Highlights in 2016 (English version)

Towards a paradigm shift: Predictions confirmed

CVIVA's progress towards a paradigm shift for vaccines consists of two interlinked processes: 1) accumulating contradictions of the old paradigm (i.e. vaccines have only specific effects) and 2) identifying the principles of the new paradigm (i.e. in addition to specific effects, vaccines have important non-specific effects (NSEs)).

We have now accumulated numerous contradictions, and with the publication of the WHO review of NSEs of BCG, measles vaccine, and diphtheria-tetanus-pertussis (DTP) vaccines in 2016, we got ***official recognition*** that vaccines indeed do have effects on mortality, which cannot be explained by their specific effects (*Higgins, BMJ 2016*).

With respect to the principles of the new paradigm, we have formulated ***ten principles*** (Table 1). Four were with us from CVIVA's start: live vaccines have beneficial NSEs, non-live vaccines have negative NSEs, NSEs are strongest in females, and NSEs are seen most strongly as long as a vaccine is the most recent vaccine. Another six are the results of CVIVA's first years.

It is fascinating that ***we become better and better at making predictions***. As stated by Lakatos, progress in science is made when theories make surprising predictions that are confirmed. Some examples:

1. **Non-live vaccines associated with increased female mortality**

In 2005, we formulated in the hypothesis that non-live DTP vaccine is associated with increased mortality in girls. In 2016, we conducted a meta-analysis. Overall, DTP was associated with a 2.54 (95% CI 1.68-3.86)-fold higher mortality in girls (but no increase in boys). If anything the effect was stronger in the studies conducted *after* the hypothesis was formulated (3.53 (1.86-6.67)) (*Aaby, Trans Roy Soc Trop Med 2016*).

Expanding our theory regarding non-live vaccines, CVIVA made the prediction that a new non-live malaria vaccine, RTS,S, which was partly protective against clinical malaria, would nonetheless be associated with increased female mortality. In 2016 we confirmed that RTS,S was associated with 2-fold higher mortality for girls, but made no difference for boys (*Klein, mBio 2016*). WHO has postponed the launch of RTS,S until safety studies have been done.

2. **Smallpox and BCG vaccine associated with lower mortality among Danes**

The live smallpox and BCG vaccines are no longer used in Denmark, but we conducted a historical study of the birth cohorts 1965-1976, who experienced the phase-out, to test the *a priori* hypothesis that being vaccinated with these vaccines would reduce mortality from natural causes of death. As predicted, those vaccinated just before phase-out had 46% (19%-64%) lower mortality than those not vaccinated (*Rieckmann, Int J Epidemiol 2016*).

Thus, the above examples illustrate how ***our theories can make important predictions and produce new facts, which are improbable according to the current paradigm***.

Support from immunology: Via two interacting streams of experiments, we identified a BCG signature. *1.* In an established sepsis model in newborn mice, BCG was associated with a ~50% reduction in mortality. We identified a rapid increase in the production of neutrophils following a neonatal dose of BCG. *2.* We identified the same signals following BCG in human newborns, namely a systems biological signature centered around increased neutrophils. As neutrophils are pivotal for protection from infection, this provides a ***likely mechanistic explanation for the observed beneficial NSEs of BCG***.

In human volunteers, providing a BCG vaccine 4 weeks before a challenge with a yellow fever vaccine lowered the yellow fever viral load in the blood. This is ***the first in vivo study to demonstrate that BCG vaccine effectively can affect the course of a subsequent completely unrelated pathogen challenge***.