Evidence based recommendations on non-specific effects of BCG, DTP-containing and measles-containing vaccines on mortality in children under 5 years of age

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Today's questions

- Is the current evidence on non-specific effects of vaccines sufficient to lead to **adjustments in policy recommendations**?

- Is the current evidence on non-specific effects of vaccines sufficient to **warrant further scientific investigation**?

Background

The WG recognises the well-documented and important impact of the vaccines under review on morbidity and mortality worldwide.

The aim of the review was not to assess whether or not the vaccines should continue to be recommended for universal use, but to evaluate if there was evidence that the timing, sequence or co-administration of these vaccines result in non-specific effects on all-cause mortality.

The epidemiology review report does not include summary estimates from meta-analyses because there was a consensus that it was not a valid exercise in this instance because of statistical heterogeneity, and heterogeneity in the mix of all-cause mortality.

IMMUNOLOGY REVIEW

CONCLUSION 1

Findings from the systematic review neither exclude nor confirm the possibility of beneficial or deleterious non-specific immunological effects of vaccines on all cause-mortality.

IMMUNOLOGY REVIEW

CONCLUSION 2

The available evidence is insufficient to draw any conclusions on non-specific immunological effects following vaccination that would provide the biological basis for non-specific effects on all-cause mortality.

There was agreement that non-specific immunological effects following exposure to any antigen are plausible and common but their biologic effects are not clearly understood in general and, not specifically for vaccines.

EPIDEMIOLOGY REVIEW: BCG

CONCLUSIONS

Overall, the Working Group found that the data from randomized studies and observational studies are suggestive of a beneficial effect of BCG in reducing all-cause mortality within the first 6-12 months of life in countries with high childhood mortality. There is no evidence of a deleterious effect of BCG on all-cause mortality.

EPIDEMIOLOGY REVIEW
DTP

CONCLUSIONS

The Working Group noted mortality data related to DTP came only from observational studies, and only when given in combination with other vaccines. These studies had significant methodological limitations.

Because of these limitations, the WG found that the data available do not provide conclusive evidence that the current DTP schedule results in deleterious effects on all-cause mortality in children less than five years of age.

NOTE: Some WG members considered that there was sufficient evidence to conclude that in specific settings, DTP vaccine might be associated with an increase in all-cause mortality.

EPIDEMIOLOGY REVIEW
DTP

SYSTEMATIC REVIEW sub-question Conclusions

Each 3–5 studies, all observational, all judged at high risk of bias: Results suggest …

DTP+BCG vs BCG before DTP

… simultaneous administration may be associated with lower mortality (one had 95% CIs that excluded no difference).

DTP before BCG compared with BCG before DTP

… no clear differences are apparent.

Co-administration of DTP and measles vaccine

… simultaneous administration may be associated with higher mortality.

Order of DTP and measles vaccine affect all-cause mortality:

… simultaneous administration may be associated with higher mortality**.**

EPIDEMIOLOGY REVIEW
Measles Vaccine

CONCLUSIONS

Overall, the Working Group found that there was evidence that measles vaccine reduced the risk of all-cause mortality independent of its effect on confirmed measles mortality (an effect that appears to be stronger in girls than boys).

Recommendations for SAGE consideration

EPIDEMIOLOGY REVIEW: BCG

Recommendation for SAGE´s consideration

The Working Group concluded that the evidence does not support a change in policy for BCG.

Additional lives might be saved by emphasizing the implementation of the WHO recommendation that a single dose of BCG be given to neonates or as soon as possible after birth in countries with a high prevalence of tuberculosis.

The available data suggest that the current WHO recommended schedule for BCG vaccine has a beneficial effect on all-cause mortality in children.

EPIDEMIOLOGY REVIEW: DTP

Recommendation for SAGE consideration

The Working Group concluded that the evidence does not support a change in policy for DTP.

The current WHO policy recommends three DTP doses during the first year of life. In areas where pertussis is of particular risk to young infants, DTP should be started at 6 weeks with two subsequent doses at intervals of 4-8 weeks each.

The data available do not provide conclusive evidence that the current schedule results in deleterious effects on all-cause mortality in children less than five years of age.

EPIDEMIOLOGY REVIEW: Measles

Recommendation for SAGE´s consideration

The Working Group concluded that the evidence does not support a change in policy for measles vaccine.

The current WHO recommendation states that reaching all children with 2 doses of measles containing vaccine should be the standard for all national immunization programmes. In countries with ongoing transmission, measles containing vaccine should be given at age 9 months. WHO recommends that the second dose should be given between 15-18 months of age. In countries with low rates of measles transmission, the first dose may be administered at age 12 months.

The available data suggest that the current WHO recommended schedule for standard titre measles-containing vaccine has a beneficial effect on all-cause mortality in children.

Additional lives might be saved by improving implementation of the WHO recommendation.

Research Agenda

- Insufficient time for the Working Group to fully explore future research directions.
- Some broad principles emerged during the review.
- Broader considerations of morbidity in human population studies (with embedded immunologic investigation that will inform putative effect determination and underlying mechanisms) should form part of future research considerations.

Research Agenda
RANDOMIZED CONTROLLED TRIALS

- Need more high quality randomised controlled trials, wherever feasible.There are ethical and methodologic challenges.
- RCTs of any DTP versus no DTP, even with narrow time windows for outcome evaluation, and even in settings where endemic pertussis is low, may not be able to be conducted. The widespread use of pentavalent vaccine further complicates examination of NSEV.
- If RCTs were to be conducted, it may be appropriate to aim for several large studies across a number of countries using the same protocol.
- RCTs of EPI schedule variants designed to minimise post-vaccination DTP person-time exposure before MCV vaccine could be considered.

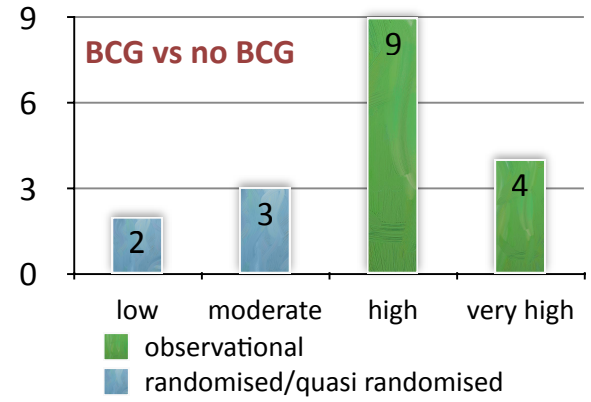
Research Agenda

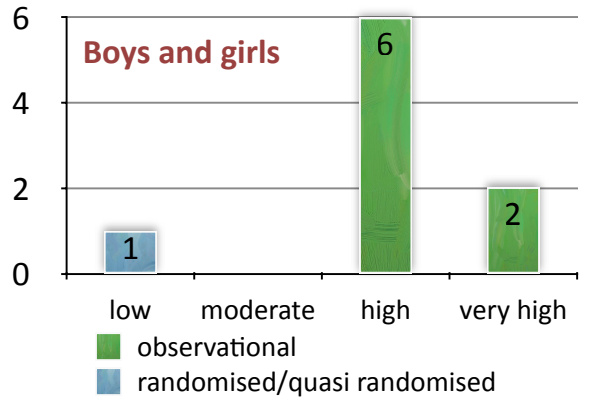
- Any future studies should be designed and powered to examine gender effects. In addition, immunological analysis should become a specific objective of future studies based on formulating specific research questions that the study could answer.
- This could include assays that cover a breadth of immunological responses including antibodies, T-cell responses, cytokines, etc. However, the Working Group argued against a shotgun approach given that it would make interpretation of occasionally significant results among hundreds of comparisons difficult.
- Systems biology approaches may be particularly informative in providing a profile of host immune response.

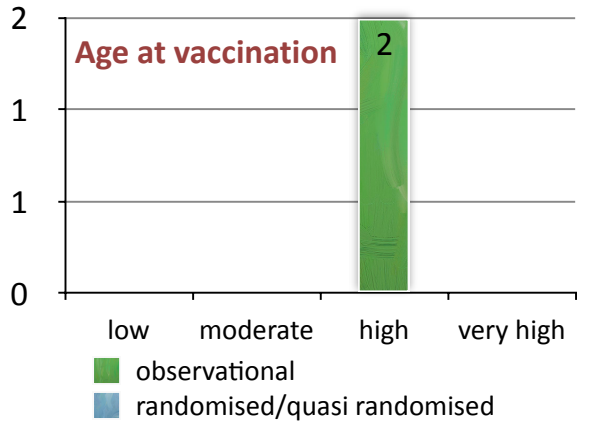
Research Agenda
OBSERVATIONAL STUDIES

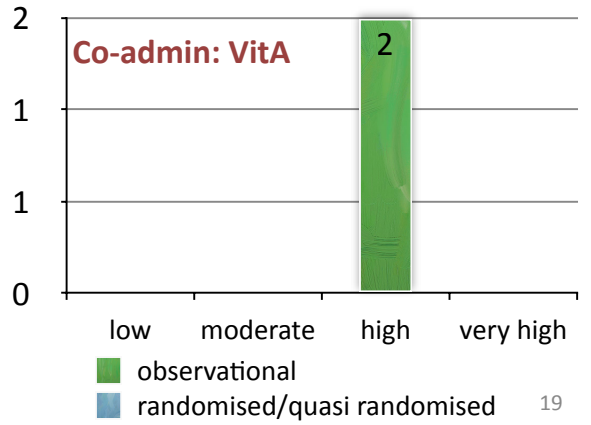
- Further observational studies with inherent and substantial risk of bias would be unlikely to provide conclusive evidence about putative non-specific mortality effects.
- If observational studies are to be contemplated, their design and analysis should mimic what would be undertaken if it were to be a randomised controlled trial.
- Future studies should draw upon a broad investigator pool and from a wide range of geographic locations and burden of disease settings.
- The development of standardized protocols for both RCTs and observational studies of mortality effects, that address now well-recognised bias issues, should be considered.

BCG vs no BCG comparisons: studies by type of design and risk of bias

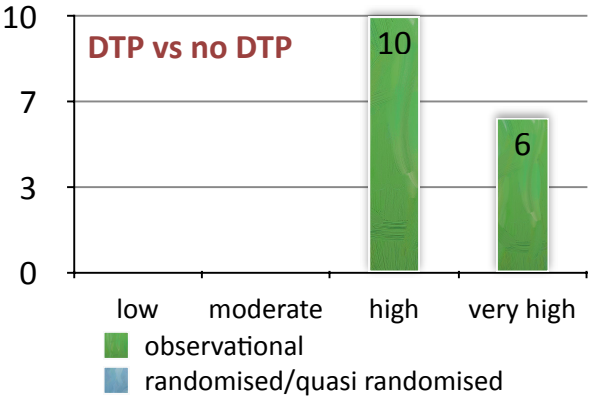


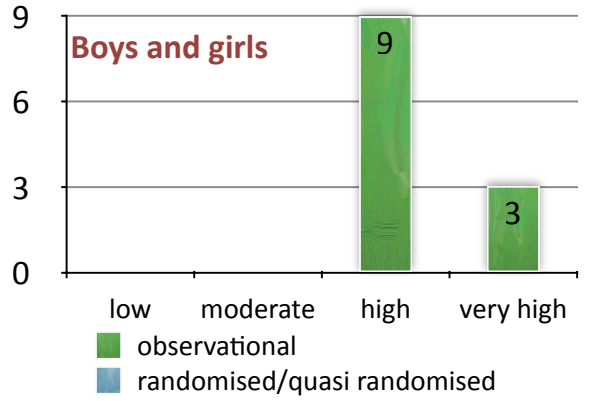


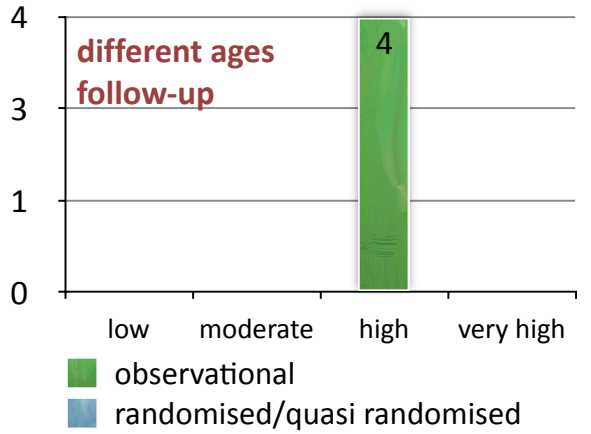


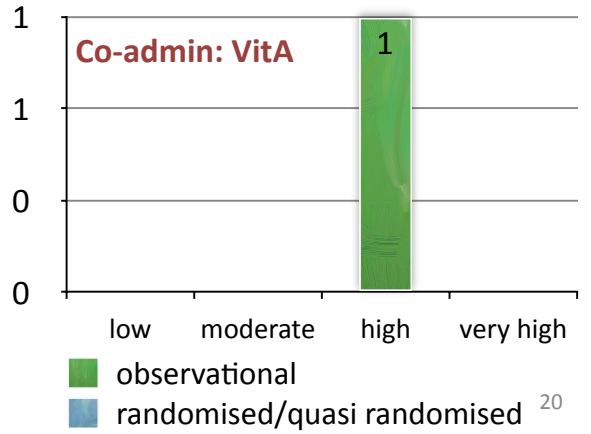


DTP vs no DTP comparisons: studies by type of design and risk of bias









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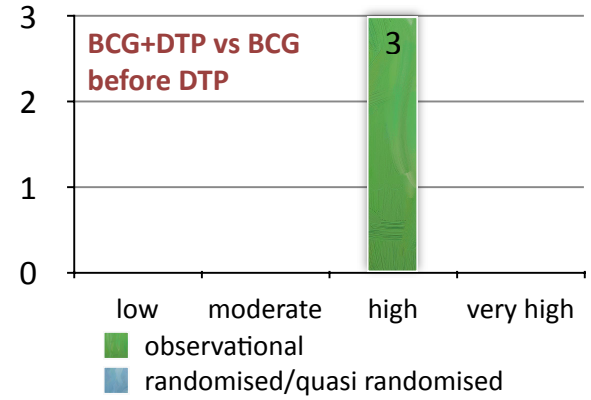

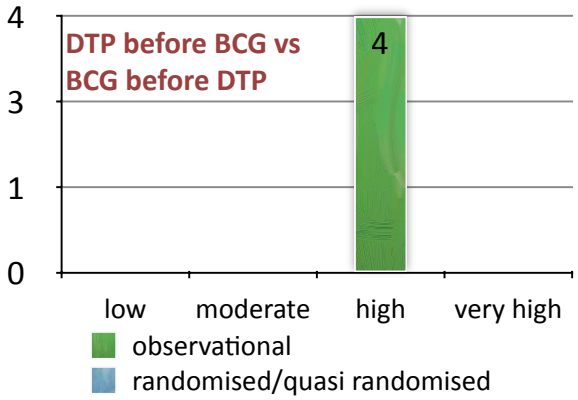

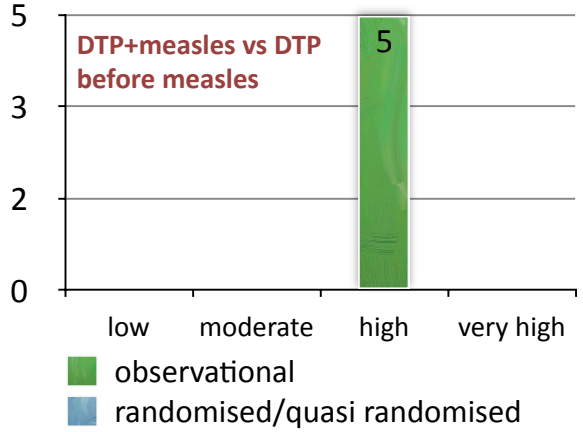

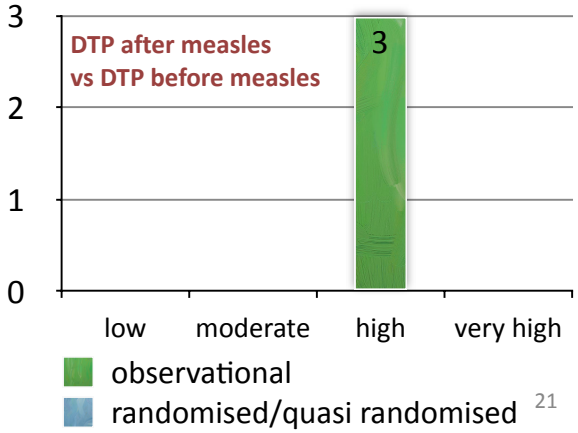

Measles vaccine vs no measles vaccine comparisons: studies by type of design and risk of bias