

Highlights in 2015 (English version)

Non-live vaccines: The “bad news” got worse

Diphtheria-tetanus-pertussis (DTP) vaccine: We examined what happened when DTP was introduced in urban Guinea-Bissau in 1981. DTP-vaccinated infants had 5-fold higher mortality than infants who had not yet received DTP, and 10-fold higher mortality than infants receiving oral polio vaccine (OPV) only. In children aged 1-2 years DTP was associated with 2.3-fold increased mortality. Thus, all studies of DTP-introduction show higher overall mortality and thus negative “non-specific effects” (NSEs). The new *pentavalent vaccine* (DTP+hepatitis B/H. influenza) has similar negative NSEs as DTP.

Malaria vaccine: The final results for RTS,S, the first malaria vaccine (GSK), were published; RTS,S provided 18-36% protection against clinical malaria and was quickly approved for use by EMA. CVIVA showed that RTS,S was associated with 2-fold higher female mortality; thus, RTS,S seems to possess similar negative NSEs as other non-live vaccines.

Live vaccines: The “good news” got even better

Oral polio vaccine: We found that OPV has much stronger beneficial NSEs than we had assumed. We conducted a randomized controlled trial of OPV at birth; OPV was associated with 32% (0-55%) lower infant mortality. During the last decades, numerous OPV campaigns were carried out to eradicate polio. We found that the OPV campaigns are associated with 19-25% reduction in the mortality rate; this beneficial NSE is more pronounced with each additional dose of OPV. In Denmark, OPV was associated with reduced risk of infectious disease hospitalizations.

Measles vaccine: We analyzed the effect of two measles vaccine (MV) campaigns and found strong reductions in overall mortality, especially among children who had previously received routine MV. With the findings for OPV, BCG and *Vaccinia* there is now strong evidence that “boosting” with live vaccines confers even stronger beneficial NSEs. The repeated OPV and MV campaigns may have been the main drivers for the fantastic decline in child mortality during the last decades.

BCG: The Danish Calmette Study showed BCG to be associated with 12% (0-22%) reduction in atopic dermatitis, the effect being most marked in atopic families (17% (4-28%) reduction) and children of BCG vaccinated mothers (29% (4-48%) reduction). For children with atopic predisposition, one case of atopic dermatitis would be prevented by vaccinating 24 children; among children of BCG-vaccinated mothers, vaccinating 15 children would prevent a case.

Support from immunology: Our immunological studies confirmed marked differences between live and non-live vaccines; the live BCG and *Vaccinia* vaccines induce trained innate immunity, the non-live influenza and typhoid fever vaccines induce innate immune tolerance.

Mother matters: Live vaccines work even better in children of vaccinated mothers. Since MV in the presence of maternal measles antibodies is associated with strong beneficial NSEs, we collected data on maternal BCG status in The Calmette Study. BCG had protective effects against infectious disease admissions in children of BCG-vaccinated mothers, but no effect in children of BCG-unvaccinated mothers. The pattern was similar for atopic dermatitis.

Light ahead? Though WHO concluded in 2014 that BCG and MV are associated with halving of overall mortality and DTP with increased mortality in most studies, little has happened.

In 2015, we showed that vitamin A supplementation (VAS) is immunomodulatory and the effect of VAS is modified by vaccines in a sex-differential manner. In vaccinated communities, VAS to children >6 months may be harmful for males. Nonetheless, VAS >6 months is still policy and many resources are spent on this possibly useless and sometimes harmful intervention. WHO is reviewing its VAS guidelines in 2016; we hope that our paper will influence the process.

Spotlight: Our work is getting increasing attention. We were invited as keynote speakers for several conferences, and four filmmakers are now preparing films on the non-specific effects.