Systematic Review of Non-Specific Immunological Effects of Vaccination

Professor Andrew J Pollard
Dr Rama Kandasamy
Merryn Voysey
University of Oxford
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

Measles

Control

Measles antibody

T cell proliferation

IFN-gamma

T cell proliferation

IFN-gamma
Non-Specific effects

Measles

Non-specific stimulus e.g. candida or PHA

Control

Vaccine

Non-specific antibody e.g. polio

T cell proliferation

IFN-gamma

T cell proliferation

IFN-gamma
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- All available evidence (published and unpublished)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

- Target population
  - infants under five years of age
  - not limited to this age group

- Record
  - sex
  - age at vaccination
  - co-administration of vitamin A

- Vaccines
  - BCG
  - measles
  - diphtheria
  - tetanus
  - pertussis

- Exclusions
  - Specific responses
  - Animal, ecological and in vitro studies
  - Studies reporting recombinant vaccines or no vaccine
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
<table>
<thead>
<tr>
<th>Study Author</th>
<th>Vaccine</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding, All outcomes</th>
<th>Incomplete outcome data, All outcomes</th>
<th>Selective reporting</th>
<th>Other bias</th>
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## Combination of reporting parameters

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<th>MMR</th>
<th>DTP</th>
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<tr>
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<td>20</td>
<td>10</td>
<td>8</td>
<td>3</td>
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<td>88</td>
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<td>23</td>
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<tr>
<td>N. Stimulants</td>
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<td>Cytokine/Stimulant combinations</td>
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<td>36</td>
<td>35</td>
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<td>N. different units (pg/mL, SI, %, mm², cpm)</td>
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<td>11</td>
<td>9</td>
<td>3</td>
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<tr>
<td>N. different statistics report (Geometric mean, raw mean, median, % etc)</td>
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<td>8</td>
<td>7</td>
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<td>N. Total number of combinations of the above</td>
<td>223</td>
<td>37</td>
<td>33</td>
<td>13</td>
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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

*Fold rise or ratios of medians or geometric means where published estimates are available
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)
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

<table>
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<th>Confounder</th>
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<td>Co-administration with Vitamin A?</td>
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<td>Yes</td>
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<tr>
<td>No/Not reported</td>
<td>74</td>
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<td>Presence of attribute that may affect response?</td>
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<td>Yes</td>
<td>22</td>
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<td>No</td>
<td>55</td>
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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
The Team

- Karlijn de Nie
- Rama Kandasamy
- Merryn Voysey
- Fiona McQuaid
- Rebecca Ryan
- Olivia Orr
- Ulrike Uhlig
- Daniel O’Connor
- Ana Maria Henao Restrepo
- Ximena Riveros Balta de Laurie
- Tomas Allen