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

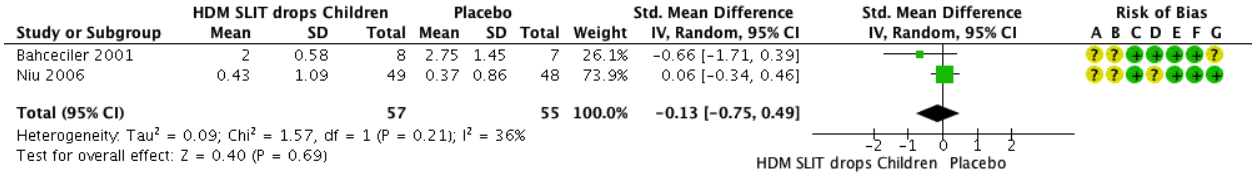
1.1.1.1. Asthma exacerbations

We found no evidence

1.1.1.2. Asthma control

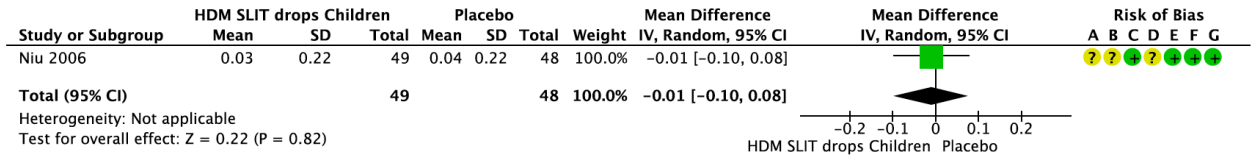
We found no evidence

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



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

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



Risk of bias legend
(**A**) Random sequence generation (selection bias)
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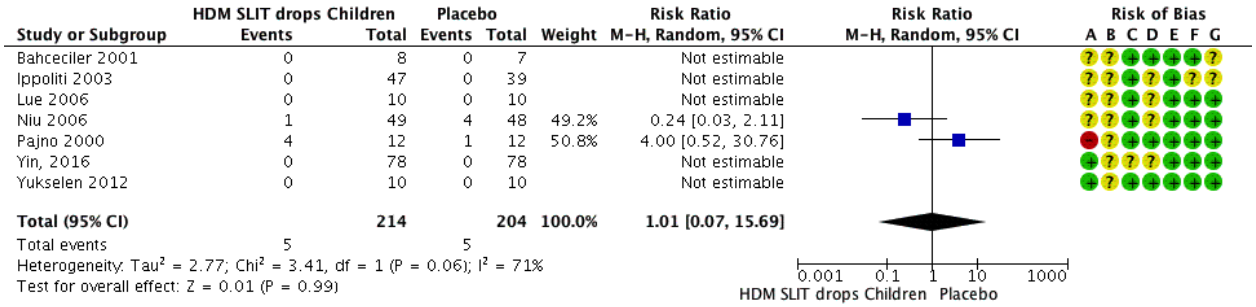
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

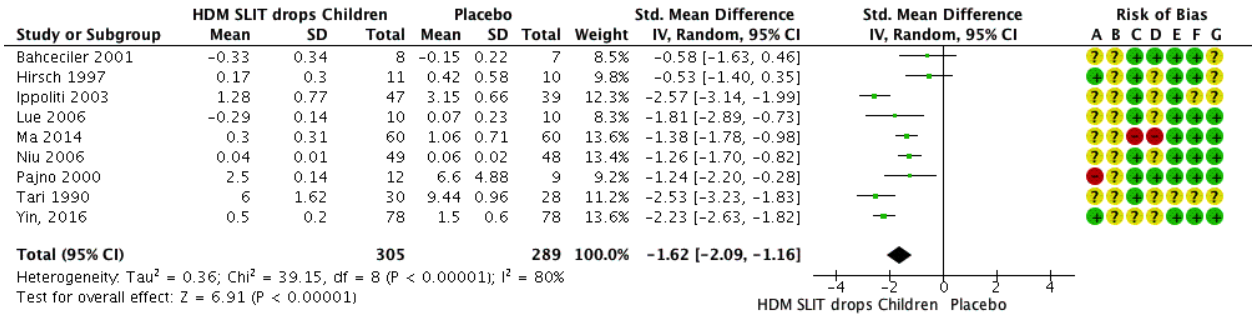
1.1.1.3. Safety (systemic reactions) – assessed as number of patients with at least one reaction



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

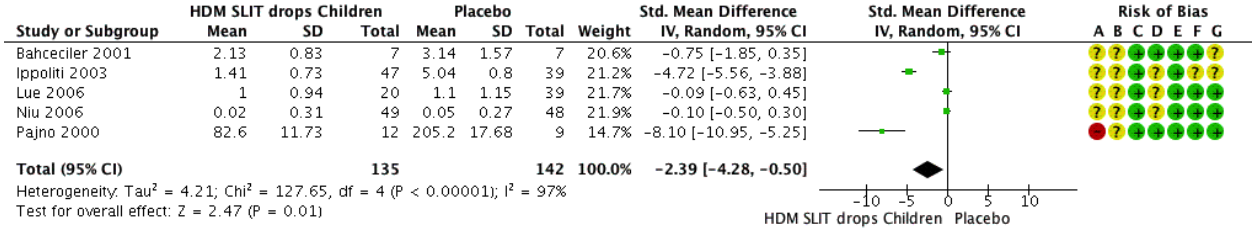
1.1.2. Important but no critical outcomes

1.1.2.1. Symptom score



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

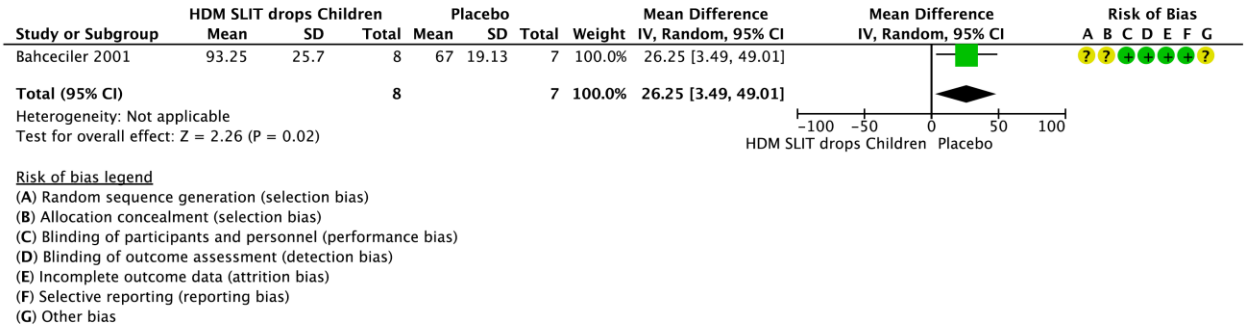


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

1.1.2.3. Quality of Life

We found no evidence

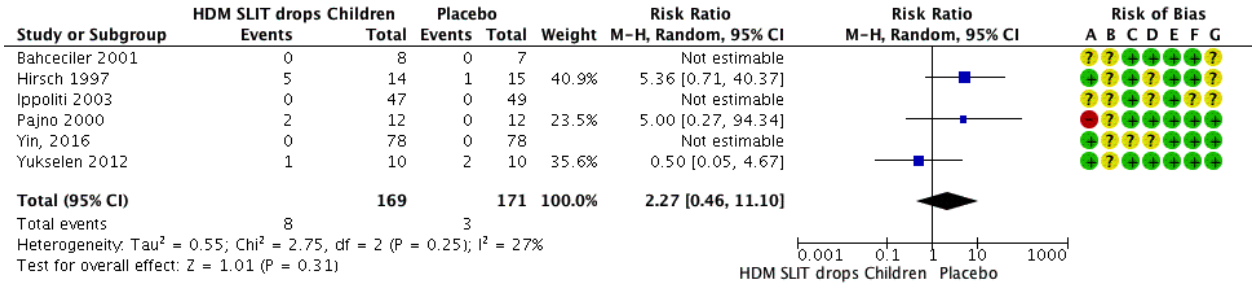
1.1.2.4. Lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75



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

We found no evidence

1.1.2.6. Safety (local reactions)



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 assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HDM SLIT drops**	**no HDM SLIT drops**	**Relative (95% CI)**	**Absolute (95% CI)**		
Asthma exacerbations - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Asthma control - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
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)	⨁⨁◯◯ LOW	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)	⨁⨁◯◯ LOW	CRITICAL
Systemic adverse events - assessed as number of patients with at least one reaction (follow up: from 6 months to 2 years)												
6	randomised trials	not serious	serious [c]	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)	⨁⨁◯◯ LOW	CRITICAL
Symptom scores (follow up: from 6 months to 2 years)												
9	randomised trials	not serious [e]	serious [f]	not serious [a]	not serious	none	305	289	-	SMD **1.62 lower** (2.09 lower to 1.16 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Medication scores (follow up: from 6 months to 2 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HDM SLIT drops	no HDM SLIT drops	Relative (95% CI)	Absolute (95% CI)		
5	randomised trials	not serious [g]	serious [h]	not serious [a]	serious [i]	none	135	142	-	SMD **2.39 lower** (4.28 lower to 0.5 lower)	⨁⨁◯◯ LOW	IMPORTANT
Asthma QoL - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
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 [j]	very serious [b]	none	8	7	-	MD **26.25 higher** (3.49 higher to 49.01 higher)	⨁⨁◯◯ LOW	IMPORTANT
Lung function: Allergen specific bronchial provocation tests (ABPT) assess as PD20 FEV1 to allergen challenge - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Local adverse 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)	⨁⨁◯◯ LOW	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.
3. Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study. Allergol Immunopathol (Madr). 1990;18(5):277-84.
4. Bahceciler NN, Isik U, Barlan IB, Basaran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. Pediatr Pulmonol. 2001;32(1):49-55.
5. Niu CK, Chen WY, Huang JL, Lue KH, Wang JY. Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: a multi-center, double-blind, randomized, and placebo-controlled study in Taiwan. Respir Med. 2006;100(8):1374-83.
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.
7. Lue KH, Lin YH, Sun HL, Lu KH, Hsieh JC, Chou MC. Clinical and immunologic effects of sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, randomized, placebo-controlled study. Pediatr Allergy Immunol. 2006;17(6):408-15.
8. Yukselen A, Kendirli SG, Yilmaz M, Altintas DU, Karakoc GB. Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study. Int Arch Allergy Immunol. 2012;157(3):288-98.
9. MA Cai-xia LM-f, GE Li-ping, QIAN Xi-min, ZHANG Ming-zhi3. Clinical evaluation of sublingual allergen specific immunotherapy in treatment to children with bronchial asthma and allergic rhinitis. Journal of Shanghai Dao Tong University Medical Science. 2014;34(6):873.
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 effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no HDM SLIT drops	**Risk with HDM SLIT drops**				
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 [a,b]	

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 effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no HDM SLIT drops	**Risk with HDM SLIT drops**				
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)	⨁⨁◯◯ LOW [b]	
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 [a,c,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)	⨁⨁◯◯ 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 effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no HDM SLIT drops	**Risk with HDM SLIT drops**				
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%)
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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.