Assessing non-specific effects (NSE) of a new TB vaccine during clinical development

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As a member of TBVI Product & Clinical development team I declare receiving a honorarium for consultancy on TB vaccine clinical development

NSE of BCG

Protective effect against mortality and morbidity due to other causes than tuberculosis (TB), the disease targeted by BCG vaccination

Reported in settings with a high infant mortality and morbidity

Previous clinical trials and observational studies Higgins et al, 2016

BCG has a beneficial effect on all cause mortality within the first 6-12 months of life

- Average relative risk of 0,70 (in 5 clinical trials)
- 48% reduction in low-birth-weight infants (in 2 clinical trials)
- Average relative risk of 0,47 (in 9 observational studies)

Effect predominant in the first 6-10 weeks of life

BCG Danish most frequently used vaccine

Mortality primarily due to infections other than TB

Decreasing susceptibility to BCG untargeted infections

Previous clinical trials and observational studies Higgins et al, 2016

Findings fraught with controversy

-No data on the cause of deaths. However TB death is infrequent in this age group and no difference was found in the effect between infants exposed to TB and unexposed to TB

-Bias related to baseline confounding

Overall data suggest a beneficial effect of BCG on all cause mortality in infants and young chidren.
WHO SAGE and IVIR-AC concurred that implementation of high quality prospective studies, including randomized controlled trials where feasible, is needed to provide conclusive evidence on the NSE of BCG .

Prospective study design considered by WHO*

Randomized controlled trial of early (at birth) versus late (at 14 weeks) vaccination with BCG to estimate its NSE in infancy

To compare the risk of death and severe illness in infants less than 14 weeks who had BCG administered at birth with that in infants who had BCG at 14 weeks of age

Assuming a 15% reduction in the risk of death and a risk of 1% to 3% in the deferred BCG group, the sample size ranges from 60,000 to 177,000 participants for 90% power and α risk of 0,05.

Assuming a 15% reduction in the risk of severe illness in the first 14 weeks and a risk of 2% to 5% in the deferred BCG group sample size ranges from 32,000 to 89,000 participants for a 90% power and α risk of 0,05.

*Ad-hoc expert consultation on epidemiological studies for NSE of vaccines, Geneva, 16-17 February 2016.

BCG-induced NSE on heterologous infectious disease in Ugandan neonates*

Prospective randomised observer blind study in 560 healthy newborns assigned in a 1:1 ratio to receive BCG Danish either at birth or at 6 weeks of age (with first DTP dose)

Active follow up of infants until to the age of 10 weeks

Rate of physician-diagnosed non-TB infectious disease:

- During the first 6 weeks of life: lower rate among infants vaccinated at birth, HR = 0·71 (p=0·023),
- During the subsequent 6-10 weeks of life: no difference between both groups, HR= 1·10 (p=0·62)

Similar trend for serious illness as defined by the WHO integrated management of childhood illness

- Beneficial NSE of BCG given at birth on non-TB infectious disease in the first 6 weeks of life.

* thelancet.com/infection Published online February 17, 2021 https://doi.org/10.1016/S1473-3099(20)30653-8

New TB vaccines for immunisation of neonates

Vaccine candidates against TB meant to replace neonatal BCG are currently in clinical development stage, Phase2 or 3 trials with the objective to demonstrate relative protective efficacy against TB disease compared to BCG

Despite controversy i t is assumed that BCG induces NSE which may have important implications for Public Health policy

As to whether those candidate vaccines confer similar NSE should be evaluated

Prospective randomized study comparing birth and deferred vaccine administration as proposed by WHO can only be considered once these new vaccines have demonstrated safety and specific protective efficacy and have been licensed.

NSE of a new TB vaccine cannot currently be inferred from immunological studies as biological mechanism(s) underlying NSE remain to be elucidated in infants

Assessment of relevant endpoints for the NSE in New TB vaccines Phase 3 efficacy trials (1)

New TB vaccine phase 3 efficacy trials

- Prospective, randomized, ideally double blind, BCG Controlled
- Active follow-up of study participants for careful monitoring of adverse events

Adverse events corresponding to clinical outcomes relevant to NSE (not due to TB)

- Deaths
- Severe illness associated with any of the following danger signs observed or verified by a study clinician: inability to feed or vomiting of everything, lethargy or unconsciousness, severe lower chest in-drawing, axillary temperature of ≥37.5oC or <35.5oC, grunting, cyanosis, convulsions or a history of convulsions
- Less severe illness.

Such Adverse Events are recorded as

- Serious adverse events (SAE) including Death and Hospitalisation
- Medically Attended Adverse Events

Events classified as MEDRA SOC « infections and infestations »

Assessment of relevant endpoints for the NSE in New TB vaccines Phase 3 efficacy trials (2)

Comparison of endpoints of interest for NSE between recipients of BCG and the new TB vaccine

- Incidence of ”all causes” Death and Death due to infections (not TB)
- Rate of “all cause” Hospital admissions and admissions due to infections(not TB)
- Rate of Medically Attended Adverse Events due to infections (not TB)

Time windows

- Day 0 to day 42 (or first dose of DTP)
- Day 42 to day 365

Similar rate of clinical outcomes relevant to NSE would suggest that a new TB vaccine has a comparable beneficial NSE potential compared to BCG

Conclusions

Despite controversy NSE of BCG may have important implication for Public health policy

Documenting conclusively NSE of a new TB vaccine for newborns can reasonably not be completed before licensure

The framework of phase 3 efficacy trials of new TB vaccine offers the possibility to compare clinical outcomes relevant to NSE between BCG and the new TB vaccine and inform about the potential NSE of new TB vaccines