Systematic Review of Non-Specific Immunological Effects of Vaccination

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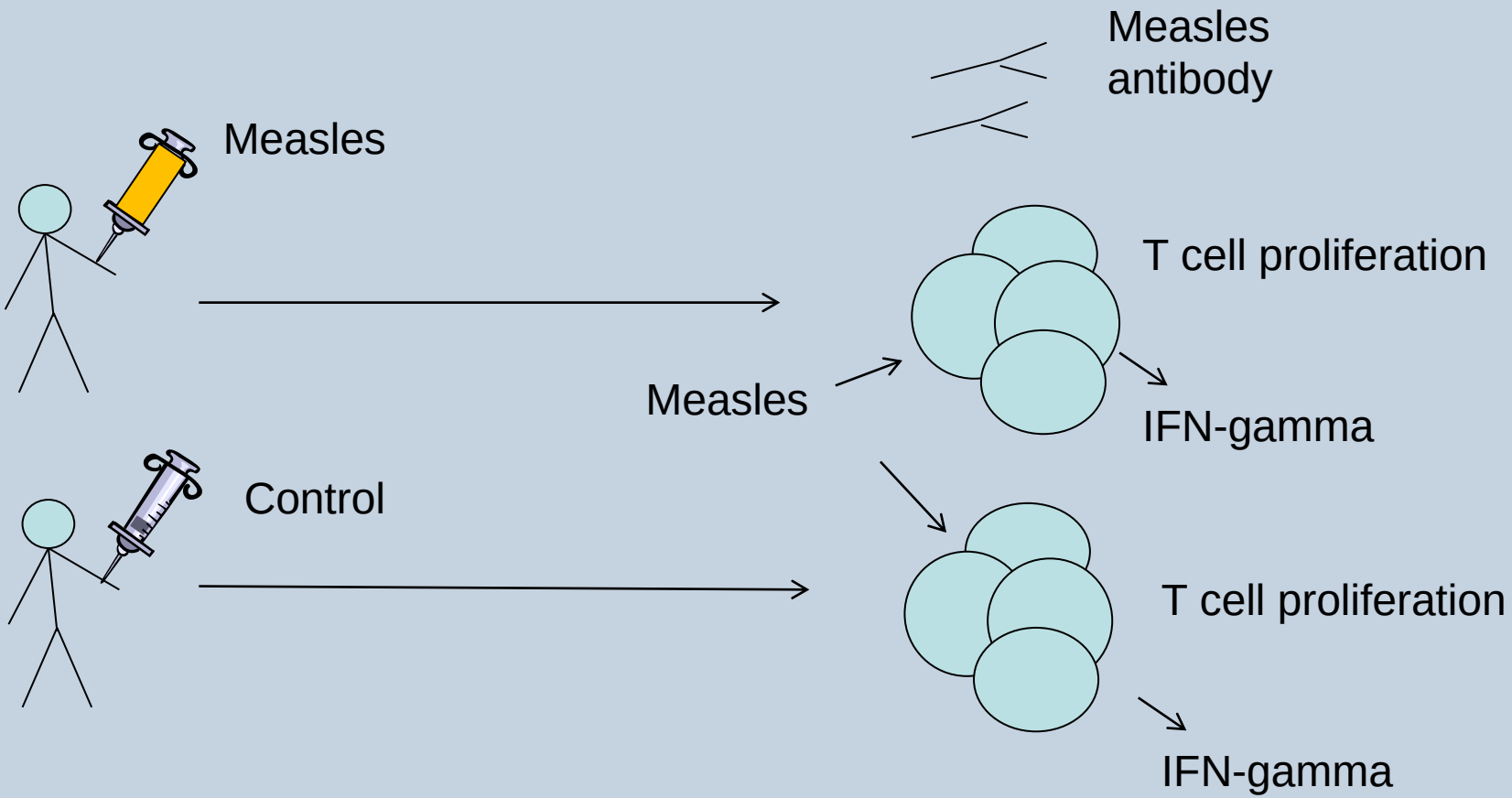
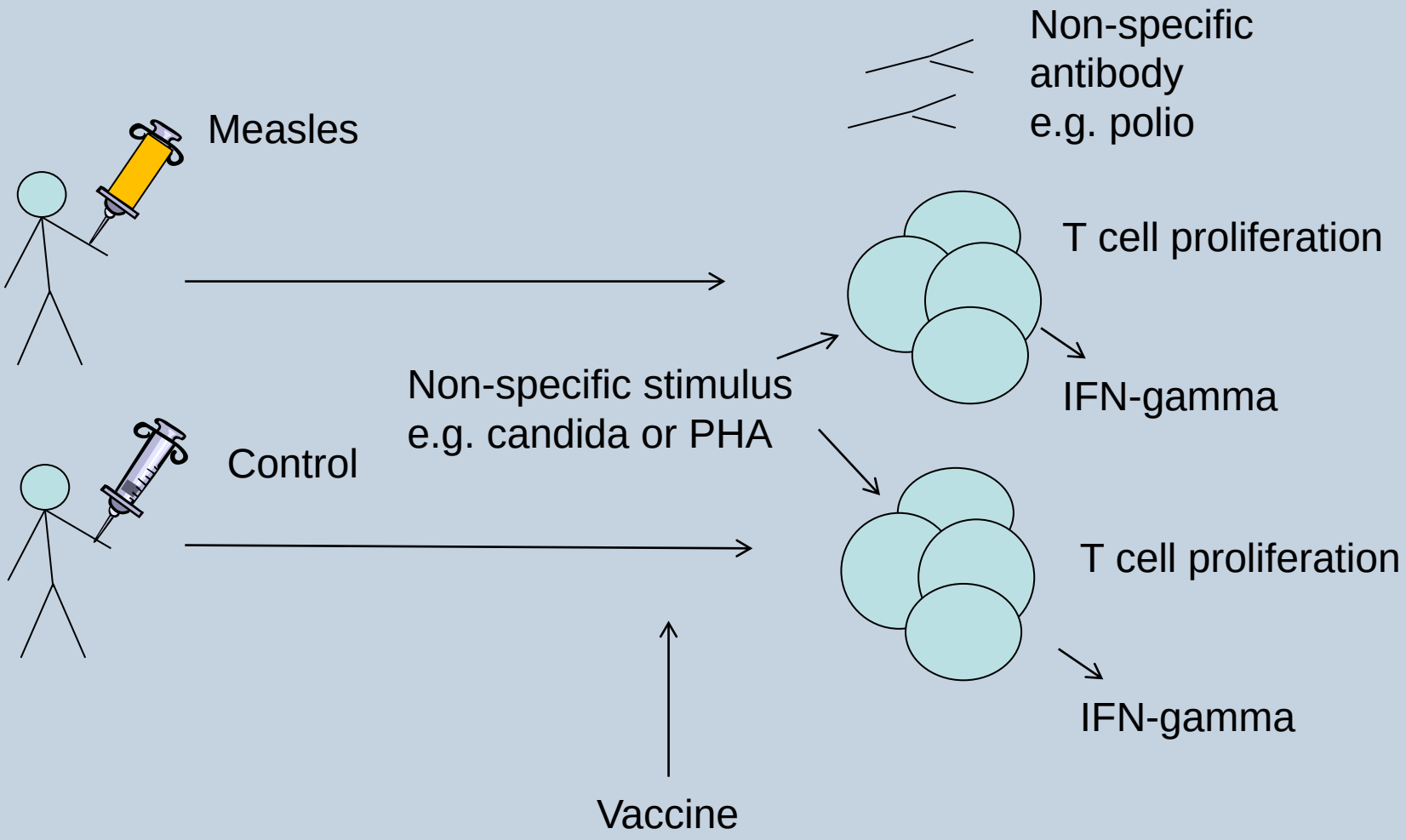
Immunology

- Non-specific effects of the immune system (innate immune system)
  - Infectious disease, inflammation, adjuvants, vaccines – e.g. BCG, combination vaccines, animal data, microbiome, nutrition, environmental factors, genetics and epigenetics
- Biological plausibility
  - Infections, removal of infections by vaccines, vaccines, vaccine adjuvants
- Live vs killed
  - Systemic effects of a replicating live vaccine
  - Local effects of inactivated vaccines
  - Adjuvants enhance effects of inactivated vaccine and easier to detect systemically

Specific effects



Non-Specific effects



Systematic review

- All available evidence (published and unpublished)
  - RCTs
  - quasi-randomized control trials
  - clinical trials
  - cohort studies
  - case-control studies
  - case series and case reports
- Vaccines
  - BCG
  - measles
  - diphtheria
  - tetanus
  - pertussis
- Target population
  - infants under five years of age
  - not limited to this age group
- Record
  - sex
  - age at vaccination
  - co-administration of vitamin A
- Exclusions
  - Specific responses
  - Animal, ecological and in vitro studies
  - Studies reporting recombinant vaccines or no vaccine

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Overview

- 77 studies
- 3-2345 of total study participants involved across the studies.
- 48% of studies utilised BCG
- 68% were exclusively conducted in a paediatric population.
- 32% were RCTs
- 28% from Europe, 25% from Africa
- The final time-point of outcome measurement was primarily performed (70%) between one and 12 months after vaccination

Study Author	Vaccine	Random sequence generation	Allocation concealment	Blinding, All outcomes	Incomplete outcome data, All outcomes	Selective reporting	Other bias	Overall
Akkoc *et al* 2010	BCG	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk		Unclear
Anderson *et al* 2013	BCG	High risk	High risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High
Black *et al* 2001	BCG	Low risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk	High
Black *et al* 2002	BCG	Low risk	Low risk	Low risk	Low risk	Unclear risk		Unclear
Burl *et al* 2010	BCG	Low risk	Low risk	Unclear risk	Low risk	Low risk		Unclear
Burl *et al* (Aug.)	BCG	Low risk	Low risk	Unclear risk	Low risk	Unclear risk		Unclear
Djuardi *et al* 2010	BCG	High risk	High risk	Unclear risk	Unclear risk	Unclear risk		High
Elliot *et al* 2011	BCG	High risk	High risk	Unclear risk	High risk	Low risk	High risk	High
Faustman *et al* 2012	BCG	Low risk	Low risk	Low risk	Low risk	Unclear risk		Unclear
Fjallbrant *et al* 2007	BCG	Unclear risk	High risk	High risk	Low risk	Unclear risk		High
Gruber *et al* 2000	BCG	Unclear risk	High risk	Unclear risk	High risk	Low risk		High
Hoft *et al* 1998	BCG	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk		Unclear
Hoft *et al* 1999	BCG	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk		Unclear
Hussey *et al* 2002	BCG	High risk	High risk	Unclear risk	Unclear risk	Unclear risk		High
Kagina *et al* 2009)	BCG	Low risk	Low risk	Unclear risk	Low risk	Unclear risk		Unclear
Kleinnijenhuis *et al* 2012	BCG	High risk	High risk	Unclear risk	Low risk	Low risk		High
Lalor *et al* 2009	BCG	High risk	High risk	Unclear risk	Unclear risk	Unclear risk	High risk	High
Lalor *et al* 2010	BCG	High risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	High
Lalor *et al* 2011	BCG	High risk	High risk	Unclear risk	Unclear risk	Low risk	High risk	High
Libraty *et al* 2014	BCG	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk		Unclear
Lowry *et al* 1998	BCG	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk	High
Marchant *et al* 1999	BCG	Low risk	Low risk	Unclear risk	High risk	Unclear risk		High
Marks *et al* 2003	BCG	High risk	High risk	High risk	Unclear risk	Low risk		High
Miles *et al* 2008	BCG	High risk	Unclear risk	Unclear risk	High risk	High risk	High risk	High
Miles *et al* 2009	BCG	High risk	High risk	Unclear risk	Unclear risk	Unclear risk	High risk	High
Ota *et al* 2002	BCG	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk		Unclear
Smith *et al* 2012	BCG	High risk	Unclear risk	Unclear risk	Low risk	Low risk		High
Soares *et al* 2013	BCG	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk		Unclear
Steenhuis *et al* 2007	BCG	High risk	Unclear risk	Low risk	Low risk	Unclear risk	High risk	High
Tastan *et al* 2005	BCG	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear
van den Biggelaar *et al* 2009	BCG	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk		Unclear
Vargas *et al* 2004	BCG	Low risk	Unclear risk	Unclear risk	Low risk	Low risk		Unclear
Vekemans *et al* 2004	BCG	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk		Unclear
Vijaya Lakshmi V, *et al* 2005	BCG	High risk	High risk	High risk	Unclear risk	Unclear risk	High risk	High
Weir *et al* 2004	BCG	Low risk	Low risk	Low risk	Low risk	Unclear risk		Unclear
Weir *et al* 2008	BCG	Low risk	High risk	Unclear risk	Unclear risk	Unclear risk		High

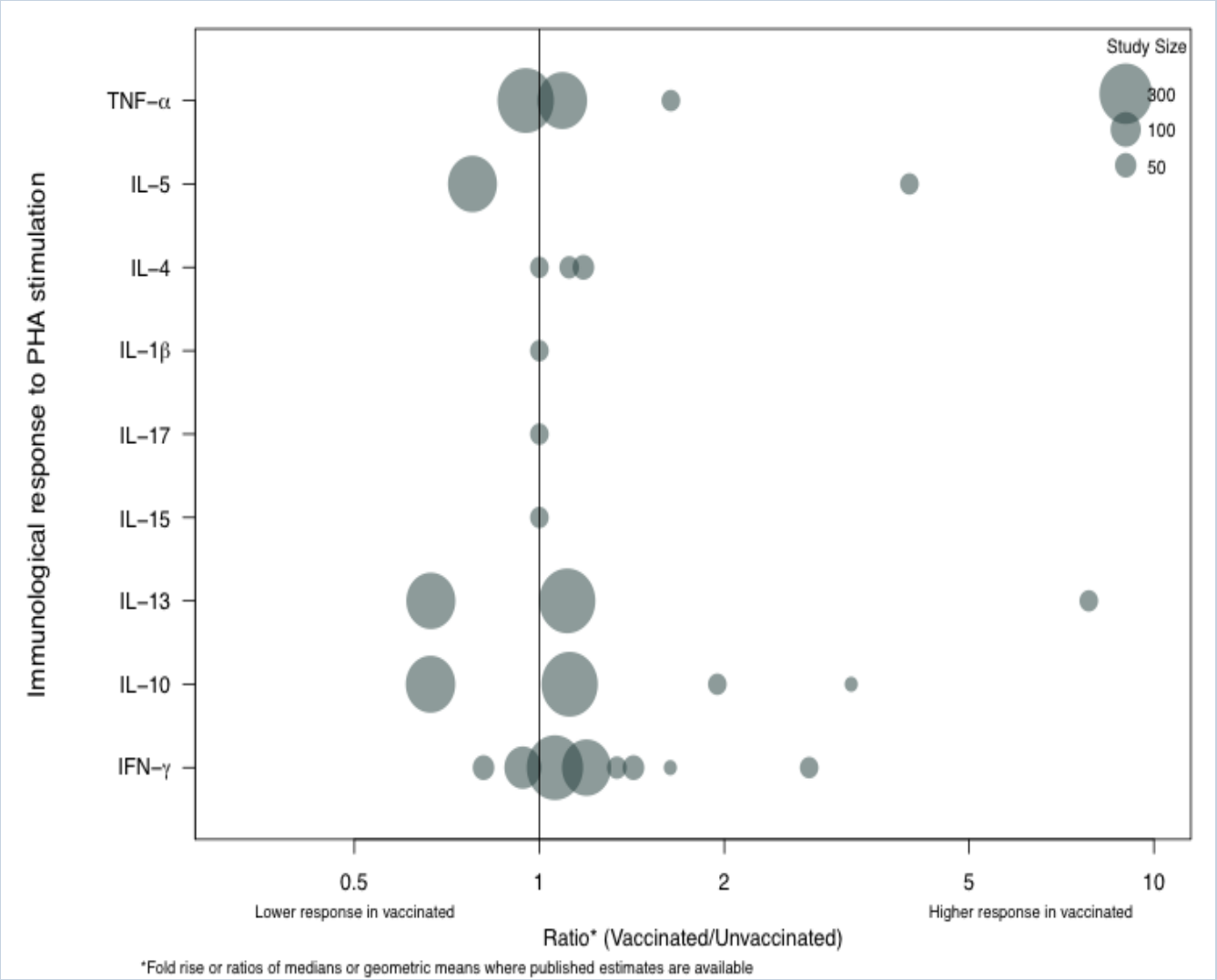
Combination of reporting parameters

	Vaccine				
Counts	**BCG**	**TT**	**Measles**	**MMR**	**DTP**
N. Studies reporting data in usable format or supplying raw data	20	10	8	3	1
N. Immunological parameters (Cytokines/Chemokines)	88	21	23	10	1
N. Stimulants	20	14	6	5	7
Cytokine/Stimulant combinations	167	36	35	13	7
N. different units (pg/mL, SI, %, mm2, cpm)	16	11	9	3	1
N. different statistics report (Geometric mean, raw mean, median, % etc)	17	8	7	3	1
N. Total number of combinations of the above	223	37	33	13	7

BCG vaccine studies

- 37 studies included from search
  - 24 of these studies involved children less than 5 years
- 89 different parameters reported
- IFN-γ the most commonly measured cytokine
  - (only 2 studies reported a significant change from baseline)

PHA stimulated responses to BCG vaccination



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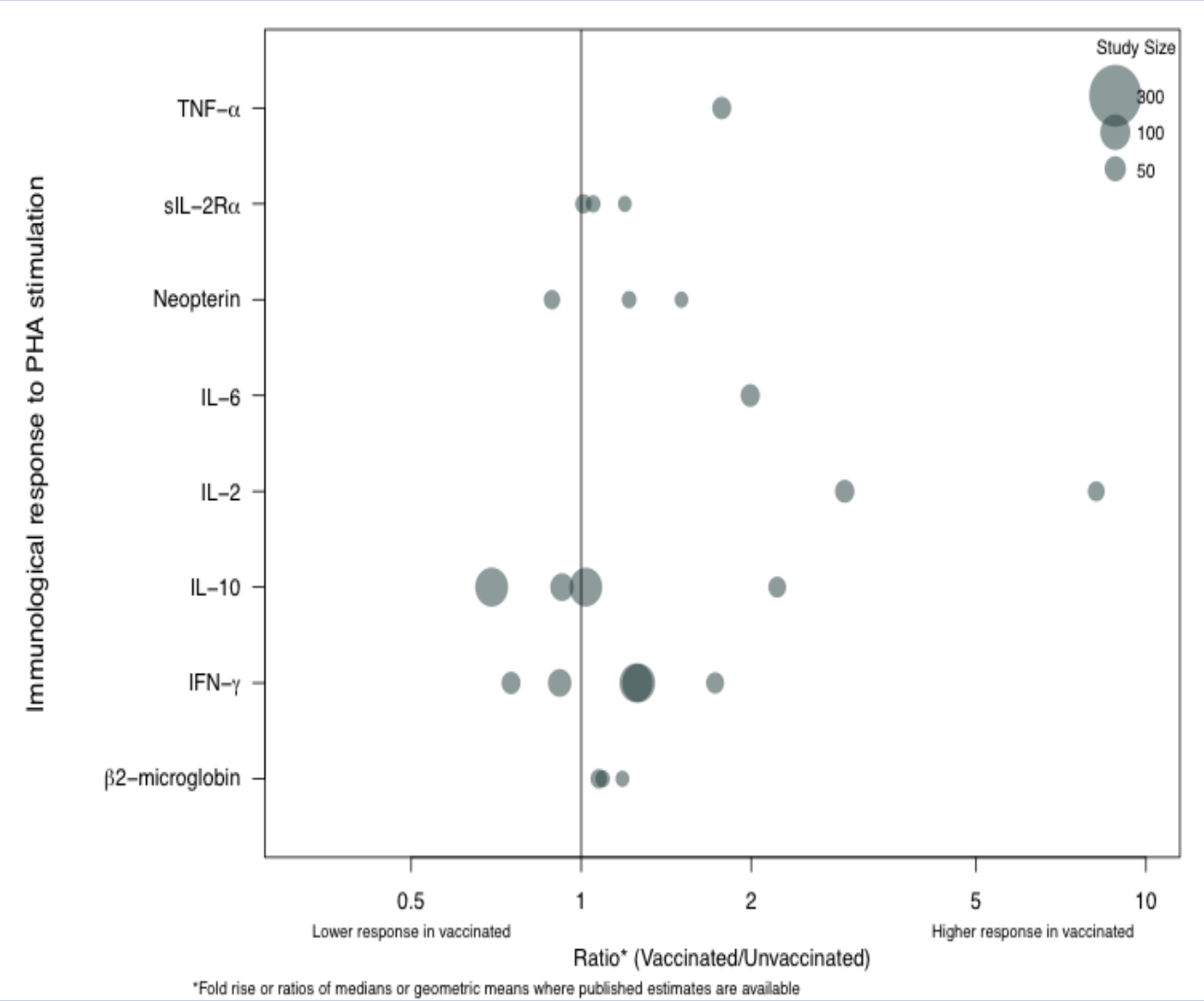
Tetanus Toxoid vaccine studies

- 11 studies, all of which were essentially in study cohorts greater than 5 years of age
- 21 different immunological parameters measured
- No two papers reported the same parameter
- Four papers reported a significant change in a non-specific immunological parameter. All of which were changes from baseline (rather than in comparison to a placebo group)

Measles vaccine studies

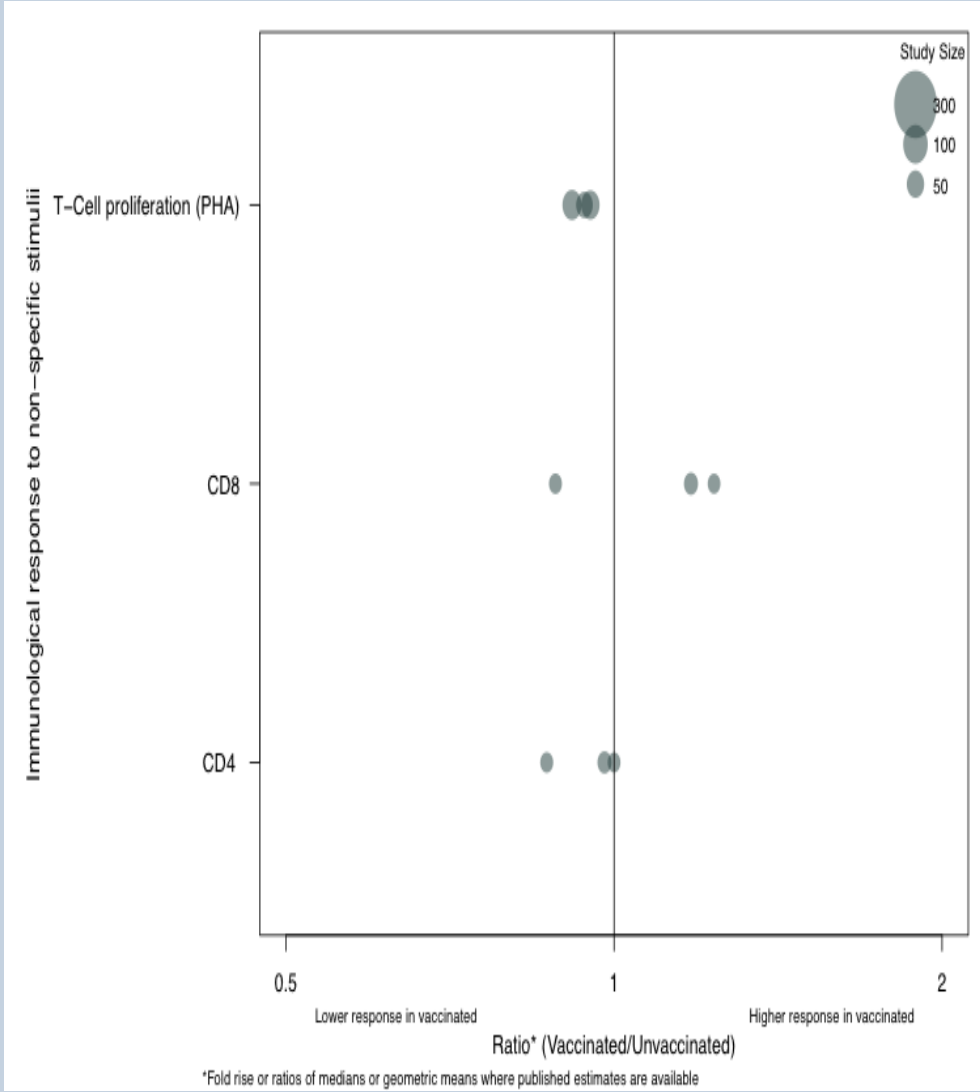
- 14 studies included from search
  - 12 of these were in children less than 5 years of age
- 23 different immunological parameters reported
- IFN-γ the most frequently reported cytokine
- 4 studies reported significant changes from baseline.
- 1 study reported a significant change when comparing two different strains of measles vaccine

PHA stimulated responses to measles vaccination



MMR vaccine studies

- 3 studies included from search
  - 2 of these involved children less than 5 years of age.
- T cell responses were most frequently reported
- 2 papers reported significant changes from baseline for CD4 and CD8 T cell counts (however these changes were not in a consistent direction)



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DTP and DT vaccine studies

- 11 studies included from search
  - 6 of these studies involved children less than 5 years
- No two studies had data that was comparable
- 3 papers reported a significant change from baseline.
- 1 paper reported a significant change when comparing 4 doses of DTP to 5.

Methodological Attributes

- No one study was rated as having low risk of bias for all criteria.
- NSIEs do not feature as a outcome parameter in any of the RCTs but rather a by-product.
- Only 55% of the included studies actually reported data in a usable format for this review.
- A diverse array of immunological assays were utilised in conjunction with differences in measurement parameters and statistical analysis.

Methodological Attributes

- Consistently low level of evidence
- Lack of any high quality (low risk of bias) randomised controlled trial with focussed endpoints designed around non-specific immunological outcomes.
- Data sets were not reported according to effect on sex

Confounder		N
Co-administration with Vitamin A?		
	Yes	3
	No/Not reported	74
Presence of attribute that may affect response?		
	Yes	22
	No	55

Conclusions

- Results inconclusive
- Heterogeneous data, inconsistent reporting and inadequate high quality evidence to describe the non-specific immunological effects of current childhood vaccine programmes.
  - Data available not presented in a suitable fashion for particular analyses e.g. sex and Vitamin A
- There is some evidence to suggest non-specific immunological effects occur, but none to make any clear conclusions.

The Future

- Technology now makes it possible to make detailed, statistically robust, analysis of multiple parameters from small samples
  - Flow cytometry
  - Transcriptomics
  - Systems immunology
- Need high quality data on routine schedules with immunological endpoints
  - feasible and necessary to advance understanding of biology
- To address big picture questions need careful trial design and consensus about immunological endpoints (what, when)
  - Currently questionable feasibility but will be possible in the future

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