Title: Recommendations for vaccination in children with atopic dermatitis treated with dupilumab: a consensus meeting, 2020

Electronic supplemental material

Journal: American Journal of Clinical Dermatology

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Funding: none

Conflicts of interest:

SMC: none

MK: Advisor/consultant for AbbVie, Actelion, Amgen, Bausch Health, Celgene, Eli Lilly,

Janssen, Leo, Novartis, UCB, Sanofi Genzyme, and served as a speaker for AbbVie, Janssen, Leo,

Novartis, Pfizer, UCB, Sanofi Genzyme.

CC: Has received honoraria for speaking engagements for Federation of Canadian Women of Canada, GSK, Pfizer, Merck

LMF: Advisor/consultant for, has received honoraria from Sobi and Takeda.

MR: Advisor/consultant for, has received grants/honoraria from, and/or has served as a speaker for LEO Pharma, Pfizer, and Sanofi Genzyme.

A modified-Delphi Consensus Meeting

The meeting was conducted according to the modified-Delphi method, following the Guidance on Conducting and Reporting Delphi Studies (CREDES) recommended by Enhancing the QUAlity and Transparency Of health Research (EQUATOR Network) (www.equator-network.org):

1. A detailed review of the literature was performed (Table 1-5; Figure 1). This information was summarized in a PowerPoint presentation.
2. This review and the full references were sent to the participants in advance to the meeting. All members of this working group are registered clinicians with >5 years of experience and possessed significant expertise in their field (supported by an academic rank, publications, attendance at national meetings and participation in clinical trials).
3. We acknowledge the following authors who were contacted to solve unclear information:

   Dr. Yosef Uziel: Uziel Y, Moshe V, Onozo B, et al. Live attenuated MMR/V booster vaccines in children with rheumatic diseases on immunosuppressive therapy are safe: Multicenter, retrospective data collection. Vaccine. 2020;38(9):2198-2201.

   Toplak, N., Uziel, Y., 2020. Vaccination for Children on Biologics. Current Rheumatology Reports 22.. doi:10.1007/s11926-020-00905-8

   Dr. Eric L. Simpson: Abstract - Pharmacokinetics, Safety, and Efficacy of Dupilumab in Children Aged ≥ 2 to < 6 Years with Severe, Uncontrolled Atopic Dermatitis (LIBERTY AD PRE-SCHOOL). Presented at the 2019 Annual Conference of the Pediatric Dermatology Research Alliance (PeDRA); Chicago, IL, USA; November 14–16, 2019.
4. Two participants (SM; MR) developed the seven initial statements that were circulated and revised based on feedback received (MK) before the consensus meeting.
5. A single meeting with two rounds and the final consensus, set up as 75% or more agreement, were defined before the consensus (Figure 2).
6. One moderator (MR) chaired the meeting.
7. Participants voted privately through a website (poll everywhere; San Francisco, California) while maintaining anonymity. A 5-point Likert scale: 1-Strongly disagrees, 2-disagree, 3-neutral, 4-agree, and 5-strongly agree was used. Refraining from voting was not allowed.
8. Feedback was provided after each round as quantitative data using bar charts.
9. A discussion in which the participants were able to explain their rating or express disagreement with the statement followed the first round. Their responses were used to reformulate the questionnaire of statements.

10. All statements were sent to the next round for re-ranking (Table 6)

Reference: Junger S, Payne SA, Brine J, Radbruch L, Brearley SG. Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. *Palliat Med.* 2017;31(8):684-706.

Table 1. Dupilumab summary

	Adults	Adolescents 12-17 years old	Children <12 Years
FDA approval[1]	March 28, 2017	March 11, 2019	May 26, 2020: Approved in children aged 6-11 years old for use in moderate to severe AD.
EMA[2]	September 27, 2017	August 6, 2019	October 15, 2020: Dupixent is indicated for the treatment of severe atopic dermatitis in children 6 to 11 years old who are candidates for systemic therapy.
Health Canada approval[3]	November 30, 2017	September 25, 2019	License application under review (6-11 years old)
Studies	• Phase 3 Liberty AD SOLO 1 (NCT02277743) and LIBERTY AD SOLO 2 (NCT02277769): 16 weeks of duration of the study[4] • Phase 3 LIBERTY AD CHRONOS (NCT02260986): 52 weeks of duration of the study[5]	Phase 3 LIBERTY AD ADOL [6] Efficacy and Safety of Dupilumab in Participants ≥12 to <18 years of age with moderate-to-severe Atopic Dermatitis (NCT03054428) 16 weeks of duration of the study. Phase 2a open-label, ascending-dose, sequential cohort study (NCT02407756)[7] Phase 3 LIBERTY AD PED-OLE (NCT02612454) open-label extension trial 52 weeks of duration[7] Completed: • Phase 1 (NCT03050151) An Open-label, Randomized, Actual Use Study of Dupilumab Auto-injector Device in Patients with Atopic Dermatitis (≥ 12 y) Enrolling by invitation: • Phase 4 (NCT03411837) Dupilumab Registry Study (≥ 12y) Recruiting: • NCT03428646 A Prospective Observational Study of Patients receiving DUPIXENT® for Atopic Dermatitis (≥ 12 y)	Clinical trials Completed and results posted: • **Phase 2a dose-ranging (NCT02407756)[7]** Study Investigating the Safety, Pharmacokinetics, Immunogenicity, and Exploratory Efficacy of Dupilumab in patients aged ≥6 to <18 years with Atopic dermatitis • **Phase 3 (NCT03345914)[8]** A Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of Dupilumab administered concomitantly with topical corticosteroids in patients, ≥6 years to <12 years of age with severe Atopic dermatitis Enrolling by invitation: • **Phase 3 (NCT02612454)[7]** An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of Dupilumab in Patients ≥6 months to <18 years of age with Atopic dermatitis Recruiting • **Phase 2/3 (NCT03346434)** LIBERTY AD PRE-SCHOOL Study Investigating the Pharmacokinetics, Safety, and Efficacy of Dupilumab in patients aged ≥6 Months to <6 Years with Severe Atopic Dermatitis • **NCT03549416** Child, Adult, Older Adult BioDay Registry: Prospective, Observational Data Collection Regarding the Use of New Systemic Treatment Options in Patients with Atopic Diseases in Daily Practice • **NCT03687359[9]** Protocol for a Prospective, Observational, Longitudinal Study in Paediatric Patients with Moderate-To-Severe Atopic Dermatitis (PEDISTAD): Study Objectives, Design and Methodology
Dose Scheme	LD: 600 mg sc (2 injections of 300 mg) Followed: 300 mg sc (1 injection) q.o.w	<60 kg: LD: 400 mg sc (2 injection of 200 mg) MD: 200 mg q.o.w sc (1 injection 200 mg)	**LIBERTY AD PRE-SCHOOL (Part A; Phase 2)[10]**: Cohort 1: ≥2 to < 6 y old Some received 3 mg/kg single dose

		≥60 kg: (same as adult) LD: 600 mg MD: 300 mg sc q.o.w	Some received 6 mg/kg single dose **LIBERTY AD PEDS (NCT03345914; Phase 3):** Per USPI, for all pediatric patients the recommended dosing for AD is as follows:[8,11] 60kg+: 600mg LD then 300mg q2w (per adult dosing) 30-<60kg: 400mg LD then 200mg q2w 15-<30kg: 600mg LD then 300mg q4w
Laboratory	• Transient neutropenia* • Thrombocytopenia • Transient eosinophilia*[12]		
Most common side effects	• Conjunctivitis • Injection-site reactions		

*Uncommon and none of them clinically significant. Abbreviations: EMA: European Medicines Agency, FDA: U.S. Food and Drug Administration, LD: loading dose, MD: maintenance dose, q2w: every two weeks, q.o.w: every other week, sc: subcutaneous, y: years. All clinical trials were re-accessed after consensus in May 1st. Last time accessed: November 17th, 2020.

1. Regeneron Pharmaceuticals, Inc. DUPIXENT® (dupilumab). Highlights of prescribing information. U.S. Food and Drug Administration website . https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761055s014lbl.pdf. Revised June 2019. Last accessed November 2020.

2. Dupixent: EPAR. Product Information. European Medicines Agency 2017. (https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent. Revised July 2020. Last accessed November 2020.

3. Sanofi-Aventis Canda Inc. Dupixent. Public Health Agency of Canada.Summary Basis of Decision - Dupixent - Health Canada https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00381 Revised April 2019. Last modified November 13, 2020. Last accessed Novemeber 17, 2020.

4. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med.* 2016;375(24):2335-2348.

5. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet.* 2017;389(10086):2287-2303.

6. Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized Clinical Trial. *JAMA Dermatol.* 2019.

7. Cork MJ, Thaci D, Eichenfield LF, et al. Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a phase IIa open-label trial and subsequent phase III open-label extension. *Br J Dermatol.* 2020;182(1):85-96.

8. Paller AS, Siegfried EC, Thaçi D, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: a randomized, double-blinded, placebo-controlled phase 3 trial. *J Am Acad Dermatol.* 2020.

9. Paller AS, Guttman-Yassky E, Irvine AD, et al. Protocol for a prospective, observational, longitudinal study in paediatric patients with moderate-to-severe atopic dermatitis (PEDISTAD): study objectives, design and methodology. *BMJ Open.* 2020;10(3):e033507.

10. Simpson EL, Lockshin B, Davis JD, Sun X, Gadkari A, Eckert L, Rossi AB, Bansal A. Pharmacokinetics, Safety, and Efficacy of Dupilumab in Children Aged ≥ 2 to < 6 Years With Severe, Uncontrolled Atopic Dermatitis (LIBERTY AD PRE-SCHOOL). Preliminary results presented at the 7th the Pediatric Dermatology Research Alliance (PeDRA) Annual Conference; November 14-16 2019, Chicago, IL.

11. Dupilumab [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2020. Available at:https://www.regeneron.com/sites/default/files/Dupixent_FPI.pdf Accessed on July 2, 2020.

12. Wollenberg A, Beck LA, Blauvelt A, et al. Laboratory safety of dupilumab in moderate-to-severe atopic dermatitis: results from three phase III trials (LIBERTY AD SOLO 1, LIBERTY AD SOLO 2, LIBERTY AD CHRONOS). *Br J Dermatol.* 2019.

Search strategy

A literature search in Medline and Embase was conducted according to the PRISMA guidelines for systematic reviews in August 2019 (Table 2). The research question, "What is the safety of vaccinations in pediatric patients taking dupilumab for atopic dermatitis?" to be addressed, was formulated using PICO. (P: ages 0-18 on Dupilumab; I: Vaccination; C: No vaccination; O: adverse outcomes). The inclusion criteria were case series, retrospective and prospective cohort studies, and clinical trials that included patients aged younger than 18 years old on dupilumab therapy and had received vaccinations (Figure 1).

The literature search was updated on February 2, 2020. Two researchers independently screened titles and abstracts for relevant studies. If articles eligible, their full texts were reviewed for compliance with inclusion criteria, followed by deliberation between them. Although none of the articles fulfilled the inclusion criteria (Figure 1), the more relevant articles (Table 3) were reviewed and discussed in the consensus meeting and in the final manuscript.

Table 2. Search strategies

Embase search terms	Pubmed search terms
(('school'/exp OR 'pediatrics'/exp OR 'puberty'/exp OR 'minor (person)'/exp OR 'school age population'/exp OR 'postmaturity'/exp OR 'prematurity'/exp OR 'school age'/exp OR 'child'/exp OR 'adolescent'/exp OR 'juvenile'/de OR Infant* OR infancy OR Newborn* OR Baby* OR Babies OR Neonat* OR Preterm* OR Prematur* OR Postmatur* OR Child OR children* OR childhood* OR Schoolchild* OR 'School age*' OR Preschool* OR Kid OR kids OR Toddler* OR Adoles* OR Teen* OR Boys* OR boyhood* OR boy OR Girl* OR Minors* OR Pubert* OR Pubescen* OR Prepubescen* OR Pediatric* OR Paediatric* OR Peadiatric* OR 'Nursery school*' OR Kindergar* OR 'Primary school*' OR 'Secondary school*' OR 'Elementary school*' OR 'High school*' OR Highschool*) AND ('dupilumab'/exp OR 'dupilumab' OR 'dupixent' OR 'regn 668' OR 'regn668' OR 'sar 231893' OR 'sar231893') AND ('immunization'/exp OR vaccin* OR immuni* OR inoculat*))	((Infant[MeSH] OR Infant*[All Fields] OR infancy[All Fields] OR Newborn*[All Fields] OR Baby*[All Fields] OR Babies[All Fields] OR Neonat*[All Fields] OR Preterm*[All Fields] OR Prematur*[All Fields] OR Postmatur*[All Fields] OR Child[MeSH] OR Child[All Fields] OR children*[All Fields] OR childhood*[All Fields] OR Schoolchild*[All Fields] OR School age*[All Fields] OR Preschool*[All Fields] OR Kid[All Fields] OR kids[All Fields] OR Toddler*[All Fields] OR Adolescent[MeSH] OR Adoles*[All Fields] OR Teen*[All Fields] OR Boys*[All Fields] OR boy's[All Fields] OR boyhood*[All Fields] OR boy[All Fields] OR Girl*[All Fields] OR Minors[MeSH] OR Minors*[All Fields] OR Puberty[MeSH] OR Pubert*[All Fields] OR Pubescen*[All Fields] OR Prepubescen*[All Fields] OR Pediatrics[MeSH] OR Pediatric*[All Fields] OR Paediatric*[All Fields] OR Peadiatric*[All Fields] OR Schools[MeSH] OR Nursery school*[All Fields] OR Kindergar*[All Fields] OR Primary school*[All Fields] OR Secondary school*[All Fields] OR Elementary school*[All Fields] OR High school*[All Fields] OR Highschool*[All Fields]) AND ("SAR231893"[Supplementary Concept] OR "SAR231893"[All Fields] OR "dupilumab"[All Fields] OR dupixent[All Fields]) AND ("immunization"[Mesh] OR vaccin*[All Fields] OR immuni*[All Fields] OR inoculat*[All Fields]))

Figure 1. Flow diagram of the literature search

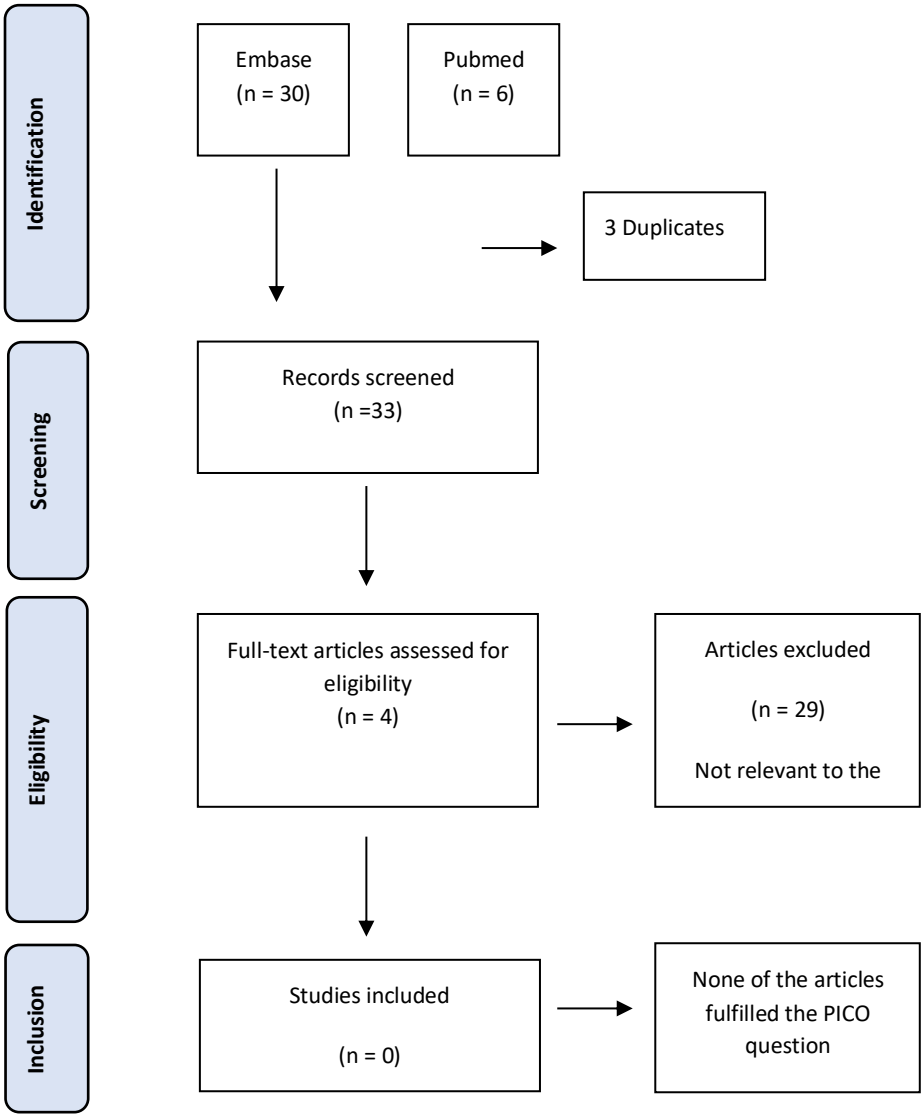

Table 3. Relevant articles assessed for eligibility (n = 4)

Author	Study design	Population	Vaccination
European Medicines Agency 2017[1]	Dupilumab monography (Annex 1 Summary of Product characteristics)	Adolescents and adults	LAV should not be given concurrently with dupilumab as clinical safety and efficacy has not been established. Patients receiving dupilumab may receive concurrent INV or non-LV. It is recommended that patients should be brought up to date with live and live attenuated immunisations in agreement with current immunisation guidelines prior to treatment with dupilumab.
Blauvelt, A., et al 2019[2]	Phase 2 randomized, double-blinded, placebo-controlled study	Adults	Antibody responses to both tetanus vaccine (Tdap) and meningococcal polysaccharide vaccine (MPSV4) were similar in dupilumab-treated and placebo-treated patients with an acceptable safety profile.
Siegfried, E. C., et al. 2019[3]	Commentary	Children	NA
Cork MJ et al. 2020[4]	Phase 2a/Phase 3 Open label extension	Adolescents	NA

LAV: live attenuated vaccines; LV: live vaccines; INV: inactivated vaccines. References:

1.Dupixent: EPAR. Product Information. European Medicines Agency 2017. (https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent). Revised February 2020. Accessed April 2020.

2.Blauvelt A, Simpson EL, Tyring SK, et al. Dupilumab does not affect correlates of vaccine-induced immunity: A randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. J Am Acad Dermatol. 2019;80(1):158-167 e151

3.Siegfried EC, Igelman S, Jaworsk JC, et al. Use of dupilimab in pediatric atopic dermatitis: Access, dosing, and implications for managing severe atopic dermatitis. Pediatr Dermatol. 2019;36(1):172-176.

4.Cork MJ, Thaci D, Eichenfield LF, et al. Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a phase IIa open-label trial and subsequent phase III open-label extension. Br J Dermatol. 2020;182(1):85-96.

Second literature search

A structured English literature search in Medline was performed in February 2020 seeking for articles on live attenuated and inactivated vaccines in AD pediatric patients and on pediatric patients receiving biologics; national and international guidelines on vaccination of immunocompromised pediatric patients; and dermatologic guidelines for children with AD (Table 4-5).

Terminology used in the literature search: ((immunization or vaccin* or immuni* or inoculat* or vaccination or vaccine or "vaccination guideline" or "inactivated vaccin*" or "live vaccin*" or "conjugate vaccin*" or "polysaccharide vaccin*" or "mumps vaccin*" or "measles vaccin*" or "rubella vaccin*" or "varicella vaccin*" or "influenza vaccin*" or booster or revaccination) adj5 (Paediatric* or Pediatric or Minors* or toddler* or child or children or infancy or childhood or "school age population" or schoolchild or adoles*) AND (Immunosuppression or Immunosuppressed or immunocompromised or "secondary immunodeficiencies" or "immunosuppressive therapy" or biologic* or "biologic therapy" or "anti-cytokine therapy" or "anti-interleukin" or immunomodulators or anti-IL-4 or Dupixent or dupilumab)).

The literature search was enhanced by hand searching from the references of the articles of interest. Also, we seek for the mechanism of action of dupilumab, published and ongoing clinical trials of dupilumab in the pediatric and adolescent population; US Food and Drug Administration (FDA) and Public Health Agency of Canada (PHAC) product monographs (Supplement A); IL4 and IL13 functions (Table 2); the basis of immune responses to vaccination (Figure 2); dermatologic guidelines for the management of atopic dermatitis (Table 5); and recommendations for vaccination of immunocompromised patients from health care authorities such as CDC and PHAC

Table 4. Studies from the second English literature search considered for this consensus

Year	Authors	Study	Study type	Reference
2020	Uziel Y, et al.	Live attenuated MMR/V booster vaccines in children with rheumatic diseases on immunosuppressive therapy are safe: Multicenter, retrospective data collection.	Retrospective study	Vaccine. 38(9):2198-2201, 2020 Feb 24.
2020	Cagol L, et al.	Vaccination rate and immunity of children and adolescents with inflammatory bowel disease or autoimmune hepatitis in Germany.	Retrospective study Vaccination rate and immunity of children and adolescents with inflammatory bowel disease (IBD) and autoimmune hepatitis (AIH).	Vaccine. 38(7):1810-1817, 2020 Feb 11.
2020	Igelman, S et al.	Off-label use of dupilumab for pediatric patients with atopic dermatitis: A multicenter retrospective review	Retrospective study: N= 111	J Am Acad Dermatol 82, 407-411 (2020)*
2020	Silverberg	Dupilumab treatment results in early and sustained improvements in itch in adolescents and adults with moderate to severe atopic dermatitis: Analysis of the randomized phase 3 studies SOLO 1 and SOLO 2, AD ADOL, and CHRONOS.	Review	*J Am Acad Dermatol.* 2020.*
2019	Treister AD and Lio PA.	Long-term off-label dupilumab in pediatric atopic dermatitis: A case series	Retrospective study: N= 6	Pediatric Dermatol. 2019. 85-88. *
2019	Siegfried EC, et al.	Use of Dupilimab in Pediatric Atopic Dermatitis: Access, Dosing, and Implications for Managing Severe Atopic Dermatitis	Review	Pediatric Dermatology. 2019;36:172–176.*
2019	Egholm C, et al.	The Regulatory Effects of Interleukin-4 Receptor Signaling on Neutrophils in Type 2 Immune Responses		Front Immunol 2019 Oct 24;10:2507*
2019	Bosma AL, et al.	TREatment of ATopic eczema (TREAT) Registry Taskforce: protocol for a European safety study of dupilumab and other systemic therapies in patients with atopic eczema	This protocol delineates a safety study for dupilumab in adult and paediatric patients with atopic eczema across several national registries.	Br J Dermatol 10.1111/bjd.18452 (2019)*

2019	Moraitis E, et al	Scientific abstracts: SAT0508 An International survey on approached towards immunisation un children with rheumatic diseases: a report of the PRES vaccination working group.	Cross-sectional study: An online survey in 289 paediatric rheumatologists (53 countries)	Ann Rheum Dis 78 (2019)*
2019	Shetty VU, et al.	Rationale for the Immunization Schedule: Why Is It the Way It Is?	Review	Pediatr Rev. 2019 Jan;40(1):26-36.*
2019	U.S. Food and Drug Administration	Regeneron Pharmaceuticals, Inc. DUPIXENT® (dupilumab). Highlights of prescribing information. U.S. Food and Drug Administration website	Monography	https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761055s014lbl.pdf.
2019	Mollanazar NK, et al.	Use of dupilumab in patients who are HIV-positive: report of four cases	Case series	Br J Dermatol 181, 1311-1312 (2019).
2019	Public Health Agency of Canada	Sanofi-Aventis Canada Inc. Dupixent.	Monography	https://hpr-rps.hres.ca/query.php?drugquery=DUPIXENT. Revised April 2019. Accessed April 2020.
2019	Ly K, et al	Dupilumab in patients with chronic hepatitis B on concomitant entecavir	Case series	JAAD Case Rep **5**, 624-626 (2019).*
2019	Marin M, et al.	Transmission of Vaccine-Strain Varicella-Zoster Virus: A Systematic Review.	A Systematic Review.	Pediatrics. 144(3), 2019 09.
2019	Martinelli M, et al.	Vaccinations and Immunization Status in Pediatric Inflammatory Bowel Disease: A Multicenter Study From the Pediatric IBD Porto Group of the ESPGHAN.	Retrospective cohort investigation about Vaccination rates.	Inflammatory Bowel Diseases. 2019 Nov 05
2019	Papp KA, et al.	Vaccination Guidelines for Patients with Immune-Mediated Disorders on Immunosuppressive Therapies.	Immunization guidelines by Consensus	Journal of Cutaneous Medicine & Surgery. 23(1):50-74, 2019 Jan/Feb.
2018	Speth F, et al.	Varicella-zoster-virus vaccination in immunosuppressed children with rheumatic diseases using a pre-vaccination check list.	Prospective study	Pediatric Rheumatology Online Journal. 16(1):15, 2018 Mar 02.
2018	Jeyaratnam J et al.	The safety of live-attenuated vaccines in patients using IL-1 and IL-6 blockade: an international survey.	Retrospective study	Pediatric Rheumatology Online Journal. 16(1):19, 2018.

2018	Sastre J, et al.	Dupilumab: A New Paradigm for the Treatment of Allergic Diseases	Review	J Investig Allergol Clin Immunol. 2018 Jun;28(3):139-150.*
2018	Gooderham MJ, et al.	Dupilumab: A review of its use in the treatment of atopic dermatitis	Review	J Am Acad Dermatol. 2018;78(3 Suppl 1):S28-s36.*
2018	Public Health Agency of Canada	Canadian Immunization Guide Part 3-Vaccination of Specific Populations. Immunization of immunocompromised persons: Canadian Immunization Guide	Canadian Immunization Guide	www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-8-immunization-immunocompromised-persons Reviewed on May 2018. Accessed on March 2020.
2017	Park JK, et al.	Effect of methotrexate discontinuation on efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial.	RCT	Ann Rheum Dis. 2017;76:1559-1565.*
2017	Patel DP, et al.	Decreased Hepatitis B vaccine response in pediatric patients with atopic dermatitis, psoriasis, and morphea.	Case series	Vaccine. 35(35 Pt B):4499-4500, 2017 08 16.
2017	Groot N, et al.	Varicella vaccination elicits a humoral and cellular response in children with rheumatic diseases using immune suppressive treatment.	Prospective study	Vaccine. 35(21):2818-2822, 2017 05 15.
2017	Bieber T, et al.	Clinical Phenotypes and Endophenotypes of Atopic Dermatitis: Where Are We, and Where Should We Go?	Review	J Allergy Clin Immunol. 2017;139(4S):S58-S64*
2017	Croce E et al.	Safety of live vaccinations on immunosuppressive therapy in patients with immune-mediated inflammatory diseases, solid organ transplantation or after bone-marrow transplantation - A systematic review of randomized trials, observational studies and case reports	A systematic review	Vaccine 35, 1216-1226 (2017).*
2016	Winthrop KL, et al.	The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis.	RCT: study A and study B	Ann Rheum Dis 75, 687-695 (2016).*

2016	Werfel T, et al.	Cellular and molecular immunologic mechanisms in patients with atopic dermatitis	Review	J Allergy Clin Immunol. 2016 Aug;138(2):336-49.*
2016	Hakim H, et al.	Immunogenicity and safety of high-dose trivalent inactivated influenza vaccine compared to standard-dose vaccine in children and young adults with cancer or HIV infection.	Randomized open label study	Vaccine. 2016;34(27):3141-3148.*
2016	Pinto MV, et al.	Immunisation of the immunocompromised child.	Review	Journal of Infection. 72 Suppl:S13-22, 2016 07 05.
2015	Toplak N and Avcin T	Long-term safety and efficacy of varicella vaccination in children with juvenile idiopathic arthritis treated with biologic therapy.	Prospective study	Vaccine. 33(33):4056-9, 2015 Aug 07.
2015	Groot N, et al.	Vaccinations in paediatric rheumatology: an update on current developments. [Review]	Review	Current Rheumatology Reports. 17(7):46, 2015 Jul.
2015	Banaszkiewicz A, et al.	Immunogenicity of 13-Valent Pneumococcal Conjugate Vaccine in Pediatric Patients with Inflammatory Bowel Disease.	Prospective, and controlled study	Inflammatory Bowel Diseases. 21(7):1607-14, 2015 Jul.
2014	Lu Y, et al.	Immunizations in children with inflammatory bowel disease treated with immunosuppressive therapy.	Review	Gastroenterology & Hepatology. 10(6):355-63, 2014 Jun.
2014	Rubin LG, et al.	2013 IDSA clinical practice guideline for vaccination of the immunocompromised host.	Immunization guidelines by Consensus	Clinical Infectious Diseases. 58(3):309-18, 2014 Feb.
2013	Heijstek, MW, et al.	Effects of the live attenuated measles-mumps-rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial	RCT	Jama 309, 2449-2456 (2013)*
2012	deBruyn JC, et al.	Immunogenicity and safety of influenza vaccination in children with inflammatory bowel disease.	Prospective study	Inflammatory Bowel Diseases. 18(1):25-33, 2012 Jan.
2011	Heijstek MW, et al.	EULAR recommendations for vaccination in paediatric patients with rheumatic diseases.	Immunization guideline by consensus	Annals of the Rheumatic Diseases. 70(10):1704-12, 2011 Oct.
2011	Ogimi C, et al.	Immunogenicity of influenza vaccine in children with pediatric rheumatic diseases receiving immunosuppressive agents.	Prospective study	Pediatr Infect Dis J. 2011;30(3):208-211*

2011	Meier S, et al.	Antibody responses to natural influenza A/H1N1/09 disease or following immunization with adjuvanted vaccines, in immunocompetent and immunocompromised children.	Prospective study	Vaccine. 29(19):3548-57, 2011 Apr 27.
2010	Schenider J, et al.	Immune Response to Varicella Vaccine in Children with Atopic Dermatitis Compared with Nonatopic Controls	Prospective study	J Allergy Clin Immunol. 2010 Dec;126(6):1306-7.e2*
2009	Borte S, et al	Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept.	Prospective study	Rheumatology (Oxford). 2009;48(2):144-148*
2006	Howell, et al.	Cytokine Milieu of Atopic Dermatitis Skin Subverts the Innate Immune Response to Vaccinia Virus	Experimental study	Immunity 2006 Mar;24(3):341-8*
2005	Dunstan JA et al	Atopic Dermatitis in Young Children Is Associated with Impaired interleukin-10 and Interferon-Gamma Responses to Allergens, Vaccines and Colonizing Skin and Gut Bacteria	Experimental study	Clin Exp Allergy 2005; 35:1309–1317*
1997	Pabst HF, et al	Kinetics of immunologic responses after primary MMR vaccination	Experimental study	*Vaccine* **15**, 10-14 (1997)*
	Centers for Disease Control and Prevention (CDC).	The Advisory Comittee on Immunization Practices (ACIP) General Best Practice Guidelines for Immunization: Altered immunocompetence.	Guidelines	https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.pdf. Accessed April 2020.:119-145.

RCT: Randomized clinical trials. *Hand searched studies

Table 5. Atopic dermatitis international guidelines

Year	Author	Medical societies	Summary of recommendations on vaccination
2012	Schneider L	Joint Task Force of the AAAAI, ACAAI, and the JCAAI	1. To avoid smallpox vaccine in patients with AD or their household contacts
2013	Rubel D	Asia–Pacific Consensus Group	None
2014	Sidbury R	AAD section 3	1. To consider booster vaccines in pediatric patients on long-term steroids. 2. In patients receiving MMF, AZA, CsA, or MTX live vaccines may be contraindicated dependent on medication, dose, and the type of vaccine to be administered.
2017	Katayama I	Japanese Society of Allergology	None
2018	Wollenberg A	European guidelines EADV, EDF, EAACI, ETFAD, EFA, ESDaP, ESPD, GA2LEN and the UEMS	1. To consult a specialist before LAV vaccinate patients on immunosuppressive therapy with CsA or related drugs 2. All children diagnosed with AE should be vaccinated according to the national vaccination plan 3. VZV vaccination is recommended for children with atopic dermatitis 4. Life vaccine is contraindicated during CsA therapy 5. CsA should be stopped of 2 weeks before and 4–6 weeks after vaccination 6. To not vaccinate during acute flares 7. Smallpox vaccination is contraindicated in AE patients
2020	Katoh N	Japanese Society of Allergology, Japanese Dermatology Association	None

AAAAI: American Academy of Allergy, Asthma & Immunology; ACAAI: American College of Allergy, Asthma & Immunology; AE: atopic eczema; AD; atopic dermatitis; AZA: azathioprine; CsA: cyclosporine; EDF: European Dermatology Forum, EADV: European Academy of Dermatology and Venereology, EAACI: European Academy of Allergy and Clinical Immunology, ETFAD: European Task Force on Atopic Dermatitis; EFA: European Federation of Allergy and Airways Diseases Patients' Associations; ESDaP: European Society for Dermatology and Psychiatry; ESPD: European Society of Pediatric Dermatology; GA2LEN: Global Allergy and Asthma European Network; JCAAI: Joint Council of Allergy, Asthma and Immunology; MMF: mofetil mycophenolate; MTX: methotrexate; UEMS: European Union of Medical Specialists.

Figure 2. Flow chart of consensus meeting with 2 modified-Delphi rounds

The meeting was conducted according to the modified-Delphi method, following the Guidance on Conducting and Reporting Delphi Studies (CREDES) recommended by Enhancing the QUAlity and Transparency Of health Research (EQUATOR Network). A single meeting with two rounds and the final consensus, set up as 75% or more agreement, was defined before the consensus.

5-point Likert scale: 1-Strongly disagree, 2-disagree, 3-neutral, 4-agree, and 5-strongly agree

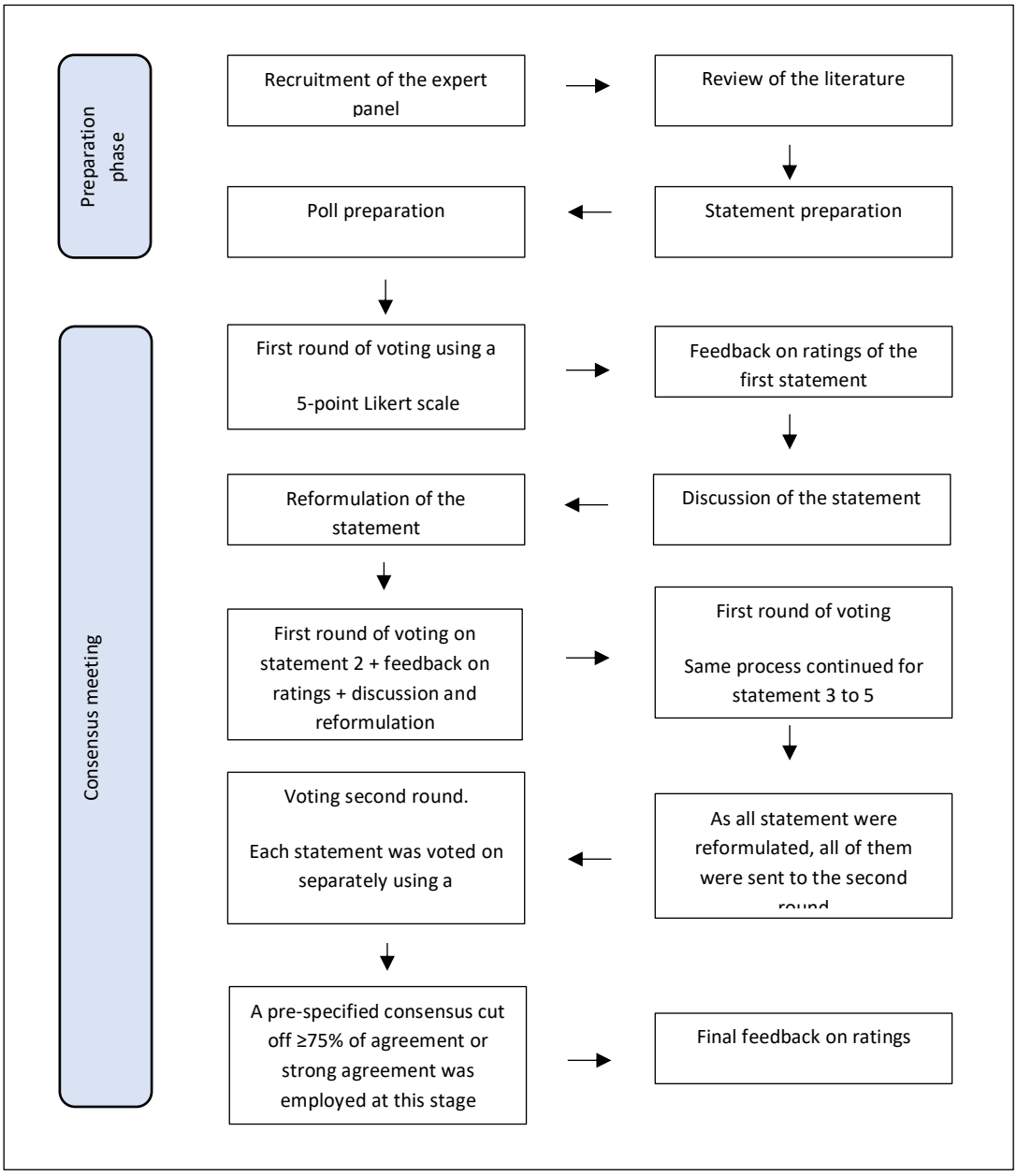

Table 6. Recommendations for vaccination in pediatric patients with Atopic dermatitis treated with dupilumab

Initial statements	Level of agreement	Final statements/Recommendations	Level of agreement
Dupilumab interferes with humoral or cellular immune responses to vaccines but does not appear to affect the development of protective titres	2 (40%) neutral 3 (60%) disagree	Based on available data, dupilumab does not appear to affect the development of protective antibodies titres to inactivated vaccines	100% strongly agree
Dupilumab should not be interrupted for inactivated vaccines	3 (60%) strongly agree 2 agree (60%)	Dupilumab treatment does not need to be interrupted for administration of inactivated vaccines	100% strongly agree
Seasonal and pandemic influenza vaccination should not be avoided while on dupilumab	2 (40%) strongly agree 3 (60%) agree	For patients on dupilumab treatment, seasonal inactivated influenza vaccination should continue as recommended	100% strongly agree
Live vaccinations should be given prior to dupilumab if possible	1 (20%) strongly agree 4 (80%) agree	Based on available data, live attenuated vaccines should be avoided while on dupilumab	100% strongly agree
Live attenuated vaccines should be avoided while on dupilumab	4 (80%) agree 1 (20%) neutral	When live attenuated vaccinations are required, they should be given at least 4 weeks prior to initiation of dupilumab treatment, if possible	100% strongly agree
Measurement of antibody levels after vaccination is necessary to ensure serologic protection	1 (20%) agree 3 (60%) neutral 1 (20%) disagree	While on dupilumab, measurement of specific antibody levels can be considered to ensure serologic protection after vaccination on dupilumab therapy	100% strongly agree

There is no risk of Atopic dermatitis exacerbation with immunization on dupilumab	1 (20%) agree 4 (80%) neutral	There is no evidence to suggest that immunization while on dupilumab causes an exacerbation of atopic dermatitis	100% strongly agree

All final statements achieved the highest level of consensus