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EDITORIALS

Non-specific effects of childhood vaccines

Evidence of any "off target" effects remains weak and vulnerable to biases

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Non-specific effects of vaccines or "off target effects" as they are sometimes called can be defined as effects of a vaccine beyond their intended target pathogen or disease. These effects can be beneficial as well as harmful.[1-3] The published evidence on non-specific effects of childhood vaccines remain confusing, so the linked systematic reviews by Higgins and colleagues (doi:10.1136/bmj.i5170)[4] and Kandasamy and colleagues (doi:10.1136/bmj.i5225)[5] looking at clinical and immunological non-specific effects are welcome.

The systematic reviews were commissioned by the WHO Strategic Advisory Group of Experts (SAGE) to decide if there was enough evidence to consider changes in scheduling or co-administration of certain vaccines.[6] It is important to emphasise that the systematic reviews were not intended or designed to assess if these vaccines are safe or should continue to be recommended for children. It is beyond debate that BCG, diphtheria, tetanus, pertussis (DPT), and measles containing vaccines (MCV) are safe. These vaccines have saved the lives of millions of children. The reviews' findings must not be hijacked to argue against their recommended use.

Higgins and colleagues provide a comprehensive collation of available data from clinical trials and cohort and case-control studies on the impact of BCG, DPT, and MCV on non-specific and all cause mortality in children aged under 5.[4] Importantly, the authors used a robust assessment of risk of bias to evaluate all eligible studies and exclude those at "very high" risk of bias. Observational studies of vaccine effects are vulnerable to confounding—unwell children are less likely to be vaccinated—as well as misclassification bias of vaccination status.

These biases are directly relevant to the controversial finding that receipt of DPT could be associated with an increase in all cause mortality (relative risk 1.38, 95% confidence interval 0.92 to 2.08).[4] This figure must be interpreted with extreme caution as all 10 studies in the analysis were observational and classified as "high risk of bias." Most were from the same setting, limiting generalisability. Importantly, the authors found no randomised trial data on this association.

In contrast, what they did find were randomised trial data suggesting that BCG vaccine could reduce all cause mortality (relative risk 0.70, 95% confidence interval 0.49 to 1.01).[4] Clinical trials of MCV also suggested a possible protective effect against mortality, especially for girls, but the low numbers of deaths and short follow-up prevent confident conclusions.

Complementing the epidemiological review, Kandasamy and colleagues (doi:10.1136/bmj.i5225) reviewed evidence for non-specific immunological effects of BCG (48% of included papers), measles, MMR, DTP, DT, and pertussis vaccines.[5] The Achilles' heel of all such studies is that we do not have any established immunological markers for clinically relevant non-specific effects. This is reflected in the large number (143) of different immunological outcomes in the reviewed papers.[5] Meta-analysis of these heterogeneous studies wasn't possible, but a systematic review did find a trend of increased IFN-γ levels in BCG vaccinated individuals relative to unvaccinated controls.[5] Reviewed studies also reported lymphoproliferation in response to exposure to tetanus toxoid and *Candida albicans* antigen in people who had received measles vaccine.[5] Finally, DTP, DT, and pertussis vaccines were found to be capable of generating immune responses—lymphocyte proliferation and production of various cytokines—to heterologous antigens.[5] The actual relevance of these findings in relation to non-specific immunological effects of vaccines remains unclear.

Taken together, the two systematic reviews suggest that vaccines could have non-specific effects, but the evidence remains weak. After reviewing both studies, the WHO's expert group (SAGE) rightly concluded that there was no need to modify current vaccination schedules or policies.[6]

Perhaps the most important message from these two well conducted systematic reviews is that further small observational studies will not take us any closer to the truth about non-specific effects of childhood vaccines. Inherent biases and confounders (especially unknown confounders) cannot be eliminated by simply doing more of the same. If randomised controlled trials are not feasible, large observational study designs incorporating innovative methods to control for confounders, conducted with standardised protocols across multiple settings and countries is

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the only alternative. Similarly, coordination, standardisation, and a systems approach in immunological research on non-specific effects is urgently required.

The rapid advancement in immunological methods and technologies could complicate the evidence base still further if they result in the proliferation of studies reporting new immunological variables of unknown clinical relevance. Ideally, both epidemiological and immunological efforts need to be integrated. If we fail to come together, it is highly likely that we will still be in the same situation when these systematic reviews are updated in five or even 10 years.

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3 Krishnan A, Srivastava R, Dwivedi P, Ng N, Byass P, Pandav CS. Non-specific sex-differential effect of DTP vaccination may partially explain the excess girl child mortality in Ballabgarh, India. *Trop Med Int Health* 2013;18:1329-37. doi:10.1111/tmi.12192 pmid:24103109.

4 Higgins JPT, Soares-Weiser K, López-López JA, et alAssociation of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *BMJ* 2016;355:i5170.

5 Kandasamy R, Voysey M, McQuaid F, et al. Non-specific immunological effects of selected routine childhood immunisations: systematic review. *BMJ* 2016;355:i5225.

6 World Health Organization. SAGE. Evidence based recommendations on non-specific effects of BCG, DTP-containing and measles-containing vaccines on mortality in children under 5 years of age. http://www.who.int/immunization/sage/meetings/2014/april/1_NSE_Backgroundpaper_final.pdf?ua=1