Early vaccination protects against childhood leukemia: A systematic review and meta-analysis

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Supplementary Table 1: PRISMA 2009 checklist of items to include when reporting a systematic review or meta-analysis¹.

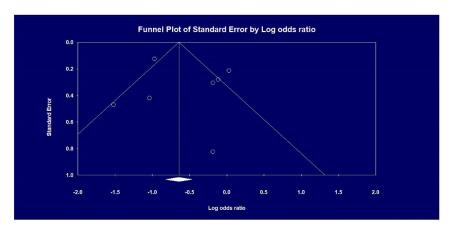
| Section/topic | # | Checklist item | Reported on page # |
|---------------------------|---|---|--------------------|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | Page 1 |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | Page 4 |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | Page 5 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | Page 6 |
| METHODS | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Page 6 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | Page 7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | Page 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Page 6 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | Page 6-7 |

| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | Page 7-8 |
|------------------------------------|----|--|-----------|
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | Page 8 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | Page 9-10 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | NA |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. | Page 8 |

Supplementary Table 2A: Quality assessment of clinical trials studies **Studies Domain of Assessment** Sequence Allocation Blinding Incomplete **Selective Outcome** Other Generation **Outcome Data** Reporting Concealment Comstock/1975 high unclear high low unclear low Sutherland /1982 low unclear low low unclear low

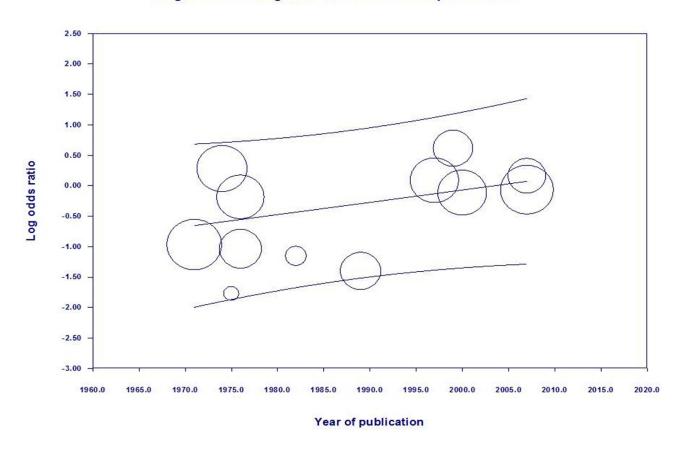
| Supplementary Table 2B | Quality | assessment of cas | se control st | udies | | | |
|------------------------|---------|-----------------------------|---------------|-------------------------|-------------------------------------|-----------|----------|
| Studies | | | | Domain of A | ssessment | | |
| | | Subject Selection | n | | | | |
| Author/year/ref | Cases | Adequacy of case definition | Controls | Comparability of groups | Ascertainment of exposure/treatment | Follow-up | Overall |
| Dockerty/1999 | 2 | 2 | 2 | 2 | 0 | 1 | High |
| Crispen/1976 | 2 | 1 | 2 | 2 | 0 | 1 | High |
| Nishi/1989 | 1 | 2 | 2 | 0 | 0 | 0 | High |
| Groves/1999 | 2 | 2 | 2 | 2 | 0 | 0 | High |
| Von Kries/2000 | 2 | 2 | 2 | 2 | 2 | 0 | high |
| MacArthur/2008 | 2 | 2 | 2 | 2 | 0 | 1 | High |
| Mallol-Mesnard /2007 | 2 | 2 | 2 | 2 | 0 | 1 | High |
| Ma/2005 | 2 | 2 | 2 | 2 | 0 | 1 | Moderate |
| Petridou/1997 | 1 | 2 | 2 | 2 | 2 | 1 | High |
| Salonen /1976 | 2 | 2 | 2 | 2 | 0 | 1 | Moderate |
| Davignon/1971 | 2 | 2 | 2 | 2 | 0 | 0 | High |
| Máthé /1974 | 2 | 1 | 2 | 2 | 0 | 0 | High |

Supplementary Figure 1: Funnel plot of publication bias assessment in the meta-analysis of association between early vaccination and childhood leukemia.



Supplementary Figure 2: The scatter-plot showing meta-regression of childhood leukemia on year of publication of BCG vaccination studies.

Regression of Log odds ratio on Year of publication



Supplementary Figure 3: Forest plot showing meta-analysis of mumps vaccination and subgroups meta-analysis.

Mumps vaccination

| Study name | | Statist | ics for e | ach study | <u>.</u> | Vaccin | ated / Total | | Odds | ratio and 95 | <u>% CI</u> | |
|------------------------|---------------|----------------|----------------|-----------|----------|-----------|--------------|------|------|--------------|-------------|-----|
| | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value | Leukemia | Non-leukemia | | | | | |
| Dockerty JD/1999 | 1.02 | 0.39 | 2.70 | 0.04 | 0.97 | 6/112 | 15 / 285 | 1 | - 1 | | 1 | - 1 |
| Groves FD/1999 | 1.03 | 0.66 | 1.59 | 0.11 | 0.91 | 395 / 439 | 394 / 439 | | | - | | |
| Ma X/2005 | 0.92 | 0.52 | 1.61 | -0.31 | 0.76 | 299 / 323 | 381 / 409 | | | — | | |
| MacArthur AC/2007 | 0.93 | 0.62 | 1.40 | -0.35 | 0.73 | 334 / 388 | 346 / 398 | | | - | | |
| Mallol-Mesnard N/ 2007 | 1.08 | 0.78 | 1.50 | 0.46 | 0.65 | 539 / 596 | 1103 / 1229 | | | | | |
| | 1.01 | 0.82 | 1.23 | 0.06 | 0.95 | | | | | • | 1 | |
| | | | | | | | | 0.01 | 0.1 | 1 | 10 | 100 |

Supplementary Figure 4: Forest plot showing meta-analysis of HiB vaccination and subgroups meta-analysis.

HiB vaccination

| Study name | | Statisti | ics for e | ach study | _ | Vaccin | ated / Total | | Odd | s ratio and 95° | % CI | |
|---------------------|---------------|----------------|----------------|-----------|---------|-----------|--------------|------|-----|-----------------|------|-----|
| | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value | Leukemia | Non-leukemia | | | | | |
| Groves FD/1999 | 0.79 | 0.61 | 1.03 | -1.75 | 0.08 | 206 / 439 | 232 / 439 | | | C | - 1 | - 1 |
| Ma X/2005 | 0.93 | 0.48 | 1.80 | -0.23 | 0.82 | 306 / 323 | 389 / 409 | | | - | | |
| Mallol Mesnard/2007 | 1.55 | 1.20 | 2.00 | 3.31 | 0.00 | 582 / 672 | 1132 / 1403 | | | 0 | | |
| | 1.06 | 0.64 | 1.76 | 0.22 | 0.83 | | | | Į | | | |
| | | | | | | | | 0.01 | 0.1 | 1 | 10 | 100 |

Supplementary Figure 5: Forest plot showing meta-analysis of rubella vaccination and subgroups meta-analysis.

HBV vaccination

| Study name | | Statist | ics for e | ach study | , | Vaccin | ated / Total | | | Odds ra | tio and | 95% CI | | |
|-----------------------|---------------|---------|----------------|-----------|------|-----------|--------------|-----|-----|---------|-------------|--------|-----|-----|
| | Odds ratio | Lower | Upper limit | • | -9 | | Non-leukemia | | | | | | | |
| Dockerty JD/1999 | 1.03 | 0.67 | 1.60 | 0.15 | 0.88 | 62 / 114 | 151 / 282 | - 1 | 1 | - 1 - | — }— | - T | - 1 | - 1 |
| MacArthur AC/2007 | 1.17 | 0.42 | 3.27 | 0.31 | 0.76 | 8 / 376 | 7 / 385 | - 1 | | + | - | _ | | |
| Mallol-Mesnard N 2007 | 1.04 | 0.86 | 1.26 | 0.38 | 0.71 | 250 / 672 | 510 / 1403 | - 1 | | | O | | | |
| Ma X/2005 | 0.75 | 0.45 | 1.23 | -1.14 | 0.25 | 289 / 323 | 376 / 409 | - 1 | | + | — | | | |
| | 1.00 | 0.85 | 1.18 | 0.06 | 0.95 | | | | | | • | | | |
| | | | | | | | | 0.1 | 0.2 | 0.5 | 1 | 2 | 5 | 10 |

Supplementary Figure 6: Forest plot showing meta-analysis of triple vaccination and subgroups meta-analysis.

Triple vaccination

| Study name | | Statist | ics for e | ach study | | Vaccin | ated / Total | | Odds | ratio and 95 | <u>% </u> | |
|------------------|---------------|----------------|----------------|-----------|---------|-----------|--------------|------|------|--------------|--|-----|
| | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value | Leukemia | Non-leukemia | | | | | |
| Dockerty JD/1999 | 0.94 | 0.59 | 1.49 | -0.26 | 0.79 | 80 / 118 | 197 / 285 | - 1 | - 1 | - | - 1 | - 1 |
| Groves FD/1999 | 0.73 | 0.33 | 1.60 | -0.79 | 0.43 | 424 / 439 | 428 / 439 | | | | | |
| MA X/2005 | 1.05 | 0.23 | 4.74 | 0.07 | 0.95 | 320 / 323 | 405 / 409 | | | | - | |
| Petridou E/1997 | 1.94 | 1.03 | 3.64 | 2.06 | 0.04 | 139 / 153 | 251 / 300 | | | -0- | | |
| | 1.10 | 0.79 | 1.53 | 0.57 | 0.57 | | | | - 1 | - | | |
| | | | | | | | | 0.01 | 0.1 | 1 | 10 | 100 |

Supplementary Figure 7: Forest plot showing meta-analysis of polio sip vaccination and subgroups meta-analysis.

Polio sip vaccination

| Study name | | Statist | ics for e | ach study | | Vaccin | ated / Total | | Odds | ratio and 9 | 5% CI | |
|-------------------|---------------|-------------|----------------|-----------|---------|-----------|--------------|------|------|--------------|-------|-----|
| | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value | Leukemia | Non-leukemia | | | | | |
| Dockerty JD/1999 | 0.95 | 0.60 | 1.52 | -0.20 | 0.85 | 80 / 117 | 197 / 284 | - [| 1 | - | - 1 | |
| Groves FD/1999 | 1.10 | 0.46 | 2.62 | 0.22 | 0.83 | 429 / 439 | 428 / 439 | | | | | |
| Ma X/2005 | 1.05 | 0.23 | 4.74 | 0.07 | 0.95 | 320 / 323 | 405 / 409 | | - | _ | - | |
| MacArthur AC/2007 | 0.97 | 0.47 | 2.00 | -0.09 | 0.93 | 371 / 386 | 384 / 399 | | | - | | |
| | 0.98 | 0.70 | 1.39 | -0.09 | 0.93 | | | I | | • | - [| |
| | | | | | | | | 0.01 | 0.1 | 1 | 10 | 100 |

Supplementary Figure 8: Forest plot showing meta-analysis of MMR vaccination and subgroups meta-analysis.

MMR vaccination

| Study name | | Statist | ics for ea | ach study | | Vaccin | ated / Total | | Odd | s ratio and 9 | 5% CI | |
|-------------------|---------------|-------------|----------------|-----------|---------|-----------|--------------|------|-----|-------------------------|-------|-----|
| | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value | Leukemia | Non-leukemia | | | | | |
| Dockerty JD/1999 | 1.02 | 0.39 | 2.70 | 0.04 | 0.97 | 6/112 | 15 / 285 | - 1 | 1 | \rightarrow | 1 | - 1 |
| Groves FD/1999 | 1.03 | 0.66 | 1.59 | 0.11 | 0.91 | 395 / 439 | 394 / 439 | | | \(\rightarrow\) | | |
| Ma X/2005 | 0.92 | 0.52 | 1.61 | -0.31 | 0.76 | 299 / 323 | 381 / 409 | | | - | | |
| MacArthur AC/2007 | 0.93 | 0.62 | 1.40 | -0.35 | 0.73 | 334 / 388 | 346 / 398 | | | O | | |
| | 0.96 | 0.75 | 1.24 | -0.28 | 0.78 | | | | 1 | • | | |
| | | | | | | | | 0.01 | 0.1 | 1 | 10 | 100 |

Supplementary Figure 9: Forest plot showing meta-analysis of measles vaccination and subgroups meta-analysis.

Measles vaccination

| udy name | Subgroup within study | | Statist | ics for e | ach study | | Odds ratio and 95% CI |
|-------------------|-----------------------|------------|----------------|----------------|-----------|---------|-----------------------|
| | | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value | |
| ockerty JD/1999 A | Alone | 1.65 | 1.06 | 2.57 | 2.22 | 0.03 | |
| ockerty JD/1999 C | MMR | 1.02 | 0.39 | 2.70 | 0.04 | 0.97 | |
| Arthur AC/2007 | MMR | 0.93 | 0.62 | 1.40 | -0.35 | 0.73 | |
| ol-Mesnard N/ 20 | 07 Alone | 1.05 | 0.75 | 1.48 | 0.31 | 0.76 | ->- |
| √2005 | MMR | 0.92 | 0.52 | 1.61 | -0.31 | 0.76 | |
| ni M/1989 | Alone | 0.25 | 0.10 | 0.60 | -3.08 | 0.00 | ├ |
| ves FD/1999 | MMR | 1.03 | 0.66 | 1.59 | 0.11 | 0.91 | ->- |
| | | 1.02 | 0.85 | 1.23 | 0.25 | 0.80 | |

Measles vaccination subgroups

| Group by Subgroup within study | Study name | Subgroup within study | - | Statis | tics for e | ach study | | Vacci | nated / Total | | | | Odds | Odds ratio and 95% |
|-----------------------------------|------------------------|-----------------------|---------------|--------|----------------|-----------|---------|-----------|---------------|-----|---|-----|---------|--------------------|
| Subgroup within study | | | Odds ratio | Lower | Upper limit | Z-Value | p-Value | Leukemia | Non-leukemia | | | | | |
| Alone | Dockerty JD/1999 A | Alone | 1.65 | 1.06 | 2.57 | 2.22 | 0.03 | 58 / 113 | 106 / 272 | - 1 | | ı | 1 1 | |
| Alone | Mallol-Mesnard N/ 2007 | Alone | 1.05 | 0.75 | 1.48 | 0.31 | 0.76 | 541 / 596 | 1110 / 1229 | | | 1 | 1 1 | |
| Alone | Nishi M'1989 | Alone | 0.25 | 0.10 | 0.60 | -3.08 | 0.00 | 48 / 63 | 117/126 | | _ | - | - | ├ |
| Alone | | | 1.09 | 0.84 | 1.40 | 0.64 | 0.52 | | | | | 1 | | |
| MMR | Dockerty JD/1999 C | MMR | 1.02 | 0.39 | 2.70 | 0.04 | 0.97 | 6/112 | 15 / 285 | - 1 | | 1 | _ | |
| MMR | MacArthur AC/2007 | MMR | 0.93 | 0.62 | 1.40 | -0.35 | 0.73 | 334/388 | 346 / 398 | - 1 | | 1 | 1 1- | |
| MMR | Ma X/2005 | MMR | 0.92 | 0.52 | 1.61 | -0.31 | 0.76 | 299 / 323 | 381 / 409 | - 1 | | 1 | I — | |
| MMR | Groves FD/1999 | MMR | 1.03 | 0.66 | 1.59 | 0.11 | 0.91 | 395 / 439 | 394 / 439 | - 1 | | 1 | 1 . | I →— |
| MMR | | | 0.96 | 0.75 | 1.24 | -0.28 | 0.78 | | | - 1 | | 1 | 1 1 | |
| Overall | | | 1.02 | 0.85 | 1.23 | 0.25 | 0.80 | | | - 1 | | 1 | 1 1 | 1 1 🍝 |
| | | | | | | | | | | | | | | |
| | | | | | | | | | | 0.1 | | 0.2 | 0.2 0.5 | 0.2 0.5 1 |

Supplementary Figure 10: Forest plot showing meta-analysis of rubella vaccination and subgroups meta-analysis.

Rubella vaccination

| Study name | Subgroup within study | | Statist | ics for ea | ch study | _ | Vaccin | nated / Total | | | Odds r | atio and 9 | 95% CI | |
|------------------------|-----------------------|---------------|---------|----------------|----------|---------|-----------|---------------|-----|-----|--------|--------------|--------|---|
| | | Odds ratio | Lower | Upper limit | Z-Value | p-Value | Leukemia | Non-leukemia | | | | | | |
| Dockerty JD/1999 A | Alone | 0.45 | 0.05 | 3.90 | -0.72 | 0.47 | 1/115 | 5/262 | ← | - | | - | _ | • |
| Dockerty JD/1999 C | MMR | 1.02 | 0.39 | 2.70 | 0.04 | 0.97 | 6/112 | 15 / 285 | | - 1 | - | — | - | |
| Groves FD/1999 | MMR | 1.03 | 0.66 | 1.59 | 0.11 | 0.91 | 395 / 439 | 394 / 439 | | - 1 | - - | ⊸ | - | |
| Ma X/2005 | MMR | 0.92 | 0.52 | 1.61 | -0.31 | 0.76 | 299 / 323 | 381 / 409 | | - 1 | _ | | -) | |
| MacArthur AC/2007 | MMR | 0.93 | 0.62 | 1.40 | -0.35 | 0.73 | 334/388 | 346/398 | | - 1 | l – | - | 1 | |
| Mallol-Mesnard N' 2007 | Alone | 1.09 | 0.78 | 1.52 | 0.52 | 0.60 | 540 / 596 | 1104 / 1229 | | - 1 | | - | | |
| | | 1.00 | 0.82 | 1.23 | 0.03 | 0.98 | | | - 1 | | - 1 | * | ı | |
| | | | | | | | | | 0.1 | 0.2 | 0.5 | 1 | 2 | |

Rubella vaccination subgroups

| Group by Subgroup within study | Study name | Subgroup within study | Statistics for each study | | | | | | Odds ratio and 95% CI | | | | | |
|-----------------------------------|------------------------|-----------------------|---------------------------|----------------|----------------|---------|---------|-----|-----------------------|-----|-------------|----------|---|---|
| | | | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value | | | | | | | |
| Alone | Dockerty JD/1999 A | Alone | 0.45 | 0.05 | 3.90 | -0.72 | 0.47 | K | - | -+ | _ | | + | _ |
| Alone | Mallol-Mesnard N/ 2007 | ' Alone | 1.09 | 0.78 | 1.52 | 0.52 | 0.60 | | - 1 | | _ | — | 1 | |
| Alone | | | 1.07 | 0.77 | 1.48 | 0.40 | 0.69 | - 1 | - 1 | | 4 | | 1 | |
| MMR | Dockerty JD/1999 C | MMR | 1.02 | 0.39 | 2.70 | 0.04 | 0.97 | - 1 | - 1 | - | _ | | + | |
| MMR | Groves FD/1999 | MMR | 1.03 | 0.66 | 1.59 | 0.11 | 0.91 | - 1 | - 1 | | \dashv | _ | 1 | |
| MMR | Ma X/2005 | MMR | 0.92 | 0.52 | 1.61 | -0.31 | 0.76 | - 1 | - 1 | - | | _ | 1 | |
| MMR | MacArthur AC/2007 | MMR | 0.93 | 0.62 | 1.40 | -0.35 | 0.73 | - 1 | - 1 | | — o | _ | 1 | |
| MMR | | | 0.96 | 0.75 | 1.24 | -0.28 | 0.78 | - 1 | - 1 | - 1 | • | - | 1 | |
| | | | | | | | | 0.1 | 0.2 | 0.5 | - | 1 | 2 | |

| 1 | Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. G. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. <i>Annals of internal medicine</i> 151 , 264-269 (2009). |
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