nature medicine

Lessons from vaccine history

In spite of years of effort, we still lack highly efficacious vaccines against HIV, tuberculosis, malaria and numerous other widespread pathogens. Two recent setbacks in vaccine trials suggest that it's time to rethink how new vaccines are developed and to investigate what can be learned from the existing armament of childhood vaccines.

In November, a phase 3 trial of the malaria vaccine RTS,S/AS01 in African infants showed only 31% protection against clinical malaria compared with a control nonmalaria vaccine (*N. Engl. J. Med.* doi:10.1056/NEJMoa1208394). The results were disappointing to many, given the initial clinical experience with RTS,S.

In 1997, in a trial of 22 adults, one formulation of RTS,S protected six out of seven individuals from infection, whereas two other formulations of the same antigen did not. Subsequent phase 2 trials of two different formulations of RTS,S in young children also showed protective efficacy. And in early results of the phase 3 trial reported in 2011, the vaccine was 55.8% efficacious at protecting against a first episode of clinical malaria in young children aged 5 to 17 months at trial enrollment in the first 12 months after vaccination. The new results show that in infants aged 6 to 12 weeks at enrollment, which is a population at high risk of developing severe malaria, the protective efficacy of RTS,S/AS01 is substantially lower (see News story page 1723).

Similarly disappointing were the recent results of a phase 2b trial of a vaccine candidate against dengue fever, which is caused by four serotypes of dengue virus (*Lancet* **380**, 1559–1567, 2012). Although the vaccine showed 30% overall efficacy against infection, protection was limited to three of the four serotypes of dengue, and the vaccine did not confer protection against the most prevalent serotype (serotype 2) in the region where the trial was conducted. As antibodies to one serotype have been associated with enhancement of disease after infection with another serotype, the lack of complete protection could increase the risk of developing severe disease, although this was not observed in the trial.

Still, some remain optimistic about both the malaria and the dengue vaccine candidates, arguing that modest protection may be better than none, particularly in view of the hundreds of millions of individuals who are infected with these pathogens each year. But the suboptimal results of these trials are emblematic of the problems with vaccine development in general—we don't even understand how effective vaccines work, making it very difficult to identify the reasons why new candidates fail. The dengue vaccine induced an antibody response against serotype 2, yet did not protect against it. And in the initial trial of RTS,S in adults, all three formulations induced similar antibody and T cell responses, but only one formulation was protective against malaria. The fact that we don't know what kind and what quality of immune response is necessary to prevent infection greatly challenges attempts to rationally approach vaccine design.

We do, in theory, have a starting point to try to better understand the mechanisms of vaccine efficacy. In the US, within the first six years of life, children receive ten different vaccines that provide protection against 14 different viral and bacterial diseases. All but one are delivered intramuscularly. Several contain attenuated or inactivated viruses, whereas others are composed of bacterial sugars, virus-like particles or purified proteins. Some contain aluminum-based adjuvants, some do not. In spite of their differences, when primarily injected into an arm or a leg, they all succeed in inducing protective immunity against an array of pathogens that target different tissues and use different strategies of immune evasion. If there is strength in numbers, surely there are commonalities to the induction of protection by these distinct vaccines that can be understood and applied to the development of future vaccines.

The trouble is that there are limited information and data from the original trials of approved childhood vaccines and no investment—and therefore no incentive—to analyze anew the protection that they confer in humans. Nevertheless, there is impetus to rationally develop vaccines: systems biology approaches have identified molecular signatures of the immune responses to influenza and yellow fever vaccines, albeit not correlates of the protection the vaccines confer. Preclinical studies of new adjuvants have provided fresh insight into their stimulatory effects on innate immune cells, although the key pathways by which they induce protective immunity remain unclear. And improved tools exist to predict T and B cell receptor epitopes and their immunogenicity, although the present accuracy of these methods is not sufficient for routine application. Moreover, as the recent experiences with the dengue and malaria vaccines show, predicting immunogenicity is not equivalent to predicting protection. Therefore, it is incumbent on the vaccine field to increase investment into identifying the mechanisms of protection of successful vaccines in humans in order to fine-tune the application of these new tools to contribute to future vaccine success.

Different pathogens have different degrees of antigenicity, mutation rates and mechanisms to subvert protective immunity. Yet even the wiliest infection might be blocked if the right magnitude, breadth and potency of immune response were rapidly recruited upon initial infection. Understanding what those parameters should be, whether they are common to all infectious agents and how they can be induced by a vaccine will require both empirical and rational design, as well as a systematic approach to understanding the past to help guide the future.