1. Should HDM SLIT drops versus no SLIT drops be used for treatment in **paediatric** patients with asthma?

1.1. FOREST PLOTS

1.1.1. Critical outcomes

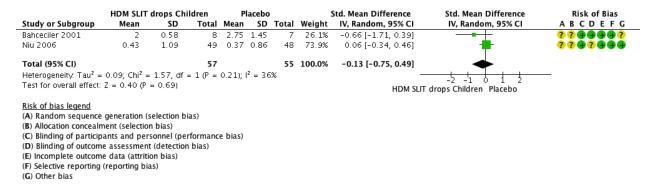
1.1.1.1. Asthma exacerbations

We found no evidence

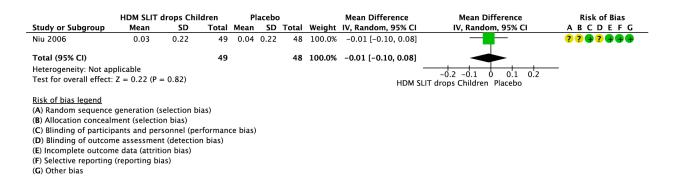
1.1.1.2. Asthma control

We found no evidence

1.1.1.1. Steroid sparing effect (inhaled steroids) assessed as score or rescue medications in number of puffs per day



1.1.1.2. Steroid sparing effect (oral steroids) assessed as rescue medications in number of tablets per day



1.1.1.3. Safety (systemic reactions) – assessed as number of patients with at least one reaction

	HDM SLIT drops Ch	ildren	Place	bo	Risk Ratio		Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% CI	ABCDEFG
Bahceciler 2001	0	8	0	7		Not estimable		???????
Ippoliti 2003	0	47	0	39		Not estimable		? ? ? ? ? ?
Lue 2006	0	10	0	10		Not estimable		??????
Niu 2006	1	49	4	48	49.2%	0.24 [0.03, 2.11]		??????
Pajno 2000	4	12	1	12	50.8%	4.00 [0.52, 30.76]	- 	• ? • • • • •
Yin, 2016	0	78	0	78		Not estimable		
Yukselen 2012	0	10	0	10		Not estimable		@?@@@@@
Total (95% CI)		214		204	100.0%	1.01 [0.07, 15.69]		
Total events	5		5				T	
Heterogeneity: Tau ² =	= 2.77; Chi ² = 3.41, d	f = 1 (P	= 0.06);	$ ^2 = 71$	%	F		
Test for overall effect: Z = 0.01 (P = 0.99)							001 0.1 1 10 10 drops Children Placebo	00
Diels of bing langed								

<u>Risk of bias legend</u> (A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

1.1.2. Important but no critical outcomes

1.1.2.1. Symptom score

	HDM SLIT	drops Chi	ildren	Р	lacebo			Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
Bahceciler 2001	-0.33	0.34	8	-0.15	0.22	7	8.5%	-0.58 [-1.63, 0.46]		??
Hirsch 1997	0.17	0.3	11	0.42	0.58	10	9.8%	-0.53 [-1.40, 0.35]	+	••••••
Ippoliti 2003	1.28	0.77	47	3.15	0.66	39	12.3%	-2.57 [-3.14, -1.99]		?? ? 🗣 ? 🗣 ? ?
Lue 2006	-0.29	0.14	10	0.07	0.23	10	8.3%	-1.81 [-2.89, -0.73]		??????
Ma 2014	0.3	0.31	60	1.06	0.71	60	13.6%	-1.38 [-1.78, -0.98]	-	?? 🗨 🗬 🗣 🗣
Niu 2006	0.04	0.01	49	0.06	0.02	48	13.4%	-1.26 [-1.70, -0.82]		??????
Pajno 2000	2.5	0.14	12	6.6	4.88	9	9.2%	-1.24 [-2.20, -0.28]	_ 	e ? e e e e
Tari 1990	б	1.62	30	9.44	0.96	28	11.2%	-2.53 [-3.23, -1.83]		?? 🗣 ??????
Yin, 2016	0.5	0.2	78	1.5	0.6	78	13.6%	-2.23 [-2.63, -1.82]	-	9 9 9 ? ? ? 9 9 9
Total (95% CI)			305			289	100.0%	-1.62 [-2.09, -1.16]	•	
Heterogeneity: Tau ² =	0.36; Chi ² =	39.15, di	f = 8 (P -	< 0.000	01); l ²	= 80%				
Test for overall effect:	Z = 6.91 (P	< 0.0000	1)					HDM SL	IT drops Children Placebo	

Risk of bias legend

(A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

1.1.2.2. Medication score

	HDM SLIT	drops Ch	ildren	F	Placebo			Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
Bahceciler 2001	2.13	0.83	7	3.14	1.57	7	20.6%	-0.75 [-1.85, 0.35]		220002
Ippoliti 2003	1.41	0.73	47	5.04	0.8	39	21.2%	-4.72 [-5.56, -3.88]	-	? ? 8 ? 8 ? ?
Lue 2006	1	0.94	20	1.1	1.15	39	21.7%	-0.09 [-0.63, 0.45]	+	??
Niu 2006	0.02	0.31	49	0.05	0.27	48	21.9%	-0.10 [-0.50, 0.30]	+	2292999
Pajno 2000	82.6	11.73	12	205.2	17.68	9	14.7%	-8.10 [-10.95, -5.25]		••••
Total (95% CI)			135			142	100.0%	-2.39 [-4.28, -0.50]	•	
Heterogeneity: Tau ² =	4.21; Chi ² :	= 127.65,	df = 4 (P	< 0.00	001); l ²	= 97%			-10 -5 0 5 10	
Test for overall effect:	Z = 2.47 (P	= 0.01)						HDM S	LIT drops Children Placebo	

<u>Risk of bias legend</u> (A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(D) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)

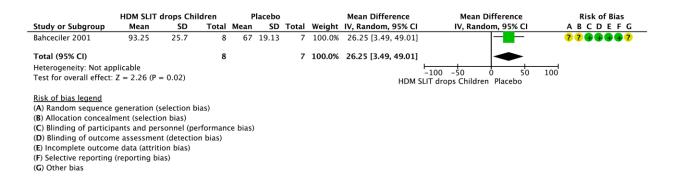
(F) Selective reporting (reporting bias)

(G) Other bias

1.1.2.3. Quality of Life

We found no evidence

1.1.2.4. Lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75



1.1.2.5. Lung function: Allergen specific bronchial provocation (ASBP)

We found no evidence

HDM SLIT drops Child		Children	Place	bo		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	ABCDEFG
Bahceciler 2001	0	8	0	7		Not estimable		??
Hirsch 1997	5	14	1	15	40.9%	5.36 [0.71, 40.37]	+ -	••••
Ippoliti 2003	0	47	0	49		Not estimable		?? +? +??
Pajno 2000	2	12	0	12	23.5%	5.00 [0.27, 94.34]		
Yin, 2016	0	78	0	78		Not estimable		
Yukselen 2012	1	10	2	10	35.6%	0.50 [0.05, 4.67]		@? @@@@@
Total (95% CI)		169		171	100.0%	2.27 [0.46, 11.10]	-	
Total events	8		3				_	
Heterogeneity: Tau ² =	= 0.55; Chi ² $= 2.75$.	df = 2 (P	= 0.25);	$ ^2 = 27$	%	F		
Test for overall effect	Z = 1.01 (P = 0.31))	.,			*1	.001 0.1 1 10 10 drops Children Placebo	00'

1.1.2.6. Safety (local reactions)

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

1.2. EVIDENCE PROFILE

Author(s): Juan J. Yepes-Nuñez Date: October 2018 Question: HDM SLIT drops compared to no HDM SLIT drops for treatment in paediatric patients with asthma Setting: Outpatients

			Certainty a	ssessment			Nº of pa	atients	Effec	t		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HDM SLIT drops	no HDM SLIT drops	Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
Asthma exa	cerbations - not r	eported					•					•
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Asthma control - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Corticostero	Corticosteroid use (inhaled steroids) assessed as score or rescue medications in number of puffs per day (follow up: 6 months)											
2	randomised trials	not serious	not serious	not serious ^a	very serious ^b	none	57	55	-	SMD 0.13 lower (0.75 lower to 0.49 higher)		CRITICAL
Corticosteroid use (oral steroids) assessed as rescue medications in number of tablets per day (follow up: 6 months)												
1	randomised trials	not serious	not serious	not serious	very serious ^b	none	49	48	-	MD 0.01 SD lower (0.1 lower to 0.08 higher)		CRITICAL
Systemic ad	lverse events - as	ssessed as number	of patients with at	least one reaction (follow up: from 6 m	onths to 2 years)	II					ł
6	randomised trials	not serious	serious °	not serious ª	serious ^d	none	5/206 (2.4%)	5/197 (2.5%)	RR 1.01 (0.07 to 15.69)	0 fewer per 1,000 (from 24 fewer to 373 more)		CRITICAL
Symptom sc	cores (follow up: f	rom 6 months to 2	years)	· · · · · · · · · · · · · · · · · · ·			II					ł
9	randomised trials	not serious °	serious ^f	not serious ª	not serious	none	305	289	-	SMD 1.62 lower (2.09 lower to 1.16 lower)		IMPORTANT
Medication s	scores (follow up	from 6 months to 2	2 years)				II			I		L

			Certainty a	ssessment			№ of p	atients	Effect	t		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HDM SLIT drops	no HDM SLIT drops	Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
5	randomised trials	not serious 9	serious ^h	not serious *	serious ⁱ	none	135	142	-	SMD 2.39 lower (4.28 lower to 0.5 lower)		IMPORTANT
Asthma QoL	Asthma QoL - not reported											
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Lung functio	Lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75 (follow up: 6 months)											
1	randomised trials	not serious	not serious	not serious i	very serious ^b	none	8	7	-	MD 26.25 higher (3.49 higher to 49.01 higher)		IMPORTANT
Lung functio	on: Allergen spec	ific bronchial provo	cation tests (ABPT)	assess as PD20 FE	EV1 to allergen cha	illenge - not reported						
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Local adver	se events (follow	up: from 6 months	to 2 years)	·								
5	randomised trials	not serious	not serious	not serious a	very serious ^k	none	8/161 (5.0%)	3/164 (1.8%)	RR 2.27 (0.46 to 11.10)	23 more per 1,000 (from 10 fewer to 185 more)		IMPORTANT

CI: Confidence interval; OR: Odds ratio; RR: Risk ratio; SMD: Standardised mean difference; MD: Mean difference

Explanations

a. Patients across studies received different HDM SCIT extracts. Allergen extracts are different between each AIT company and batch.

b. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, and no optimal information criterion met.

c. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square 0.06; I-square 71%)

d. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm.

e. One out of nine studies did not report random sequence generation, and another study did not report blinding of participants and blinding of outcome assessment.

f. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.00001; I-square 80%)

g. One out of five studies did not report random sequence generation

h. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.00001; I-square 97%)

i. No optimal information size met

j. The study used a surrogate outcome to assess HDM SCIT efficacy.

k. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 11 events in total. No optimal information size criterion met.

References

- 1. Pajno GB, Morabito L, Barberio G, Parmiani S. Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled study. Allergy. 2000;55(9):842-9.
- 2. Hirsch T, Sahn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. Pediatr Allergy Immunol. 1997;8(1):21-7.
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- 6. Ippoliti F, De Santis W, Volterrani A, Lenti L, Canitano N, Lucarelli S, et al. Immunomodulation during sublingual therapy in allergic children. Pediatr Allergy Immunol. 2003;14(3):216-21.
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- 10. Yin G, Jiang WH, Wu PQ, He CH, Chen RS, Deng L. Clinical evaluation of sublingual administration of dust mite drops in the treatment of allergic asthma and allergic rhinitis of children. Eur Rev for Med and Pharmaco Sci. 2016;20:4348-53.

1.3. SOF TABLE

Summary of findings:

HDM SLIT drops compared to no HDM SLIT drops for treatment in paediatric patients with asthma

Patient or population: paediatric patients with asthma Setting: Outpatients Intervention: HDM SLIT drops Comparison: no HDM SLIT drops

Outcomes	Anticipated absolute e	ffects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence	Comments
	Risk with no HDM SLIT drops	Risk with HDM SLIT drops			(GRADE)	
Asthma exacerbations - not reported	-	-	-	-	-	
Asthma control - not reported	-	-	-	-	-	
Corticosteroid use (inhaled steroids) assessed as score or rescue medications in number of puffs per day (follow up: 6 months)	-	-	-	112 (2 RCTs)	⊕⊕ ⊖⊖ LOW ab	

Summary of findings:

HDM SLIT drops compared to no HDM SLIT drops for treatment in paediatric patients with asthma

Patient or population: paediatric patients with asthma Setting: Outpatients Intervention: HDM SLIT drops Comparison: no HDM SLIT drops

Outcomes	Anticipated absolute ef	fects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence	Comments
	Risk with no HDM SLIT drops	Risk with HDM SLIT drops			(GRADE)	
Corticosteroid use (oral steroids) assessed as rescue medications in number of tablets per day (follow up: 6 months)	The mean corticosteroid use (oral steroids) assessed as rescue medications in number of tablets per day (follow up: 6 months) was 0 SD	The mean corticosteroid use (oral steroids) assessed as rescue medications in number of tablets per day (follow up: 6 months) in the intervention group was 0.01 SD lower (0.1 lower to 0.08 higher)	-	97 (1 RCT)		
Systemic adverse events - assessed as number of patients with at least one reaction (follow up: from 6 months to 2 years)	25 per 1,000	26 per 1,000 (2 to 398)	RR 1.01 (0.07 to 15.69)	403 (6 RCTs)	₩ LOW ac,d	
Symptom scores (follow up: from 6 months to 2 years)	-	-	-	594 (9 RCTs)	MODERATE a,e,f	
Medication scores (follow up: from 6 months to 2 years)	-	-	-	277 (5 RCTs)	H H O LOW a.g.h.i	
Asthma QoL - not reported	-	see_comment	-	-	-	

Summary of findings:

HDM SLIT drops compared to no HDM SLIT drops for treatment in paediatric patients with asthma

Patient or population: paediatric patients with asthma Setting: Outpatients Intervention: HDM SLIT drops Comparison: no HDM SLIT drops

Outcomes	Anticipated absolute e	i fects * (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence	Comments
	Risk with no HDM SLIT drops	Risk with HDM SLIT drops			(GRADE)	
Lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75 (follow up: 6 months)	The mean lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75 (follow up: 6 months) was 0	The mean lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75 (follow up: 6 months) in the intervention group was 26.25 higher (3.49 higher to 49.01 higher)	-	15 (1 RCT)	⊕⊕ ⊖⊖ LOW ^{b,j}	
Lung function: Allergen specific bronchial provocation tests (ABPT) assess as PD20 FEV1 to allergen challenge - not reported	-	see_comment	-	-	-	
Local adverse events (follow up: from 6 months to 2 years)	18 per 1,000	42 per 1,000 (8 to 203)	RR 2.27 (0.46 to 11.10)	325 (5 RCTs)	€ LOW a.k	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio; RR: Risk ratio; SMD: Standardised mean difference; MD: Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

- a. Patients across studies received different HDM SCIT extracts. Allergen extracts are different between each AIT company and batch.
- b. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, and no optimal information criterion met.
- c. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square 0.06; I-square 71%)
- d. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm.
- e. One out of nine studies did not report random sequence generation, and another study did not report blinding of participants and blinding of outcome assessment.
- f. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.00001; I-square 80%)
- g. One out of five studies did not report random sequence generation
- h. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.00001; I-square 97%)
- i. No optimal information size met
- j. The study used a surrogate outcome to assess HDM SCIT efficacy.
- k. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 11 events in total. No optimal information size criterion met.