Vaccines have sex differential non-targeted heterologous effects: a new dawn in vaccine research

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The WHO Strategic Advisory Group of Experts (SAGE) on immunization recently published their conclusions from a systematic review of the ‘non-specific’ or ‘heterologous effects’ of vaccines, hailing a new era in our understanding of what vaccines do to the immune system. The report recognizes that bacille Calmette-Guérin (BCG) vaccine and measles vaccine (MV) may provide survival benefits against infectious diseases other than those targeted by the vaccine. These non-specific or heterologous effects of vaccines, whereby vaccines alter susceptibility to infections other than that targeted by the vaccine, can be beneficial as is the case for BCG and MV; but other vaccines such as diphtheria-tetanus-pertussis (DTP) vaccine may increase susceptibility to infections, although WHO conclude that the data supporting deleterious effects of DTP are inconclusive. As a rule females seem to be more susceptible to these vaccine-induced heterologous effects than males.

This special issue contains a series of reviews and original research articles further exploring the important topic of heterologous effects of vaccines and their sex-differential nature. Many of the studies have haled from Guinea-Bissau and there has been a need for research from other countries. Peter Aaby and colleagues carried out a retrospective analysis of the effect of vaccine sequence in 4133 children in Senegal, concluding that the sequence in which vaccines are given can impact child survival in a sex-differential manner. A second paper by Aaby and colleagues reviewed all available studies containing data on MV in early life and mortality, concluding that child mortality may be reduced if MV is given earlier than currently recommended. Frank Shann offers his personal view for a revised Expanded Program on Immunization (EPI) schedule designed to reduce time of exposure to the potential harmful effect of DTP, including the use of an early dose of MV and no booster DTP in females in the second year of life. Such simple changes to the EPI schedule could reduce child mortality at minimal cost.

The immunological mechanisms for the heterologous effects of vaccines are far from understood, and studies remain scarce. A comprehensive review by Klein and colleagues summarizes the evidence for sex differences in immunity to vaccines, and explores the potential mechanisms, concluding that vaccine strategies should be sex-specific. Gil and colleagues review the data on heterologous cross-reactive T cell immunity in animals and humans, concluding that this is commonplace and that vaccine induced cross-reactive T cell responses to other infections could account for vaccine heterologous effects.

The concept of ‘trained innate immunity’ is described by Kleinjijehuis et al., whereby BCG vaccination causes a long-term increase in pro-inflammatory innate capacity via an epigenetic modification of an innate receptor on monocytes and macrophages. This provides a convincing mechanistic explanation for how BCG vaccination improves survival against infections other than TB. Levy and Levy discuss how trained immunity might be harnessed in future vaccine approaches for infants. Freyne and colleagues carried out two wide-ranging reviews of the effects of BCG vaccination: the first aimed at interrogating the literature for immunological mechanisms for the heterologous effects of BCG; and the second describes studies where BCG has been used as an intervention in animal models of infectious diseases. They conclude that BCG likely mediates protective effects via a number of mechanisms, including epigenetic modification.

It has long been known that micronutrients can have effects on immunity and vaccine responses and there has been increasing evidence that vitamin A supplementation (VAS) in particular can influence the heterologous effects of vaccines, generally enhancing them. A literature review by Jensen and colleagues provides the first comprehensive summary of the role VAS plays in modulating the heterologous effects of vaccines, and sex differences in these effects.

A study by Xiang et al. provide data demonstrating that naked polystyrene nanoparticle vaccines carrying no antigens can provide protection against a non-lethal murine malaria challenge. They go on to demonstrate that this protection is mediated by an effect on dendritic cell homeostasis, providing a novel...
mechanism by which vaccines can induce protection against heterologous infection.

This paradigm shift in our understanding of the broader effects of vaccination hails a new phase in vaccine research. At this moment WHO have concluded that the evidence is insufficient to recommend policy change, citing lack of immunological evidence and randomized controlled trials. A group of international researchers from diverse fields have formed the ‘Optimmunize Network’ aimed at galvanizing research into this important area. The challenge now is to determine the precise immunological mechanisms with the promise of being able to harness or mimic beneficial effects and avoid the deleterious effects. Furthermore, these effects would need to be taken into account in a situation where beneficial vaccines such as BCG and MV might be withdrawn due to the development of a new more efficacious vaccine or eradication of the vaccine-targeted disease.

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References