OPTIMMUNIZE 2022

Conference Statement

The OPTIMMUNIZE 2022 conference was opened by the Director-General of the World Health Organization (WHO), Dr. Tedros A. Ghebreyesus, who emphasized the importance of vaccines for global health, but also noted that child mortality remains high, and we need to examine how we can use these tried and tested tools we have in new ways, including for their non-specific effects.

The non-specific effects (NSEs) of a vaccine alter the risk of other diseases unrelated to the targeted pathogen. These effects are mediated via generalized effects on the immune system, including the innate immune system. These are often sex-differential. In the context of Public Health, vaccine NSEs may be very profound.

In his keynote presentation, the "grandfather" of vaccines, Professor Plotkin, stated that there was no doubt that non-specific effects of vaccines are a real phenomenon of extreme importance – and a part of vaccinology that needs to be explored much more.

At the OPTIMMUNIZE 2022 conference, further evidence for non-specific and sex-differential effects was presented. Highlights include:

- Since the last OPTIMMUNIZE conference in 2020, many new epidemiological studies have been published, corroborating NSEs of, for instance, BCG vaccination in children.
- Maternal vaccination with BCG and measles vaccines primes for even stronger beneficial NSEs of these vaccines in their offspring.
- Oral polio vaccine (OPV) campaigns are associated with marked NSEs and significant reductions in child mortality in Africa and Asia.
- A series of randomized trials into the NSEs of BCG and other live vaccines against COVID-19 have revealed that these vaccines reduced the risk of COVID-19 in vulnerable individuals and, furthermore, reduced all-cause mortality across trials.
- Two additional vaccines, a new tuberculosis vaccine (MTBVAC) and pneumococcal vaccine, were associated with beneficial NSEs on overall health.
- At the immunological level, measles-mumps-rubella vaccine has been shown to lead to increased activation of gamma-delta T-cells.
- The BNT162b2 mRNA vaccine against COVID-19 is associated with reduced innate responses to influenza antigens.
- Rotavirus vaccine is associated with non-specific and sex-differential immunological effects in children.
- Diphtheria-tetanus-acellular-pertussis and influenza vaccines are associated with non-specific and sex-differential immunological effects in young adults and in the elderly

For further information, see abstract book.

At a panel discussion with participation from the head of WHO's Department for Vaccines, and panelists with experience from the US FDA, UNICEF, national immunization committees and foundations, discussions focused on whether the substantive accumulated evidence for the NSEs of vaccines were sufficient for translation into action able policy. If not, which studies were needed.

Five specific areas were discussed:

1. BCG vaccination of neonates to reduce neonatal mortality
2. BCG re-vaccination of scar-negative children to reduce child mortality
3. BCG vaccination to prevent atopic dermatitis in children whose parents have atopic disease
4. OPV campaigns to reduce child mortality
5. BCG and other live vaccines as bridge-gap vaccines in epidemic/ pandemic circumstances.

1. There was consensus that there was compelling evidence for BCG vaccination at birth being associated with marked reductions in neonatal morbidity and mortality in Africa, and that biological mechanisms underlying these effects have been identified. There was a proposal to the WHO to change the indication for BCG to include reductions of neonatal mortality and to introduce vaccination program performance indicators that focus on early vaccination and the induction of a BCG scar as an indicator of correct vaccination administration.

It was noted that correct administration of BCG is required and that large-scale training programs must be implemented at the local level to promote (i) correct administration to induce a scar, (ii) to alert to the beneficial NSEs and (iii) to ensure that each vial is opened regardless of doses to be administered (as currently recommended by the WHO, but often not implemented due to wastage policies).

2. For BCG re-vaccination, there is also good evidence that among BCG-vaccinated children, a scar is associated with lower mortality and the presumption is that re-vaccination of scar-negative children would lower their mortality. Prior to implementing re-vaccination for scar-negative BCG-vaccinated children as policy, large-scale randomized trials are needed, also to address safety.

3. For the proposed use of BCG against atopic dermatitis, the discussion focused on the modest health benefit – 15% reduction – and the consensus was that this niche market was best served by private interests.

4. Regarding OPV campaigns, there was again consensus that there was compelling evidence for beneficial non-specific effects, but that large-scale randomized trials were needed. It was questioned whether nOPV, which is currently only recommended for outbreak situations under emergency use listing could be used in randomized trials, to test whether it had similar beneficial non-specific effects.

5. With respect to the beneficial NSEs of BCG and other live vaccines against influenza, there was interest in mounting clinical trials to test this strategy during a normal influenza season, as positive results would likely indicate that these vaccines could be used as bridge-gap vaccines if a novel influenza virus strain would threaten to cause a pandemic. Diverse populations must be included in these trials.

It is the hope that large funding agencies will allocate funding for these important research questions, e.g., Gates Foundation.

The OPTIMMUNIZE 2022 Organizing Committee is now taking steps to formalize this informal group of researchers interested in vaccine NSEs as an OPTIMMUNIZE Association.