in Japan describe atypical popular tuberculides after bacillus Calmette–Guérin vaccination.<sup>141</sup>

### Conclusion and Future Directions

Multiple vaccines are being actively developed for use in dermatologic diseases. Recent advances in the fields of immunotherapy, genetics and molecular technology have allowed for the design of prophylactic and therapeutic vaccines with enormous potential in the field of dermatology. Dermatologists should be aware of the availability and possible use of newer vaccines developed against acne, human papillomavirus, melanoma and other dermatologic disorders. Further studies are necessary to investigate the potential use and benefits of vaccines in the prevention of dermatologic entities such as invasive staphylococcal disease,<sup>142</sup> *Streptococcus pyogenes* infections<sup>143</sup> and scabies.<sup>144</sup> In the foreseeable future, the development of vaccines will rely more on supplying an RNA molecule instead of an antigen. This method can potentially enable a wide range of cells in our body to form a larger number of proteins and present them to the immune system in a more efficient way.<sup>145</sup> Ongoing active research in vaccine development has opened a new promising era in the field of dermatology. However, many questions remain unanswered, e.g. whether such vaccines offer adequate clinical benefits or even convincing survival advantages.

### Limitations

The major limitation of our review is its complete reliance on published data. Our review is strictly limited to the availability of published research online through available databases. Also, we did not cite any of our authors' own publications nor have we conducted previous original research studies regarding vaccines in dermatology. Strength would have been added to our paper had we conducted original studies by our research team regarding the candidate vaccines delineated in the paper.

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### Conflicts of interest

There are no conflicts of interest.

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