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Keynote Lecture

Non-specific effects of vaccination: a game changer

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Vaccinology lives in a disease-specific paradigm with eradication of diseases as the ultimate goal. Hence, the assessment of vaccines has been based on measuring disease-specific outcomes like antibodies and clinical protection. It is assumed that the effect on overall morbidity and mortality is always beneficial. However, studies of the introduction of vaccines in high-mortality areas have questioned the disease-specific approach.

The introduction of live vaccines like measles vaccines and bacille Calmette-Guérin vaccine against tuberculosis (BCG) has been associated with much larger reductions in overall mortality than can be explained by the prevention of the specific targeted infections. In contrast, some inactivated vaccines have been associated with increases in mortality in spite of preventing the targeted infections.

An increasing number of observational studies and randomised trials have supported the initial observation of a major difference between live and inactivated vaccines in terms of their impact on overall mortality; live vaccines, including measles vaccine, oral polio vaccine, BCG and vaccinia, have beneficial overall effects whereas inactivated vaccines, including diphtheria-tetanus-pertussis vaccine (DTP), Hepatitis B vaccine and inactivated polio vaccine may have deleterious effects in spite of providing protection against the targeted infections. Similar differential effects have also been found with respect to morbidity in high-income countries.

The non-specific effects of vaccines are frequently sex-differential, e.g. DTP has a stronger negative effect for girls, and vaccines often interact with other immune-modulating interventions like vitamin A. The Strategic Advisory Group of Experts on Immunization (SAGE) of WHO has recently recommended further research into the potential non-specific effects of vaccines.

These observations, not least the opposing effects of live and inactivated vaccines, contradict the current paradigm in vaccinology, that vaccines have only disease-specific effects. The non-specific effects can only be understood as a result of beneficial or deleterious immune training. A new paradigm should be able to explain contradictions in the previous disease-specific understanding; for example, though protective against measles infection, the WHO-recommended high-titre measles vaccine (live) was associated with two-fold increased female mortality in several trials in Africa and WHO had to withdraw the vaccine. The increase in mortality was due to DTP being administered after measles vaccine. A new paradigm will raise questions which have not been considered before; for example, if a live vaccine has beneficial effects, we might do harm by stopping vaccinations once the targeted disease is eradicated. There are reasons to believe that this happened when smallpox was eradicated and vaccinia was stopped. It may also happen once we have eradicated polio and measles and stop vaccinations, reduce the intensity, or replace them with inactivated vaccines. Taking the non-specific effects of vaccines into consideration in the planning of vaccination programmes could lead to major improvements in child survival in low-income countries and to major reductions in health care cost in high-income countries.