Do helminth parasites help or hinder allergic disease?

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MRC & Asthma UK Centre in Allergic Mechanisms of Asthma

MRC Medical Research Council
King's College London
Imperial College London
asthma

Industrialised countries

- 20% asthma
- 20% eczema
- 30% allergic rhinitis

Developing countries

- less allergy
- rural-urban gradient

- big cities similar prevalence levels to industrialised countries

Risk factor analysis

- “western lifestyle”
- search for individual risk factors continues

A letter in *The Lancet* in 1976

- ...I infected myself with 250 hookworm larvae of Nigerian origin to examine the haematological responses to the parasite....

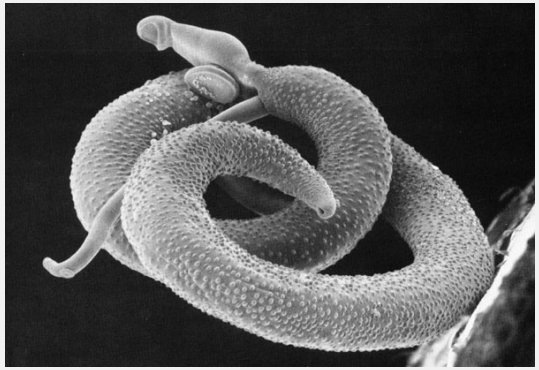
- ...The most pertinent finding in the context of the discussion on IgE, parasites and allergy was that during the summer of 1975 and 1976 I remained completely free from all symptoms of hayfever.

JA Turton

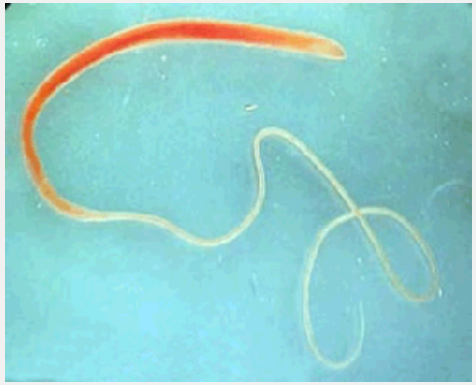
HELMINTHS

Hookworm

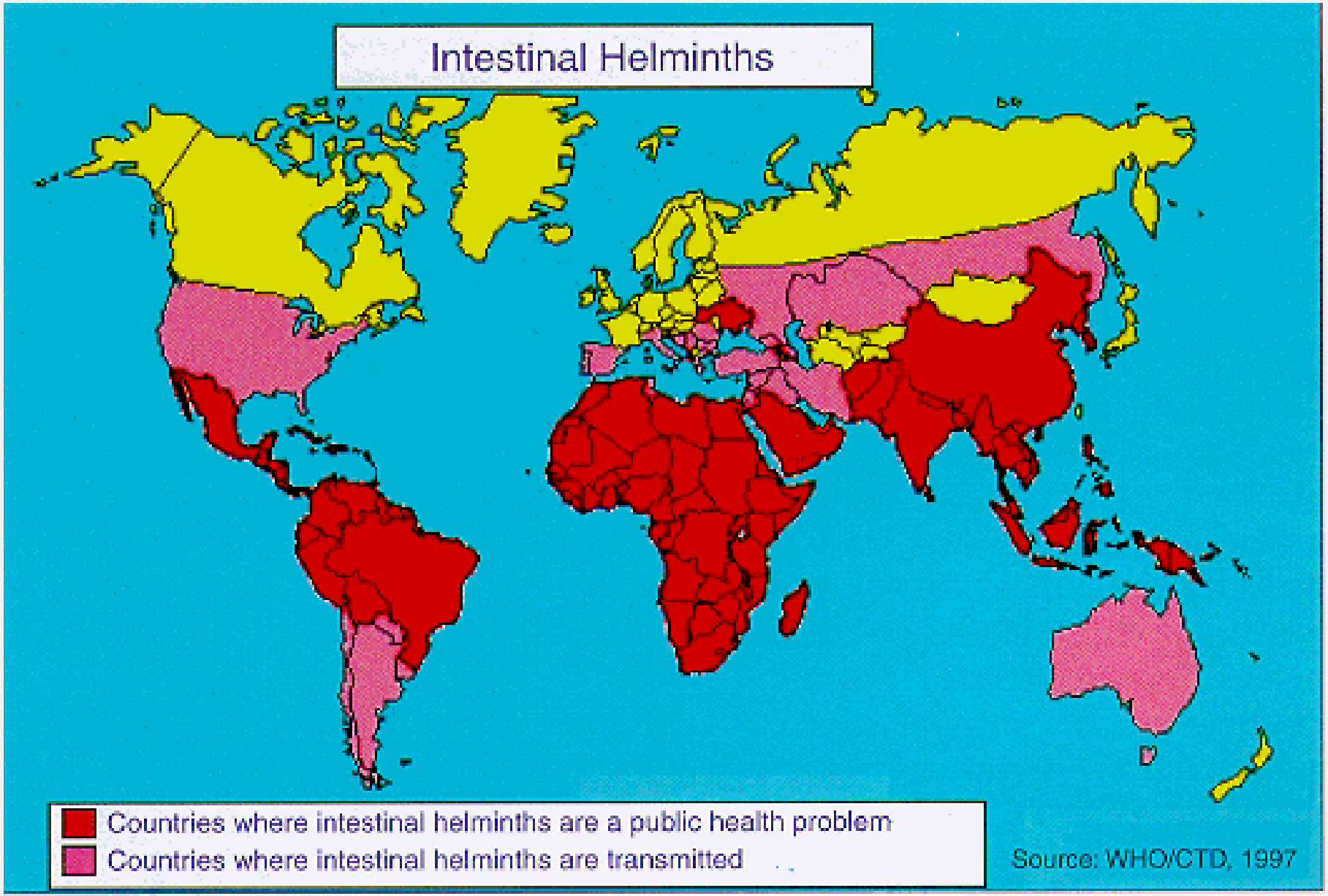
Ascaris lumbricoides

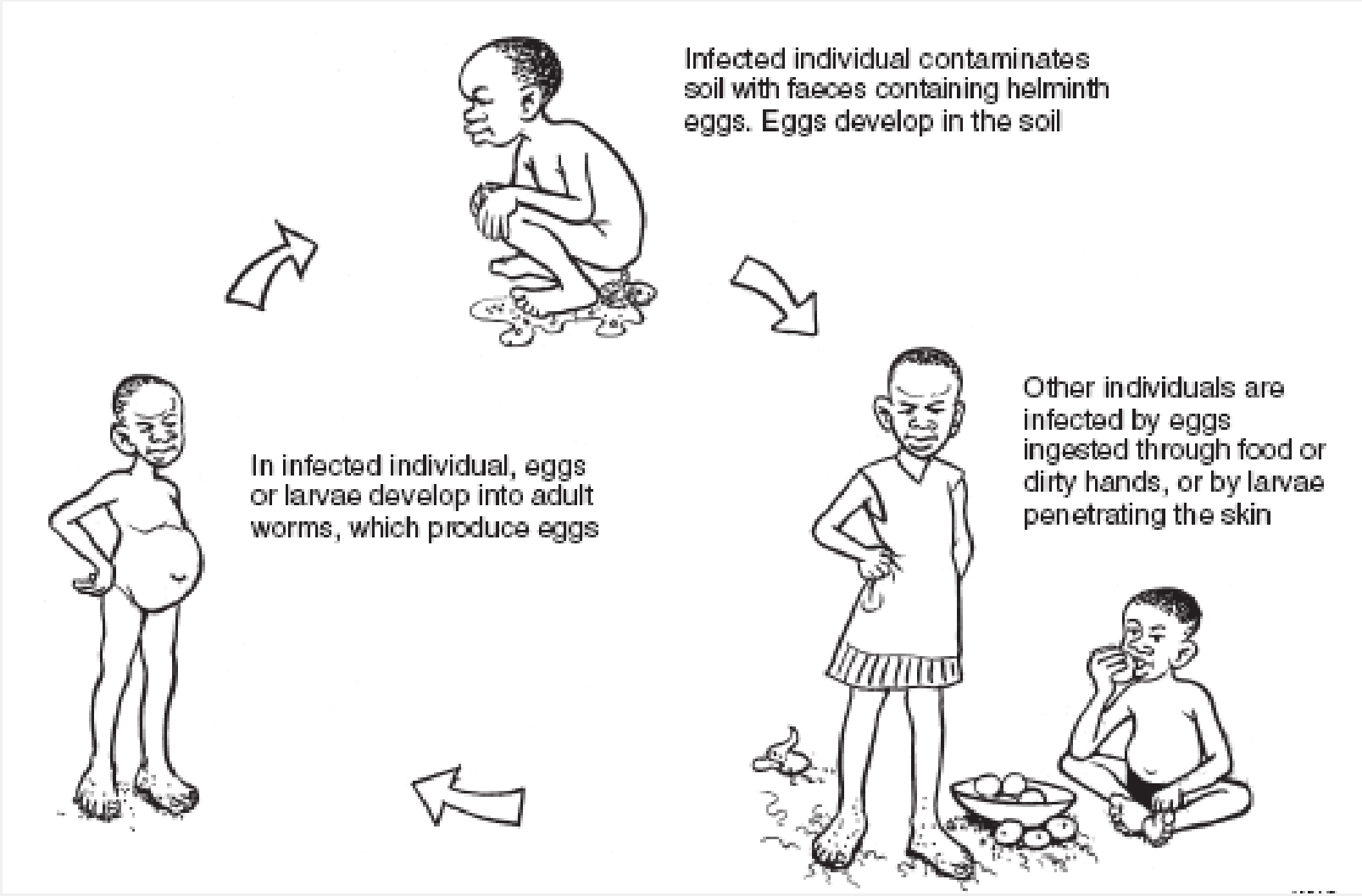


Schistosomiasis



Trichuris trichiura

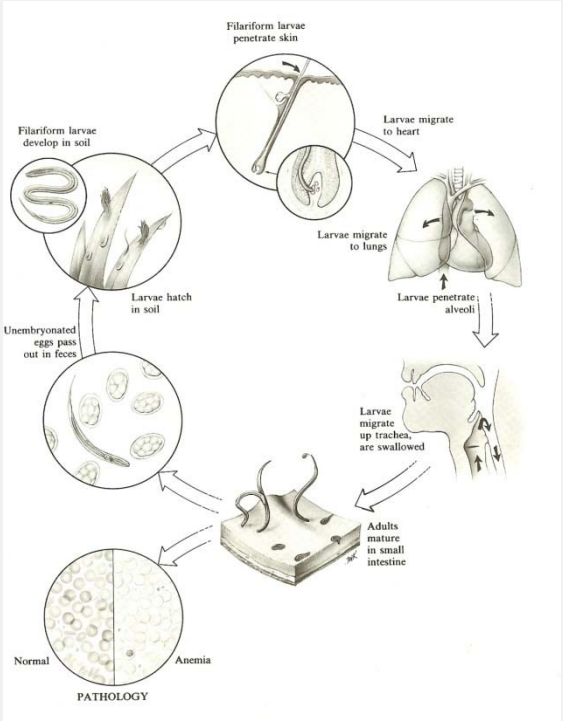




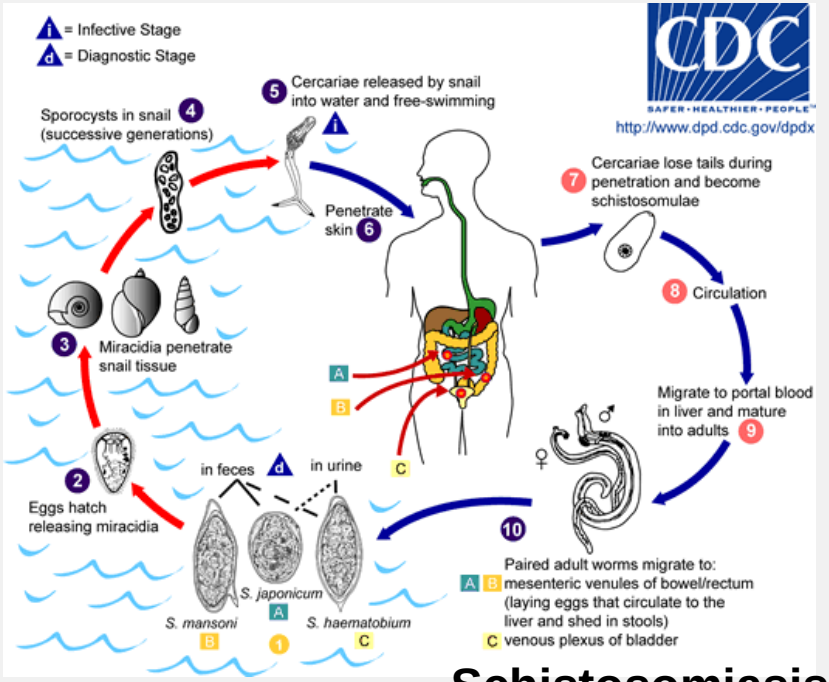
Poor hygiene – main cause of helminth infection

Helminth infections

- Host invasive (not Trichuris)
- Often asymptomatic
- Long-lasting
  - ➢ Immuno-modulation



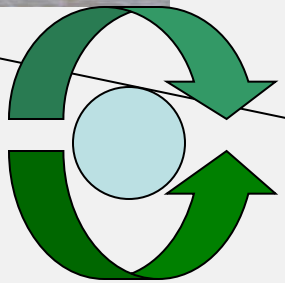
Hookworm/Ascaris lifecycle



Schistosomiasis

A matter of balance ?

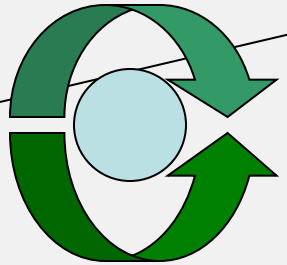
Helminths↑



Allergies↓

A matter of balance ?

Helminths↓



Allergies ↑

Menu

- **Observational evidence**
  - Allergic sensitisation (atopy)
    - Clinical allergy
- **Mechanisms**
- **Intervention studies**

Helminths and allergic sensitisation

Helminths and atopy

Type of helminth infection	Number of participants	Age	Odds ratio (95% CI)	Effect direction
ANY HELMINTH				
Cooper et al., Ecuador, 2003a [38]	4433	5-18	0.62 (0.50-0.76)	↓
Cooper et al., Ecuador, 2003b [101]	2865	5-19	0.64 (0.52-0.78)	↓
Cooper et al., , 2004 [27]	1002	7-17	0.65 (0.47-0.91)	↓
Davey et al., , 2005 [102]	7649	5-70+	0.75 (0.58-0.97)	↓
Flohr et al., , 2006 [60]	1742	6-18	0.70 (0.50-0.99)	↓
Nyan et al., The , 2001 [103]	429	15-34	0.30 (0.11-0.80)	↓
HOOKWORM				
Cooper et al., Ecuador, 2003a [38]	4433	5-18	0.67 (0.33-1.37)	**NS**
Cooper et al., Ecuador, 2003b [101]	2865	5-19	0.39 (0.18-0.85)	↓
Dagoye et al., , 2003 [24]	7155	1-4	1.20 (0.70-1.70) Dp 1.30 (0.80-2.20) Cock	**NS** **NS**
Davey et al., , 2005 [102]	7649	5-70+	0.74 (0.55-0.99)	↓
Flohr et al., , 2006 [60]	1742	6-18	0.61 (0.39-0.96)	↓
Grove & Frobes, 1975 [84]	50 atopics 139 non-atopics	All ages	0.24 (0.11-0.51)	↓
Scrivener et al., , 2001 [86]	403	14-60+	1.70 (0.88-3.27)	**NS**
ASCARIS				
Cooper et al., Ecuador, 2003a [38]	4433	5-18	0.65 (0.54-0.78)	↓
Cooper et al., Ecuador, 2003b [101]	2865	5-19	0.74 (0.60-0.91)	↓
Dagoye et al., , 2003 [24]	7155	1-4	1.10 (0.70-2.00) Dp 1.00 (0.70-1.40) Cock	**NS**
Flohr et al., , 2006 [60]	1742	6-18	0.28 (0.10-0.78)	↓
Obihara et al., , 2006 [28]	359	6-14	0.57 (0.23-1.40)	**NS**
Palmer et al., , 2002 [23]	1896	8-18	Increased no of pos SPTs	↑
Scrivener et al., , 2001[86]	403	14-60+	1.52 (0.81-2.87)	**NS**
TRICHURIS				
Cooper et al., Ecuador, 2003a [38]	4433	5-18	0.69 (0.56-0.86)	↓
Cooper et al., Ecuador, 2003b [101]	2865	5-19	0.82 (0.67-1.01)	**NS**
Dagoye et al., , 2003 [24]	7155	1-4	1.40 (0.90-2.20) Dp 1.70 (1.10-2.40) Cock	**NS** ↑
Scrivener et al., , 2001[86]	403	14-60+	1.10 (0.56-2.16)	**NS**
SCHISTOSOMIASIS				
Araujo et al., , 2000 [104]	42 cases 133 controls	6-40	0.14 (0.03-0.63)	↓
van den Biggelaar et al., Gabon, 2000 [105]	520	5-14	0.32 (0.16-0.63)	↓

Flohr *et al*., 2009

Effect of early helminth infection on atopy in later childhood

Trichuris infection 1055 Brazilian children		**OR (95% CI)**
First survey (1mth-4yr)	**Second survey (4-11yr)**	
No or light intensity	No or light intensity	1
No or light intensity	High intensity	0.75 (0.39-1.43)
High intensity	No or light intensity	**0.36 (0.14-0.97)**
High intensity	**High intensity**	**0.18 (0.04-0.78)**

Rodrigues *et al.*, 2009

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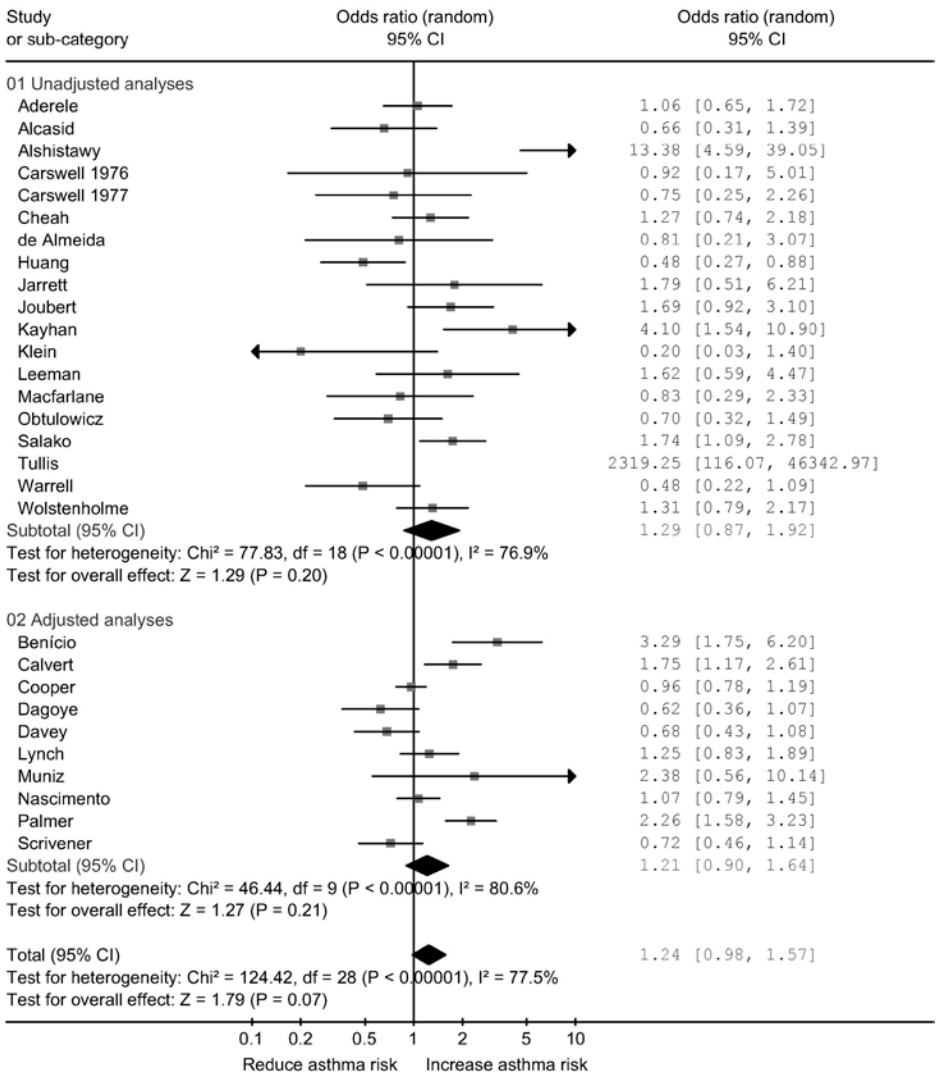
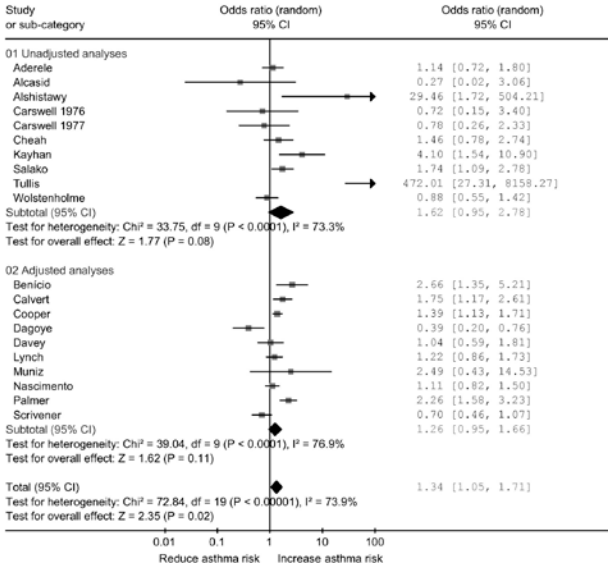
Helminths and asthma – Xsectional

Any helminth



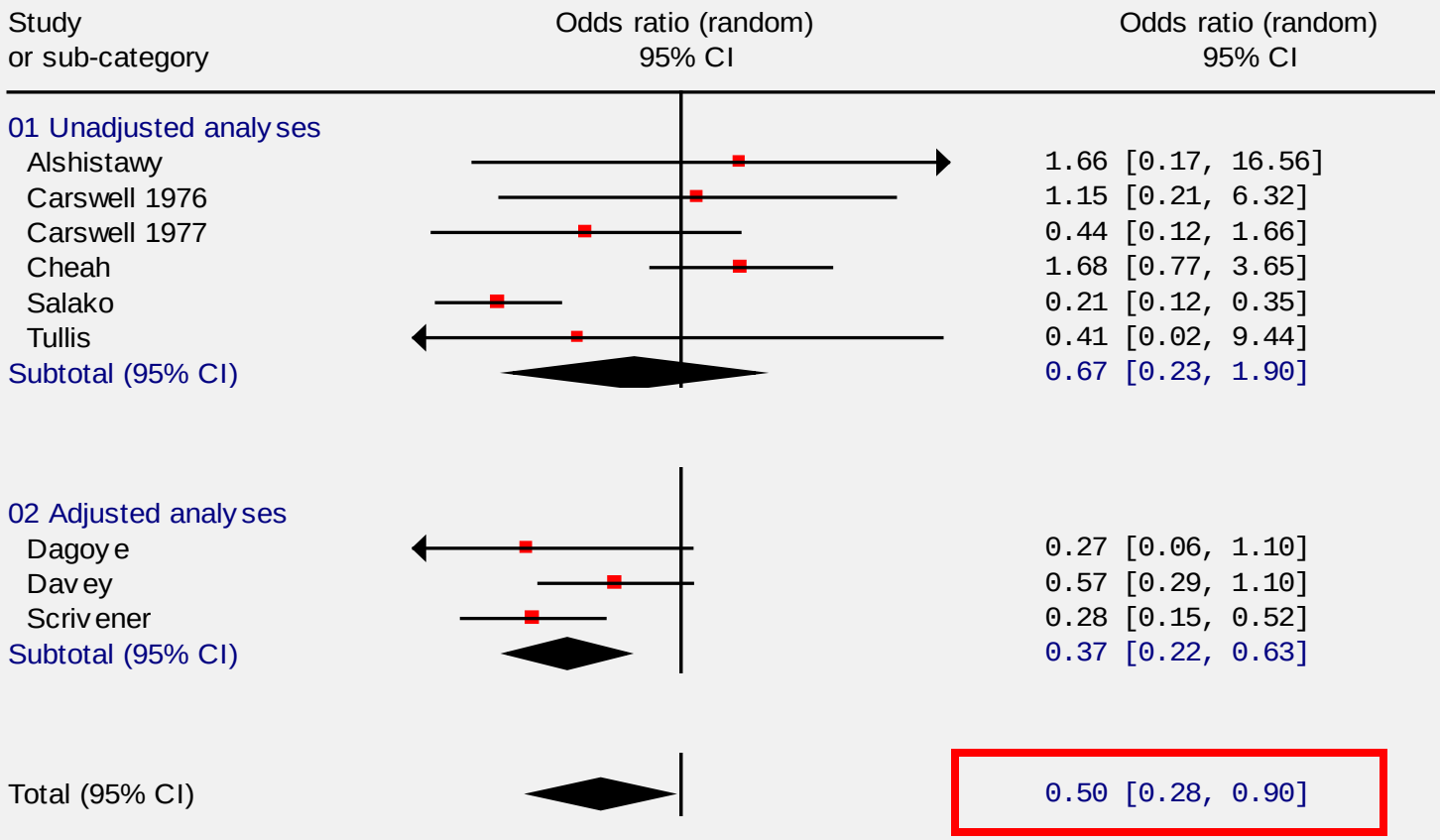
Ascaris & Trichuris



Systematic review

Leonardi-Bee *et al*. 2006

Hookworm and asthma – Xsectional



Infection intensity related
OR=0.34, 95% CI 0.19-0.62

Leonardi-Bee *et al*. 2006

Helminths and eczema

- East Germany
- ISAAC questionnaire
- n=4169, age 5-14

➢ Ascaris infection↑
Eczema↓

➢ adjusted OR=0.31 (0.18-0.56)

- Other studies no effect
- Little work on hay fever

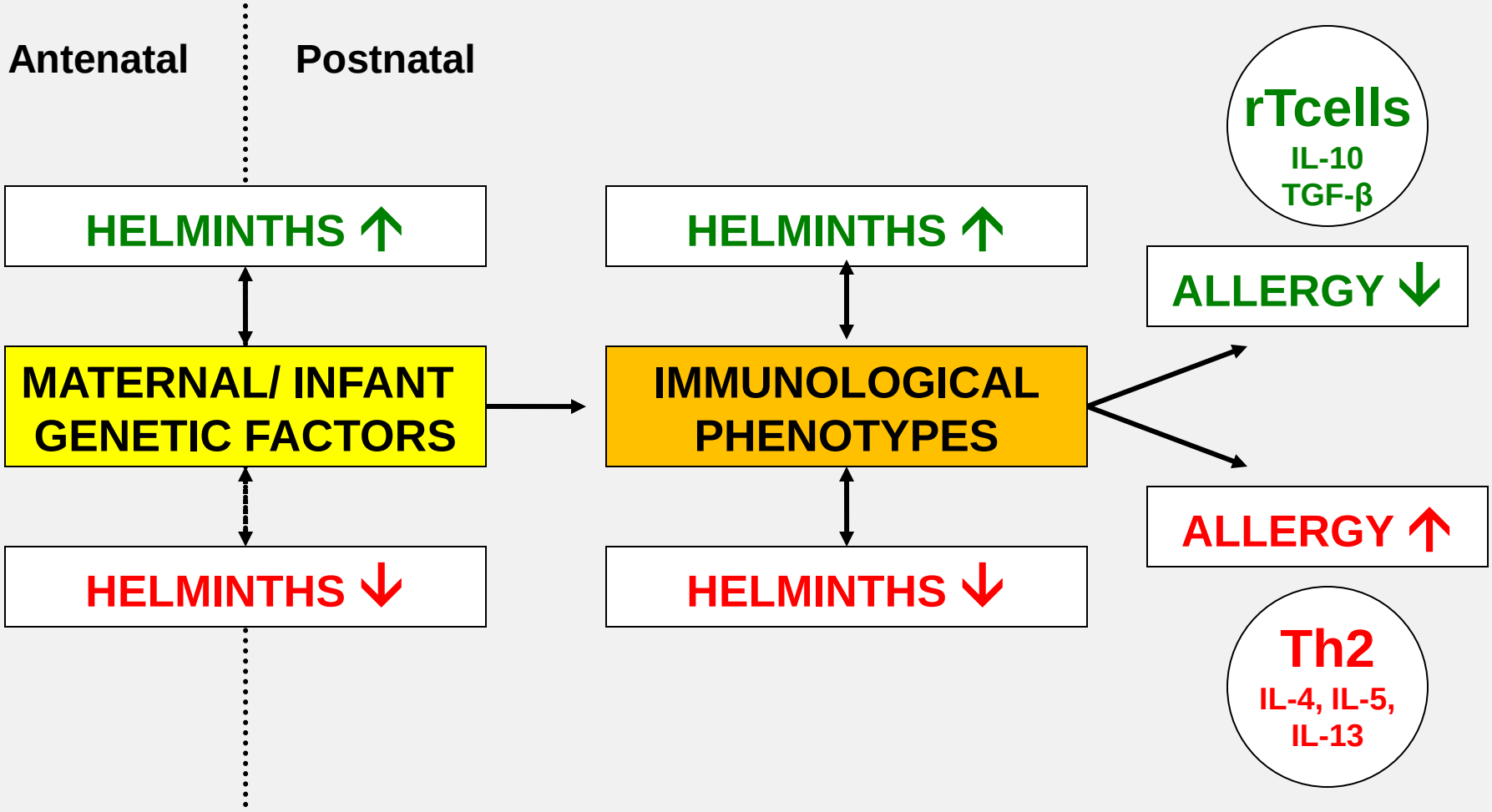
Schäfer *et al*., 2005

Summary - Cross-sectional studies

- Helminth↑ atopy↓
- Hookworm↑ wheeze↓
- Ascaris/Trichuris↑ wheeze↑
- Ascaris↑ eczema↓
- Early/heavy helminth infection
- Species matters (host invasiveness)

➢ Study heterogeneity (species, age etc)

Need for birth cohort studies



Flohr *et al*., 2009

Helminths & eczema – Birth cohort

- Uganda, n=103
- Hookworm & schistosomiasis

➢ Maternal helminth infection pregnancy↑
→Infantile eczema↓

➢ 74% eczema↓ by 15 months in infants
➢ Adjusted OR=0.26 (0.08-0.83)

Elliott *et al*., 2005

Menu

- **Observational evidence**
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Löffler Syndrome

ACUTE

hypersensitivity reaction

–

+

IL-4, IL-5, IL-13 ↑

IgE ↑ and Eosinophilia

+

T cell apoptosis

Prevention of mast cell degranulation

+

Anti-inflammatory cytokines↑

+

–

CHRONIC

Atopy & Allergic disease

Menu

- **Observational evidence**
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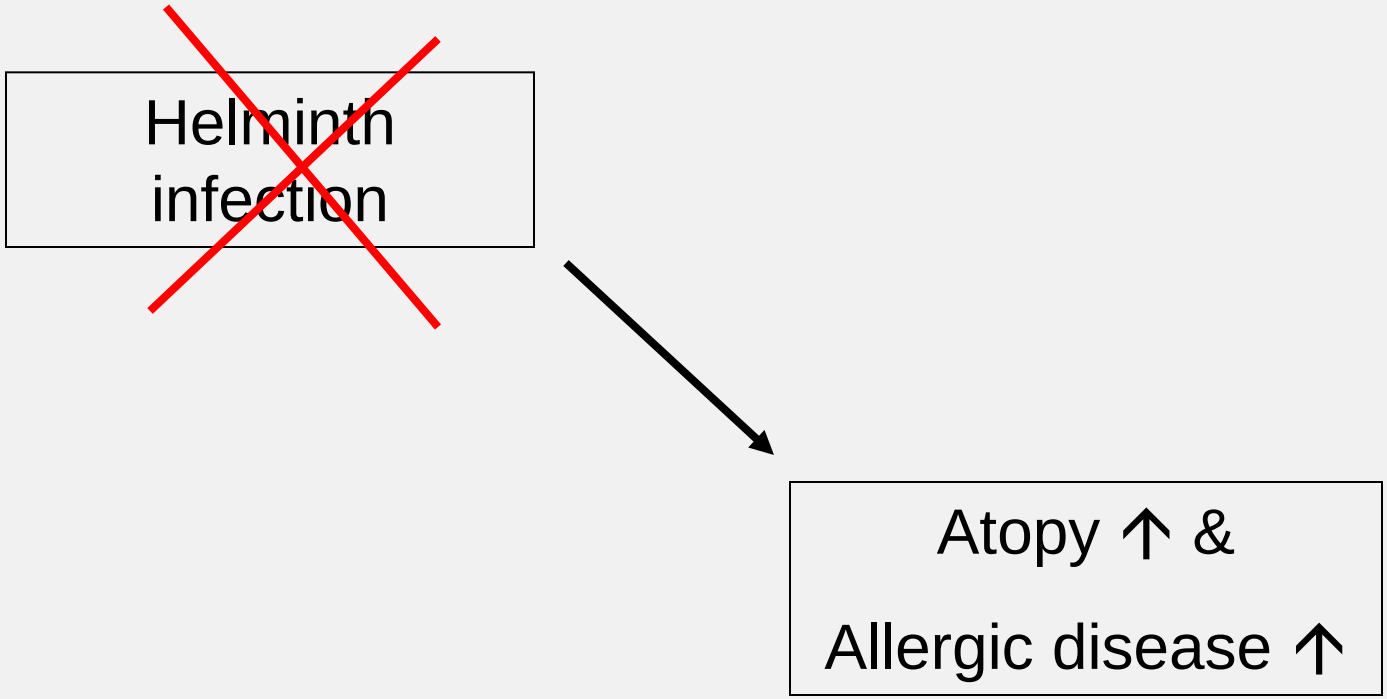
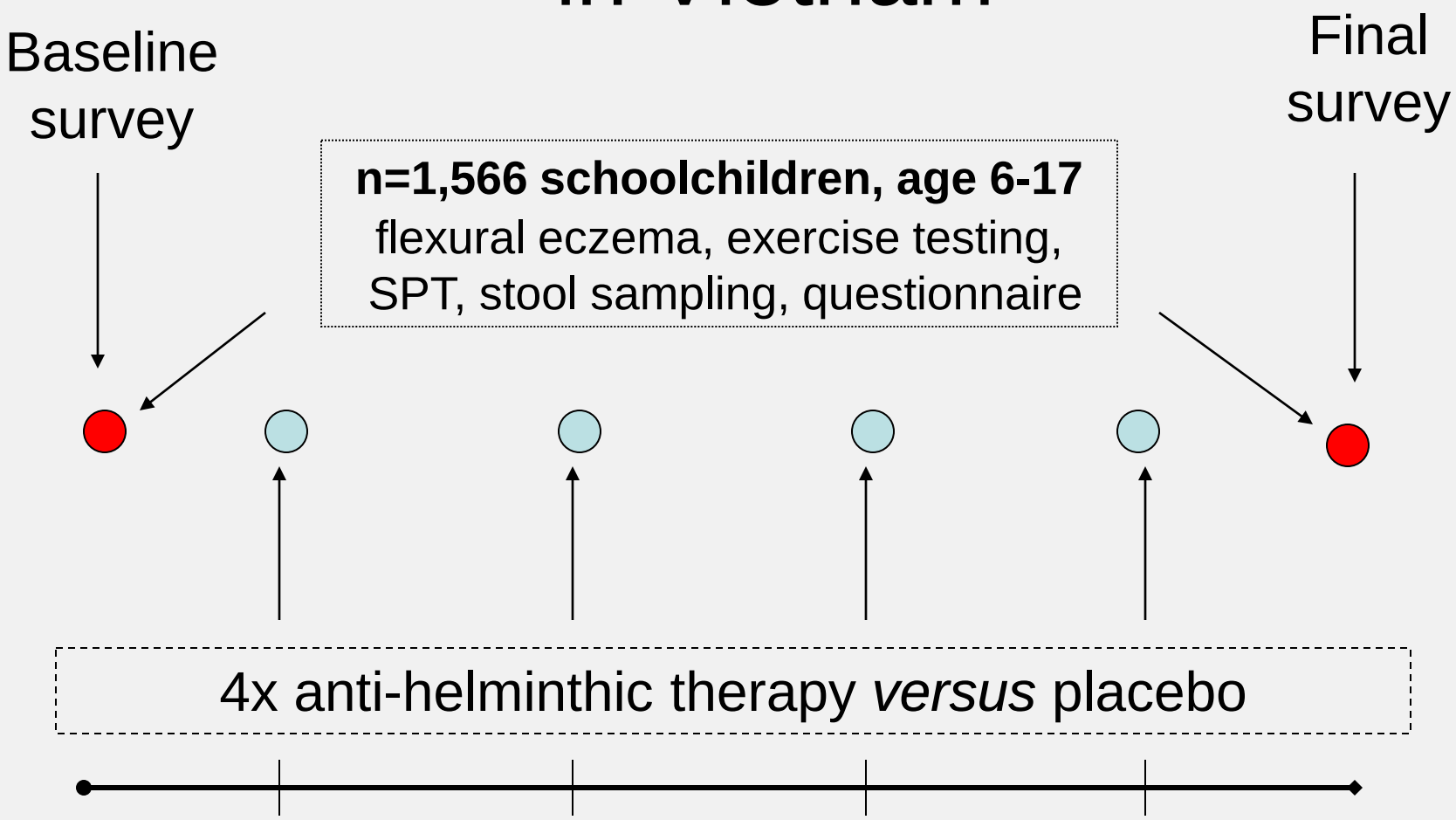
- **Mechanisms**
- **Intervention studies**
  - **Helminth-endemic areas**

Vietnam Study - Hypothesis



RCT in hookworm-endemic area in Vietnam



Hookworm 70%, Ascaris 6%, dual infected 5%

Flohr *et al*., 2010

Results Vietnam RCT

- No change in clinical allergy

BUT

- 37% SPT positivity ↑

OR = 1.37 (1.03 – 1.82), p=0.02

Flohr *et al*., 2010

Results Vietnam RCT

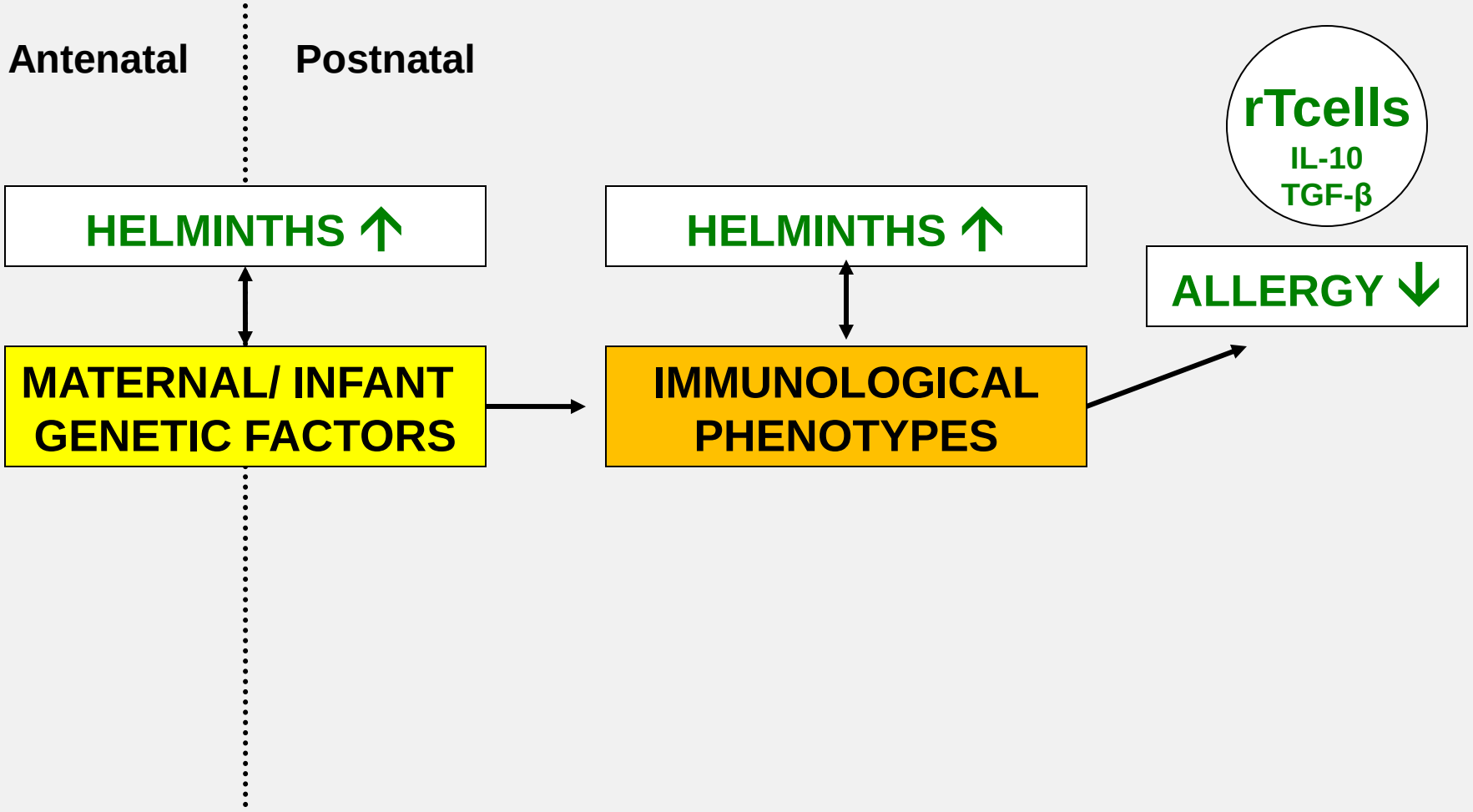
- Effect strongest for children with **dual helminth infection**

- OR=4.90 (1.48-16.19), p=0.009

➢ Synergistic effect of two helminth species

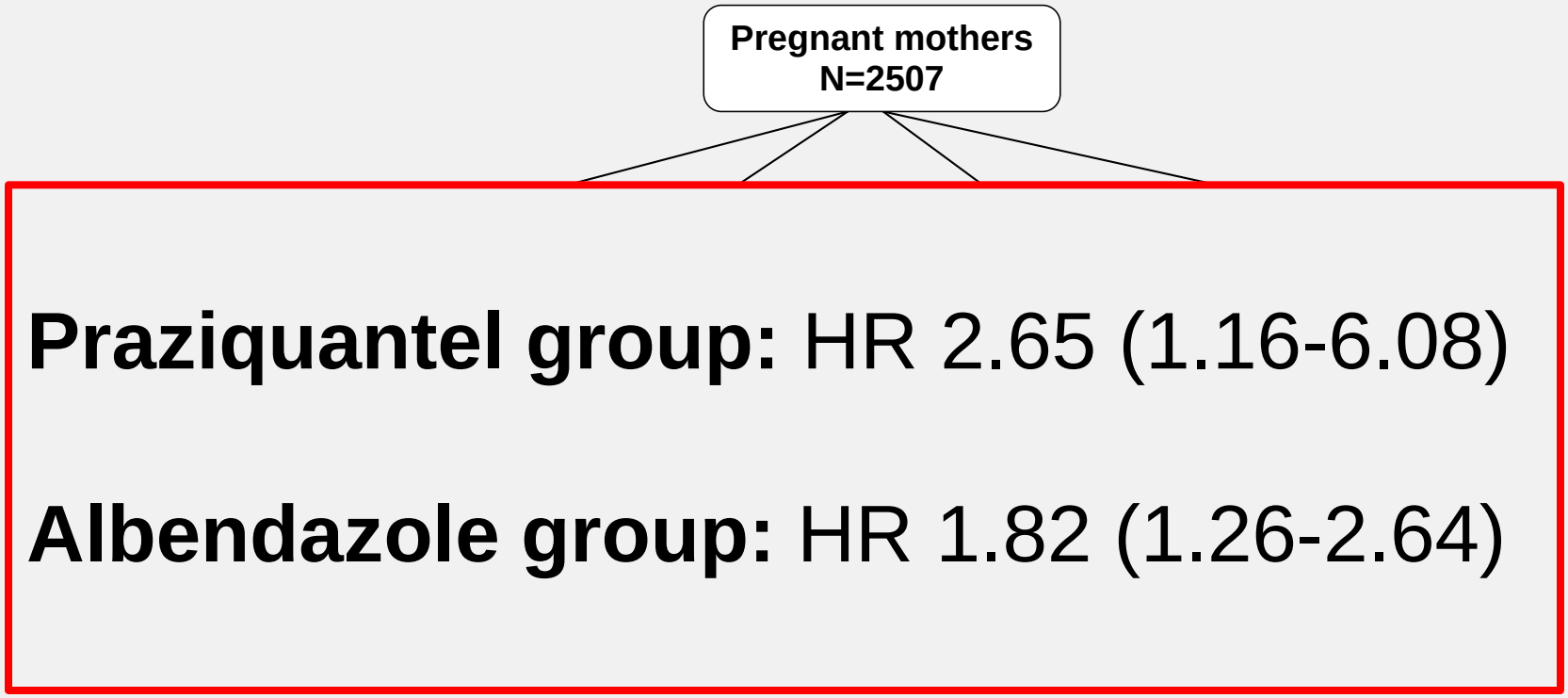
Flohr *et al*., 2010

Need for interventional birth cohort studies



Flohr *et al*., 2009

Ugandan RCT
pregnant mothers & babies



Hookworm >40%
***Schistosoma mansoni* ~20%**

Mpairwe & Elliott 2010

Summary
Intervention Studies

- Helminth↑ atopy and eczema↓
- Synergistic effect of parasite species

Menu

- **Observational evidence**
  - Allergic sensitisation (atopy)
  - Clinical allergy
- **Mechanisms**
- **Intervention studies**
  - **Helminth-naïve allergic individuals**

Intervention studies in helminth-naïve individuals

1. **Nottingham hookworm trials**
- **Dose-ranging study**
- **Hay fever**
- **Asthma**

2. Danish *Trichuris suis* trials in hay fever (modelled on ulcerative colitis trials)

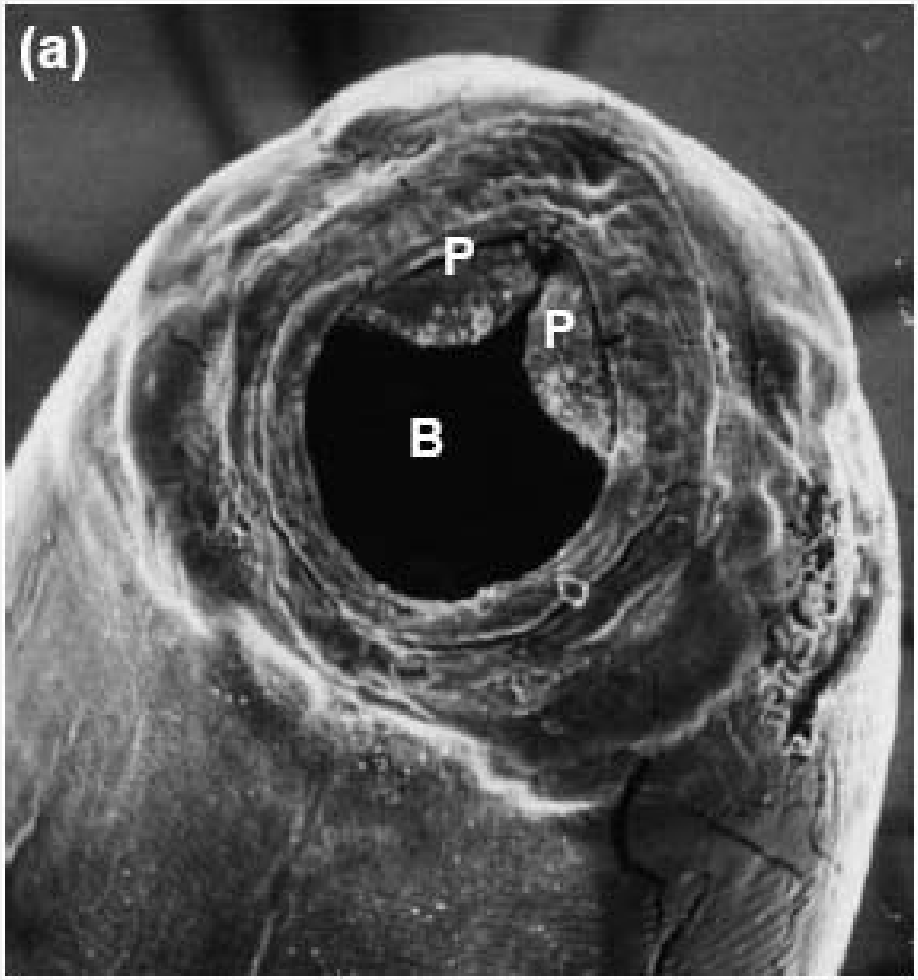
- **Immunological response**
- **No effect on allergic disease or atopy**
- **No trial in eczema sufferers yet**

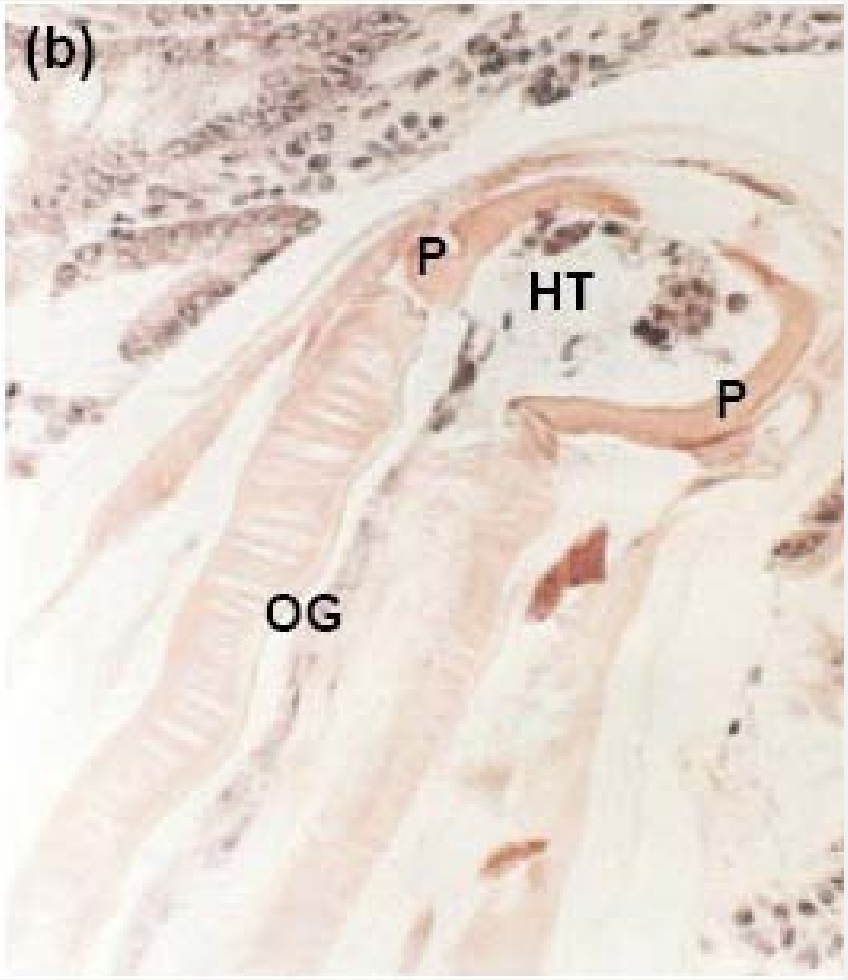
Limitations of intervention studies

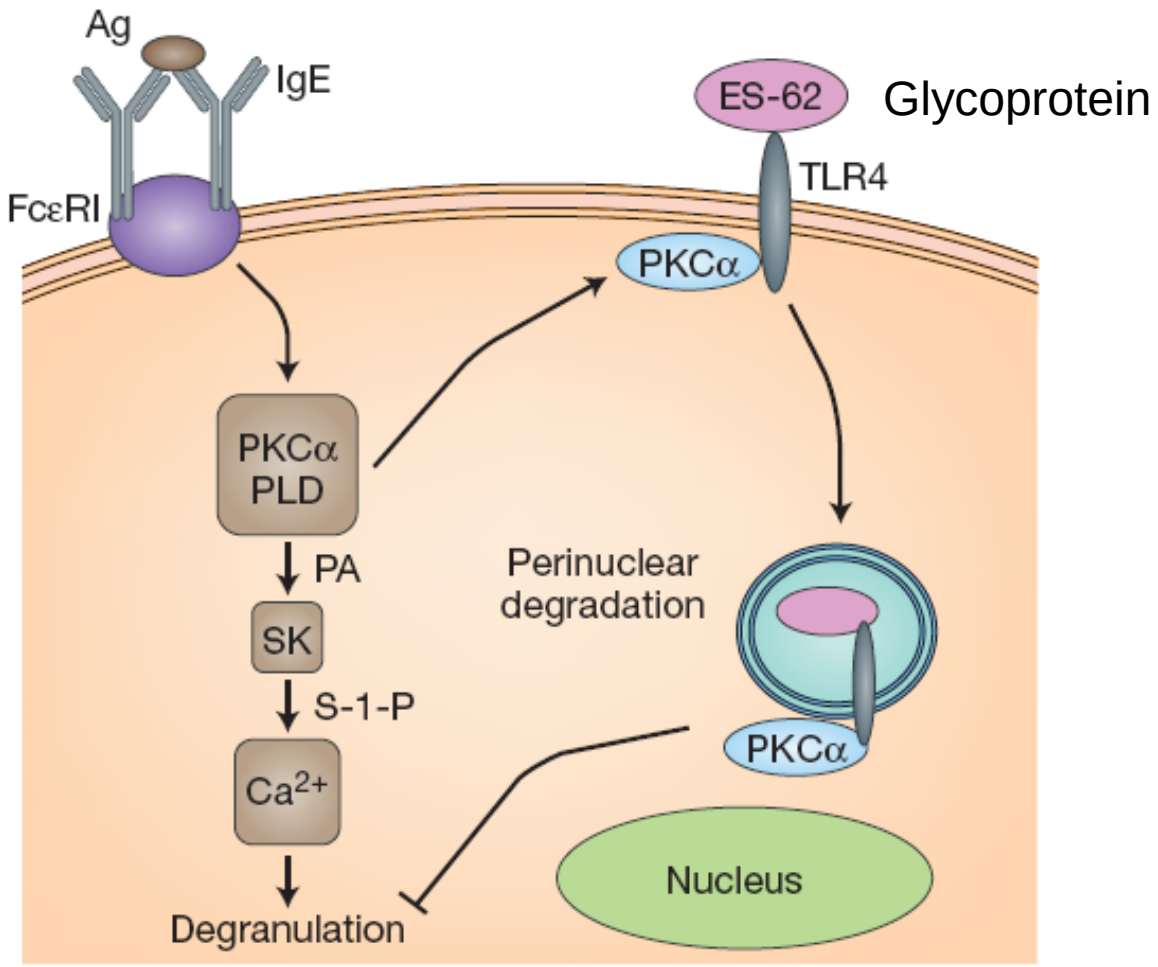
- Parasite-naïve
- Single exposure
- Low infection intensity

- Early priming
- Recurrent exposure
- High infection intensity

Ultimate aim: allergy drugs from worms







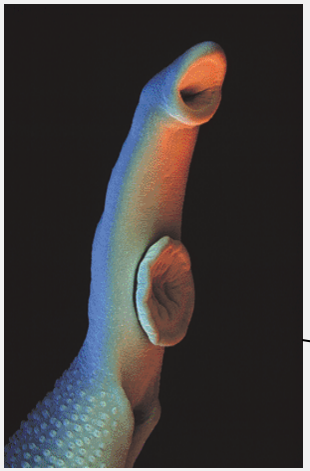
Filarial nematode-derived ES-62 induces hyporesponsiveness of mast cells by disrupting FcεRI signalling

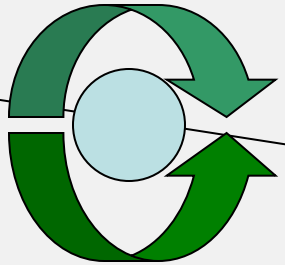
Nature, Harnett et al. 2008

Future therapy?

Immuno-
modulatory
network

reg T cell
activity





Gut worm-derived products

Bon appétit !