COVID-19 vaccines and Lichen planus

Introduction

To date, the European Medicines Agency authorised five COVID-19 vaccines for *active immunisation against SARS-CoV-2*: BioNTech/Pfizer (Comirnaty®), Moderna (SpikeVax®), AstraZeneca (Vaxzevria®), Janssen (Jcovden®), and Novavax (Nuvaxovid®) (1). BioNTech/Pfizer and Moderna are both mRNA vaccines, AstraZeneca and Janssen are both vector-based vaccines, and the newly approved Novavax is a protein subunit vaccine containing a saponin based matrix-M immune-stimulating adjuvant (2-6). All five COVID-19 vaccines encode the SARS-CoV-2 spike glycoprotein and induce a cellular and humoral immune response, including SARS-CoV-2 neutralising antibodies. COVID-19 vaccines are subject to additional monitoring.

Lichen planus (LP) is a chronic inflammatory and immune-mediated disorder that can affect skin, nails, hair, and mucous membranes including conjunctival, oropharyngeal, esophageal, and vulvovaginal mucosae (7-9). Besides different localisations of disease, there are several clinical variants based on lesion morphology; papular (classic), hypertrophic, vesiculobullous, actinic, annular, atrophic, linear, follicular, LP pigmentosus and LP pigmentosus-inversus. Patients often experience severe pruritus and skin lesions can be debilitating. Quality of life in lichen planus patients, as measured by questionnaires, was comparable to quality of life in psoriasis patients (7). Diagnosis is based on clinical presentation and confirmation should be obtained by biopsy. Histopathology reveals a lichenoid interface dermatitis. Topical corticosteroids are first-line treatment, followed by UVB phototherapy sometimes in combination with systemic corticosteroids, acitretin or other systemic immunosuppressive drugs (8, 9). In addition to topical corticosteroids, topical tacrolimus is effective for vulvovaginal lichen planus. Lichen planus may resolve spontaneously within one to two years, however, recurrences are common. Lichen planus of mucous membranes may be more persistent and resistant to treatment.

Lichen planus is a T-cell-mediated autoimmune disease mainly involving the T-helper-1 pathway (7). In addition to a possible genetic predisposition, several clinical factors are described to be associated with lichen planus, including; stress and anxiety, autoimmune diseases, malignancies, dyslipidemia, and viral infections such as hepatitis C and Herpesviridae infections. It is not clear whether these factors are actually risk factors or accompanying factors in lichen planus patients (7).

Lichenoid drug eruptions are rare skin reactions in response to several drugs which mimics cutaneous or oral Lichen planus (10). For oral lichenoid drug eruption, most commonly associated drugs are methyldopa, interferon-alfa, imatinib, and infliximab (11). For cutaneous lichenoid drug eruption, most commonly associated drugs are ACE-inhibitors (12), thiazides (13), beta-blockers (14), and immune-checkpoint inhibitors (15).

Lichen planus is most commonly diagnosed in middle-aged adults, with a slight predominance in women and no racial predilection (8). The exact prevalence of lichen planus is unknown but is estimated to range from 0.22% to 5% worldwide.

Reports

Until May 16th 2022, The Netherlands Pharmacovigilance Centre Lareb received a total of 48 reports of Lichen planus associated with COVID-19 vaccines, 46 were spontaneous reports and two reports originated from Lareb Intensive Monitoring, a web-based tool for collecting patient-reported outcomes (16, 17). Of these 48 reports, two were reported by physicians and 46 by consumers or other non-health professionals. The reports contained the following suspect vaccines: BioNTech/Pfizer, 21 reports; Moderna, 16 reports; AstraZeneca, 7 reports; Janssen, 4 reports. Most reports came from females, 38 versus 10 reports from men. The average age was 57 years, ranging from 32 to 75 years. In 37 reports it concerned new-onset Lichen planus, while in 11 reports a flare-up of previously diagnosed Lichen planus was reported. Time to onset varied from 1 to 60 days with a median of 7 days for new-onset Lichen planus, and 1 to 28 days with a median of 3 days for flare-up Lichen planus. Diagnosis was confirmed by a dermatologist, dentist or dental surgeon in 22 cases (46%) and biopsy was performed in 4 cases (8%). Treatment with prescription drugs was reported in 7 cases (15%).

Until May 16th 2022, The Netherlands Pharmacovigilance Centre Lareb received 57 reports of Lichen planus associated with vaccines in general. Table 1 provides an overview of the number of reports per vaccine type.

Table 1. Lichen planus reports for vaccines

	Reaction Preferred Term			
Vaccines	**Lichen planus**	**Oral lichen planus**	**Lichen planopilaris**	**Total no unique reports***
All vaccines	40	12	6	57
Viral vaccines	40	12	6	57
COVID-19 vaccines	33	11	6	48
Hepatitis B vaccine	1	1	0	2
Hepatitis A + B vaccine	2	0	0	2
Influenza vaccine**	3	0	0	3
Mumps-measles-rubella virus vaccine	1***	0	0	1
Bacterial vaccines	1***	0	0	1
Salmonella Typhi vaccine	1	0	0	1

*Reports can contain more than one PT therefore the total amount of unique reports can differ from the sum of reports per PT.
**Including one report with Inluenza A H1N1 vaccine as suspect vaccine.
***Report contains two suspects; mumps-measles-rubella virus vaccine, MMRVaxPro® and Vi polyoside of Salmonella Typhi (Ty2 strain) vaccine, Typhim Vi®.

Table 2 provides a more detailed overview of the 48 lichen planus cases reported for COVID-19 vaccines.

Table 2. Lichen planus cases reported for COVID-19 vaccines

No	ID sex age primary source	Drug	Concomitant medication	Reported ADRs	New-onset or flare	Latency after start	Outcome
1	NL-LRB-00504706 female 70 Years and older Consumer or other non health professional	Covid-19 Vaccin Pfizer	Atorvastatine	Lichen planus	New-onset	1 Day	Not Recovered
2	NL-LRB-00512216 female 30-40 Years Consumer or other non health professional	Covid-19 Vaccin Astrazeneca	Nortriptyline Linaclotide Mebeverine Haloperidol	Lichen planus	New-onset	-	Recovering
3	NL-LRB-00557549 male 60-70 Years Consumer or other non health professional	Covid-19 Vaccin Astrazeneca		Lichen planus	New-onset	4 Days	Not Recovered
4	NL-LRB-00569789 male 60-70 Years Consumer or other non health professional	Covid-19 Vaccin Pfizer		Lichen planus	New-onset	1 Week	Not Recovered
5	NL-LRB-00569798 female 50-60 Years Consumer or other non health professional	Covid-19 Vaccin Janssen	Multivitamine n + Mineralen Tablet	Lichen planus aggravated Burning tongue Burning gum	Flare	6 Days	Recovering

No	ID sex age primary source	Drug	Concomitant medication	Reported ADRs	New-onset or flare	Latency after start	Outcome
6	NL-LRB-00572307 female 50-60Years Consumer or other non health professional	Covid-19 Vaccin Pfizer		Lichen planus aggravated Headache Fatigue Generalized joint pain Myalgia Injection site warmth Injection site pain Injection site inflammation	Flare	-	Not Recovered
7	NL-LRB-00664901 female 60-70 Years Consumer or other non health professional	Covid-19 Vaccin Astrazeneca		Lichen planus Vascular disorder Eczema Allergy to plants Headache	New-onset	2 Days	Recovering
8	NL-LRB-COVID-00576612 male 40-50 Years Consumer or other non health professional Lareb Intensive Monitoring	Covid-19 Vaccin Moderna	Clobetasol	Injection site inflammation Malaise Fatigue Sweat odor abnormal Urine odor abnormal Lichen planus Lichen sclerosus Injection site pain Pyrexia Headache Malaise Fatigue Oral lichen planus Head pressure Concentration impaired	New-onset	1 Weeks	Recovering
9	NL-LRB-00675476 female 50-60 years Consumer or other non health professional	Covid-19 Vaccin Pfizer		Lichen sclerosus Lichen planus aggravated Condition aggravated	Flare	-	Not Recovered
10	NL-LRB-00683033 male 40-50 Years Consumer or other non health professional	Covid-19 Vaccin Janssen	Candesartan	Lichen planus Generalized joint pain Chills	New-onset	-	Not Recovered
11	NL-LRB-00632195 female 60-70 Years Consumer or other non health professional	Covid-19 Vaccin Astrazeneca	Multi-Vitamine-Pil Rode-Gist-Rijst Q10	Lichen planus Chills Headache Fatigue Injection site pain	New-onset	-	Not Recovered
12	NL-LRB-00690663 female 50-60 Years Consumer or other non health professional	Covid-19 Vaccin Pfizer		Lichen planus	New-onset	6 Days	Not Recovered

No	ID sex age primary source	Drug	Concomitant medication	Reported ADRs	New-onset or flare	Latency after start	Outcome
13	NL-LRB-00694961 female 50-60 Years Consumer or other non health professional	Covid-19 Vaccin Astrazeneca		Lichen planus	New-onset	48 Hours	Not Recovered
14	NL-LRB-00684852 female 60-70 Years Consumer or other non health professional	Covid-19 Vaccin Pfizer	Omega 3	Lichen planus aggravated	Flare	-	Recovering
15	NL-LRB-00695371 male 40-50 Years Consumer or other non health professional	Covid-19 Vaccin Janssen		Lichen planus	New-onset	-	Not Recovered
16	NL-LRB-00710952 male 40-50 Years Consumer or other non health professional	Covid-19 Vaccin Pfizer		Lichen planus	New-onset	1 Days	Not Recovered
17	NL-LRB-00703457 female 40-50 years Consumer or other non health professional	Covid-19 Vaccin Pfizer		Lichen planus	New-onset	2 Weeks	Not Recovered
18	NL-LRB-00714403 female 50-60 Years Consumer or other non health professional	Covid-19 Vaccin Moderna		Lichen sclerosus Myalgia Fatigue Injection site warmth Injection site pain Injection site inflammation Lichen planus Oral leukoplakia NOS	New-onset	14 Days	Not Recovered
19	NL-LRB-00717175 male 50-60 Years Consumer or other non health professional	Covid-19 Vaccin Pfizer		Lichen planus	New-onset	104 Hours	Not Recovered
20	NL-LRB-00718298 female 70 years and older Consumer or other non health professional	Covid-19 Vaccin Pfizer		Lichen planus	New-onset	14 Days	Not Recovered
21	NL-PFIZER INC-202101211086 female 60-70 Years Consumer or other non health professional	Covid-19 Vaccin Pfizer		Lichen planus	New-onset	-	Unknown
22	NL-LRB-00748239 female 40-50 years Consumer or other non health professional	Covid-19 Vaccin Moderna		Erosive lichen planus	New-onset	4 Weeks	Not Recovered
23	NL-LRB-00759069 male 60-70 Years Consumer or other non health professional	Covid-19 Vaccin Pfizer		Lichen planus aggravated	Flare	-	Recovered

No	ID sex age primary source	Drug	Concomitant medication	Reported ADRs	New-onset or flare	Latency after start	Outcome
24	NL-LRB-00766836 female 60-70 Years Consumer or other non health professional	Covid-19 Vaccin Moderna		Lichen planus	New-onset	-	Not Recovered
25	NL-LRB-00773436 female 50-60 years Consumer or other non health professional	Covid-19 Vaccin Moderna		Lichen planus aggravated	Flare	1 Days	Not Recovered
26	NL-LRB-00783710 female 60-70 Years Consumer or other non health professional	Covid-19 Vaccin Pfizer		Lichen planus	New-onset	-	Not Recovered
27	NL-LRB-00785287 female 50-60 years Physician	Covid-19 Vaccin Moderna		Lichen planus	New-onset	7 Days	Recovering
28	NL-LRB-00793010 female 50-60 Years Consumer or other non health professional	Covid-19 Vaccin Moderna		Lichen planus aggravated Extrasystoles Condition aggravated Nausea Malaise	Flare	4 Days	Recovering
29	NL-LRB-00802592 male 30-40 Years Consumer or other non health professional	Covid-19 Vaccin Pfizer		Lichen planus	New-onset	-	Not Recovered
30	NL-LRB-00776891 female 40-50 Years Consumer or other non health professional	Covid-19 Vaccin Moderna		Lichen planus Chills Headache Nausea Generalized joint pain Myalgia Malaise Fatigue	New-onset	-	Recovering
31	NL-LRB-00801301 female 40-50 years Physician	Covid-19 Vaccin Pfizer		Hypertrophic lichen planus	New-onset	2 Days	Recovering
32	NL-LRB-00794151 female 40-50 Years Consumer or other non health professional	Covid-19 Vaccin Pfizer	Prednison Cream prescribed by dermatologist	Lichen planus Chills Fatigue Headache Malaise Injection site rash	New-onset	2 Days	Not Recovered
33	NL-LRB-00575200 female 60-70 years Consumer or other non health professional	Covid-19 Vaccin Astrazeneca	Amlodipine Carvedilol Losartan Budesonide Inhalatie Clobetasol Mondspoeling Boswellia	Oral lichen planus Headache Myalgia Generalized joint pain Malaise Fatigue Injection site pain Injection site induration Injection site swelling Extensive swelling of	Flare	3 Days	Recovering

No	ID sex age primary source	Drug	Concomitant medication	Reported ADRs	New-onset or flare	Latency after start	Outcome
				vaccinated limb Bloated feeling			
34	NL-LRB-COVID-00520831 female 70 Years and older Consumer or other non health professional Lareb Intensive Monitoring	Covid-19 Vaccin Pfizer	Atorvastatine	Oral lichen planus Aggravation of existing disorder Myalgia Loss of taste	Flare	15 Days	Recovering
35	NL-LRB-00713655 male 40-50 Years Consumer or other non health professional	Covid-19 Vaccin Moderna		Oral lichen planus Injection site pain	New-onset	1 Weeks	Not Recovered
36	NL-LRB-00720753 female 40-50 Years Consumer or other non health professional	Covid-19 Vaccin Moderna		Oral lichen planus Myalgia Nausea	New-onset	-	Recovering
37	NL-LRB-00608398 female 50-60 Years Consumer or other non health professional	Covid-19 Vaccin Moderna	Esomeprazol Losartan Colecalciferol Hydroxocobalamine Vitamine K2 Bevattend	Oral lichen planus Palpitations aggravated Chills Nausea Myalgia Malaise Fatigue Injection site erythema Injection site warmth Injection site swelling Injection site inflammation Herpes labialis Lymphadenopathy Arthralgia	New-onset		Recovered
38	NL-LRB-00784324 female 70 Years and older Consumer or other non health professional	Covid-19 Vaccin Moderna		Oral lichen planus Myalgia Malaise Fatigue Body temperature increased	New-onset	-	Not Recovered
39	NL-LRB-00798657 female 60-70 Years Consumer or other non health professional	Covid-19 Vaccin Moderna		Oral lichen planus Lichen planus Lung disorder NOS	New-onset	3 Days	Not Recovered

No	ID sex age primary source	Drug	Concomitant medication	Reported ADRs	New-onset or flare	Latency after start	Outcome
40	NL-LRB-00791801 female 50-60 Years Consumer or other non health professional	Covid-19 Vaccin Pfizer	Estriol Ovule	Oral lichen planus Pruritic rash Lichen sclerosus	New-onset	5 Days	Not Recovered
41	NL-LRB-00797704 female 60-70 Years Consumer or other non health professional	Covid-19 Vaccin Moderna		Oral lichen planus	New-onset	-	Recovering
42	NL-LRB-00802497 female 50-60 Years Consumer or other non health professional	Covid-19 Vaccin Pfizer		Oral lichen planus Oral pain	New-onset	21 Days	Not Recovered
43	NL-LRB-00723436 female 60-70 Years Consumer or other non health professional	Covid-19 Vaccin Pfizer	Atorvastatine Colecalciferol	Frontal fibrosing alopecia	New-onset	-	Not Recovered
44	NL-LRB-00717917 female 60-70 Years Consumer or other non health professional	Covid-19 Vaccin Janssen	Colecalciferol	Frontal fibrosing alopecia	Flare	-	Recovering
45	NL-LRB-00720330 female 60-70 Years Consumer or other non health professional	Covid-19 Vaccin Moderna		Frontal fibrosing alopecia Lichen sclerosus Androgenetic alopecia	New-onset		Not Recovered
46	NL-LRB-00734199 female 60-70 Years Consumer or other non health professional	Covid-19 Vaccin Astrazeneca		Frontal fibrosing alopecia	New-onset	1 Month	Not Recovered
47	NL-LRB-00786921 female 40-50 Years Consumer or other non health professional	Covid-19 Vaccin Pfizer		Lichen planopilaris Condition aggravated	Flare	4 Weeks	Recovering
48	NL-LRB-00792205 female 60-70 years Consumer or other non health professional	Covid-19 Vaccin Moderna		Frontal fibrosing alopecia Tinnitus	New-onset	1 Month	Recovering

Detailed description of well documented reports (positive re-challenge)

NL-LRB-00569789 (spontaneous report)
A 60-70-year old male developed a skin rash with an unknown latency after his first Pfizer COVID-19 vaccination that was diagnosed as Lichen Planus by his general physician. One week after his second Pfizer COVID-19 vaccination his Lichen planus was aggrevated. There was no medical history of COVID-19 infection. Patient was treated with topical corticosteroids.

NL-LRB-COVID-00576612 (Lareb Intensive Monitoring report)
A 40-50-year old male developed symptoms of injection site inflammation, general malaise, fatigue, and a change in urine and sweat odor after his first Moderna COVID-19 vaccination. One week after his vaccination, he developed a flare-up of anal lichen sclerosis and the first episode of oral lichen planus. His dentist first considered an oral bacterial infection for which he was treated with 2% chlorhexidine/0.0% cetylpyridinium chloride. After the second Moderna COVID-19 vaccination, he developed a flare-up of the oral lichen planus alongside complaints of injection site pain, fever, headache, general malaise, fatigue, sensation of pressure on forehead and nose, and impaired concentration. There was no medical history of COVID-19 infection.

NL-LRB-00793010 (spontaneous report)
A 50-60-year old female with a history of oral lichen planus developed a flare-up of oral lichen planus with ulcera in her mouth, esophagus, stomach, abdomen, and nose after her first Pfizer COVID-19 vaccination. She suffered relapses of oral lichen planus after her second Pfizer COVID-19 vaccination and four days after her third Moderna COVID-19 vaccination. She was treated with prednisone suppositories. In addition to oral lichen planus, she suffered from relapsing cardiac arrhythmias with increasing severity after each vaccination. She was not recovered at the time of reporting.

NL-LRB-COVID-00520831 (Lareb Intensive Monitoring report)
A 70-years and older female developed oral lichen planus and myalgia one day after her first Pfizer COVID-19 vaccination. The lichen planus recovered after eight days. She suffered a relapse of oral lichen planus 14 days after her second COVID-19 vaccination, for which she was treated with clobetasol propionate 0.025% oral rinsing fluid. After this treatment she experienced an impaired sense of taste. Her medical history reveals a dust mite allergy and she uses atorvastatin. There was no history of COVID-19 infection.

NL-LRB-00773436 (spontaneous report)
A 50-60-year old female suffered from a pruritic rash and a mucosal rash one day after her first Janssen COVID-19 vaccination. These symptoms were still present six months later at the time of her Moderna COVID-19 booster vaccination. One day after this booster her symptoms aggravated and she was diagnosed with lichen planus by a dermatologist and treatment was started with topical corticosteroids. Her medical history reveals hay fever and food allergy. There was no history of COVID-19 infection.

NL-LRB-00776891 (spontaneous report)
A 40-50-year old female suffered from new-onset skin and oral lichen planus ten days after her second Moderna COVID-19 vaccination. After her Moderna COVID-19 booster she experienced from chills, headache, nausea, generalized joint pain, myalgia, malaise, and fatigue within the first two days after vaccination. After ten days she suffered a relapse of skin and oral lichen planus. She was treated with coconut oil and oral rinsing fluids and is recovering after three weeks. There was no medical history of COVID-19 infection.

NL-LRB-00801301 (spontaneous report)
A 40-50-year old female suffered from a pruritic rash over her entire body two days after her first Pfizer COVID-19 vaccination. Two days after her second Pfizer vaccination this rash aggravated and was accompanied by symptoms of the oral mucosa and crumbling toenails. A skin biopsy confirmed the diagnoses of hypertrophic lichen planus. Patient was treated with UVB during four weeks and topical corticosteroids in combination with salicylic acid. Nine months after onset she is recovering. She had never suffered similar symptoms before. She did not use any concomitant medication and she did not have any relevant medical history. There was no family history of auto-immune diseases.

Detailed description of well documented reports (without positive re-challenge)

NL-LRB-00512216 (spontaneous report)
A 30-40-year old female healthcare worker developed genital lichen planus two days after her first AstraZeneca COVID-19 vaccination. She also experienced high fever. She was diagnosed with genital lichen planus by a dermatologist and gynaecologist. After two months her symptoms have not subsided yet. She was treated with systemic prednisone pulse therapy, topical corticosteroids, topical tacrolimus and topical lidocaine/prilocaine. There was no medical history of COVID-19 infection.

NL-LRB-00684852 (spontaneous report)
A 60-70-year old female previously diagnosed with oral lichen planus suffers a relapse two days after her second Pfizer COVID-19 vaccination. Her main complaints are pain on the inside of her cheeks which causes difficulty eating. Before her second vaccination the symptoms were mild and self-managed by a change in diet (no egg, sugar or chocolate). Her general physician, dentist and an undefined hospital specialist observed many Wickham striae and a poor condition of the oral mucosa. After four months her symptoms improved without further treatment. She was used to an increase of symptoms in times of sickness but never as severe as after this second COVID-19 vaccination. After her first COVID-19 vaccination she did not experience a lichen planus relapse.

NL-LRB-00703457 (spontaneous report)
A 40-50-year old female develops new-onset lichen planus, diagnosed by a dermatologist, of the soles of her feet and palms of her hands approximately two weeks after her first Pfizer COVID-19 vaccination. There was no medical history of COVID-19 infection or other illnesses precipitating the onset of lichen planus. She was treated with topical corticosteroids and UVB therapy. She has not yet recovered after five months.

NL-LRB-00714403 (spontaneous report)
A 50-60-year old female developed new-onset lichen planus of the skin and new-onset vaginal lichen sclerosis. In addition, she developed oral leucoplakia, diagnosed by a dental hygienist and dental surgeon. All three disorders emerged two weeks after her first Moderna COVID-19 vaccination. She also suffered from myalgia, fatigue, and injection site inflammation in the first days after vaccination. She was treated with topical corticosteroids and lanette/cetomacrogol cream. Her medical history reveals vitiligo (diagnosed 28 years ago) but no COVID19 infection.

NL-LRB-00713655 (spontaneous report)
A 40-50-year old male developed new-onset erosive oral lichen planus one week after his first Moderna COVID-19 vaccination. He was diagnosed by a dental surgeon and treated with clobetasol propionate 0.025% oral rinsing fluid. He has not recovered

after six months. The dental surgeon considered the Moderna vaccination the most likely trigger. His medical history reveals alopecia universalis and anal lichen sclerosis.

NL-LRB-00734199 (spontaneous report)
A 60-70-year old female developed new-onset frontal fibrosing alopecia one month after her second AstraZeneca COVIDCOVID-19 vaccination. She was treated with topical corticosteroids, topical tacrolimus, and hydroxychloroquine. There was no medical history of COVID-19 infection.

Other sources of information

SmPC

Lichen planus is not included in the SmPC of any of the COVID-19 vaccines as an adverse drug reaction (2-6). Also, new-onset or relapse auto-immune disease is not included in any of the SmPC.

Considering other vaccines; for the hepatitis B vaccine (Engerix B), however, lichen planus is included in the 4.8 section of the SmPC without mention of reported frequency (18).

Other databases

In the WHO global database of individual case safety reports, VigiBase, a total of 708 lichen planus cases associated with COVID-19 vaccines were recorded. Analysis revealed disproportionality for all PT included in our analysis: Lichen planus, IC_{025} 0.4; Oral lichen planus, IC_{025} 1.0; Lichen planopilaris, IC_{025} 1.2 In Vigibase, there is one report of Anogenital lichen planus. Table 3 provides an overview of disproportionality analyses for each COVID-19 vaccine. Remarkably, the vector-based vaccines AstraZeneca and Janssen are not associated with Lichen planus, with exception of the PT Oral lichen planus for AstraZeneca.

*Table 3. Disproportionality analayses in Vigibase**

COVID-19 vaccines	Reaction PT	$N_{observed}$	$N_{expected}$	N_{drug}	$N_{Reaction}$	IC_{025}	IC	ROR_{025}	ROR
All	Lichen planus	522	363	3,851,598	2,927	0.4	0.5	1.4	1.5
	Oral lichen planus	151	63	3,851,598	509	1.0	1.3	2.5	3.0
	Lichen planopilaris	34	10	3,851,598	80	1.2	1.7	3.4	5.2
Pfizer	Lichen planus	323	188	2,000,997	2,927	0.6	0.8	1.6	1.8
	Oral lichen planus	98	33	2,000,997	509	1.3	1.6	2.8	3.5
	Lichen planopilaris	21	5	2,000,997	80	1.2	1.9	3.1	5.2
Moderna	Lichen planus	105	72	760,979	2,927	0.3	0.5	1.2	1.5
	Oral lichen planus	25	12	760,979	509	0.4	1.0	1.4	2.1
	Lichen planopilaris	11	2	760,979	80	1.2	2.2	3.4	6.3
AstraZeneca	Lichen planus	87	75	795,092	2,927	-0.1	0.2	0.9	1.2
	Oral lichen planus	24	13	795,092	509	0.2	0.9	1.3	1.9
	Lichen planopilaris	3	2	795,092	80	-1.6	0.5	0.5	1.5
Janssen	Lichen planus	13	16	171,700	2,927	-1.2	-0.3	0.5	0.8
	Oral lichen planus	4	3	171,700	509	-1.3	0.4	0.5	1.4

**Access date: 01-06-2022 (de-duplicated dataset); MedDRA version: 25.0; number of de-duplicated cases in background: 31,071,201*

Literature

A literature search on PubMed resulted in 20 case-reports describing cases of new-onset or relapse of lichen planus after COVID-19 vaccination (19-38). Several case-reports describe histological confirmation of diagnosis and absence of other possible causes. One case-report describes the development of new-onset lichen planus on 30-year old vitiligo spots after the first COVID-19 vaccination with a relapse after the second vaccination (31).

A retrospective cohort analysis compared 217,863 patients with an injection of at least one mRNA or adenovirus vector-based COVID-19 vaccine with age and sex matched patients who were not vaccinated against COVID-19 (39). The primary outcome was onset of oral lichenoid lesions or oral lichen planus within six days after COVID-19 vaccination for the vaccinated cohort, and six days after visit of a health care organisation for any other reason for the unvaccinated cohort. Oral lichenoid

lesions cannot be distinguished from oral lichen planus neither from clinical presentation nor from histopathology. In the vaccinated cohort, 146 patients developed oral lichenoid lesions or oral lichen planus compared to 59 patients in the unvaccinated cohort. The risk of developing oral lichenoid lesions or oral lichen planus was 0.067% for the vaccinated cohort compared to 0.027% for the unvaccinated cohort. The obtained risk difference of 0.04% was statistically significant ($p<0.001$), risk ratio was 2.475 (95% confidence interval, 1.829; 3.348).

A literature search on PubMed on the association of lichen planus with vaccination in general provided several case-reports, mainly for viral vaccines. There are two case-reports which describe positive re-challenges after hepatitis B vaccination (40, 41). A Vaccine Adverse Event Reporting System (VAERS) study on the top three related vaccines in lichen planus reports revealed the hepatitis B vaccine, influenza vaccine, and herpes zoster vaccine as the most frequently related vaccines in lichen planus reports (42).

Mechanism

Lichen planus is a T-cell-mediated autoimmune disease mainly involving the T-helper(Th)-1 pathway. All COVID-19 vaccines induce a strong Th-1 cell response with consecutive release of Th-1 cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-2, interferon (INF)γ, IL-6 and IL-15. These cytokines are also described in relation to lichen planus pathogenesis, INF-γ and TNF-α are known for their pro-apoptotic properties, as seen in keratinocytes of lichen planus patients (27, 32, 43). In a subgroup analysis performed in a meta-analysis of lichen planus and oral lichen planus patients, a significant increase of IL-6 expression level was identified among Asian patients but not in Caucasian patients (44). A meta-analysis comparing IL-6 levels in serum and saliva of oral lichen planus patients found significantly higher serum and saliva IL-6 levels in oral lichen planus patients compared to healthy controls (45). Another study showed a significantly higher expression of regulatory T cells and IL-15 levels in peripheral blood of oral lichen planus patients compared to healthy controls (46).

Data on usage

Table 4. Most recent overview of number of doses administered per vaccine in the Netherlands (47)

	Startdate vaccination	**Number of vaccinations up to May 15th, 2022**
Comirnaty®	January 6th, 2021	24,612,595
Vaxzevria®	January 25th, 2021	2,780,129
SpikeVax®	February 12th, 2021	7,904,551
Jcovden®	April 21st, 2021	868,899
Nuvaxovid®	March 14th 2022	1,267

Discussion and conclusion

Until May 16th 2022, The Netherlands Pharmacovigilance Centre Lareb received 48 reports of Lichen planus associated with COVID-19 vaccines. The degree of documentation of diagnostics and symptoms varied. In 22 cases (46%) diagnosis was confirmed by a medical specialist (dermatologist, dentist or dental surgeon.

Six cases described a positive re-challenge after one subsequent COVID-19 vaccination (all new-onset Lichen planus), and one case described positive re-challenges after two subsequent COVID-19 vaccinations (patient was already diagnosed with Lichen planus before the first vaccination). None of these positive re-challenge cases had a history of COVID-19 infection.

The exact prevalence of Lichen planus is unknown, it is estimated to be in the range of 0.22% to 5% worldwide. The diverse clinical presentation can cause patient and doctor delay in diagnosis (7).

Lichen planus and other vaccines

Based on the hypothesis that activation of the T-helper-1 pathway may trigger this T-cell-mediated autoimmune disease, all currently used vaccines could theoretically trigger Lichen planus. However, most case-reports concern viral vaccines. A Vaccine Adverse Event Reporting System (VAERS) study on the top three related vaccines in lichen planus reports revealed the hepatitis B vaccine, influenza

vaccine, and herpes zoster vaccine as the most frequently related vaccines in lichen planus reports. Two case-reports describe positive re-challenges after hepatitis B vaccination (40, 41). Until May 16th 2022, The Netherlands Pharmacovigilance Centre Lareb received 57 reports of Lichen planus associated with viral vaccines and one report of Lichen planus associated with a bacterial vaccine.

Lichen planus and COVID-19 infection
There are only few case-reports published describing an association between Lichen planus and COVID-19 infection. Of the 48 Lichen planus cases received by the Netherlands Pharmacovigilance Centre Lareb, 8 patients had a history of COVID-19 infection.

Conclusion
A causal relationship between Lichen planus and COVID-19 vaccines seems plausible based on the 48 cases of Lichen planus received by the Netherlands Pharmacovigilance Centre Lareb. Disproportionality analysis of the WHO global database of individual case safety reports, VigiBase, revealed disproportionality for Lichen planus in association with COVID-19 vaccines. In addition, 20 case-reports describing Lichen planus development after COVID-19 vaccination are published and a large cohort study found a risk ratio of 2.5 for ''oral lichenoid lesions or oral lichen planus'' development for COVID-19 vaccinated versus unvaccinated individuals. Furthermore, a hypothesis on the pharmacological mechanism underlying the association has been postulated. Therefore, this association should be further investigated.

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This signal has been raised on July 6, 2022. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl