"Imperfect" vaccines may encourage more potent pathogens, model suggests

A model that uses evolutionary theory to investigate the potential effect of vaccines on public health suggests that vaccines designed to reduce pathogen growth rate or toxicity might lead to more severe disease in unvaccinated individuals. "Vaccines rarely provide full protection from disease, but imperfect vaccines are used to protect individuals and whole populations. If a vaccine selects for pathogens of higher virulence, this may lead to an increase in mortality overall", explains lead researcher Andrew Read (Institute of Cell, Animal and Population Biology, University of Edinburgh, UK).

"The impact of vaccines that are not expected to provide full immunity, such as candidate vaccines for malaria, is of particular concern", he adds. Read and colleagues applied their model to assess the potential effects of various malaria vaccines currently in development. These include vaccines that stimulate immunity to the three stages of the life cycle of *Plasmodium* species, and also antitoxin vaccines. The model was set up with values typical of year-round endemic *P falciparum* malaria in a high transmission area. "The malaria model predicts that antigrowth rate and antitoxin vaccines select for higher virulence, while anti-infection vaccines select for lower parasite virulence", explains Read. In the right combination, however, the beneficial effect of anti-infection vaccines can be used to reduce the evolutionary risk of blood stage or antitoxin vaccines.

The investigators also estimated how long virulence evolution in a parasite might take after a vaccination programme starts. "When we used malaria as an example to track the spread of a virulence mutant through time, a 90% vaccine coverage with an antigrowth rate vaccine of 80% efficacy caused the evolution of a mutant parasite with twice the virulence", says Read. "In 38 years, the higher-virulence mutant would have increased to 50% of the parasite population, after which it would have very rapidly become the dominant form." Although this time-scale is relevant to public health, it is outside the scope of clinical trials (*Nature* 2001; **414:** 751–56).

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Vaccine effect on virulence

Read warns that antigrowth rate and antitoxin malaria vaccines that are widely used for their short-term beneficial effect at the individual level could increase the risk of mortality for unvaccinated people, such as young children and travellers.

Anthony Stowers (National Institute for Allergy and Infectious Diseases, Bethesda, MD, USA) welcomes the principle of using models to assess the effect of vaccines, but asks whether this model fits what we know about malaria. "There has been widespread use of antimalarial drugs at suboptimal doses since at least the early 1980s in areas like Papua New Guinea and resistant parasites have emerged. This is analogous to the partial coverage of a partially effective antigrowth vaccine but has not resulted in a noticeable increase in deaths from malaria in these high endemic areas as far as I am aware", he says.

Kathryn Senior

Neuroglobin might protect brain cells during stroke

Neuroglobin, a recently discovered cerebral protein with myoglobin-like affinity for oxygen, is expressed at increased levels in brain cells in response to oxygen deprivation, and protects neurons, a US study of hypoxia in mouse cells reports this week.

"Their observation that neuroglobin promotes the survival of neuronal cells upon hypoxia will have, if confirmed by future studies, very important medical implications", comment Thorsten Burmester and Thomas Hankeln (Johannes-Gutenberg-University Mainz, Mainz, Germany), part of the team who discovered neuroglobin (*Nature* 2000; 407: 520–23). "This would make neuroglobin a putative target for the therapy of diseases involving hypoxia and ischaemia such as stroke, but also for a variety of neurodegenerative diseases", they add.

David Greenberg and colleagues (Buck Institute for Age Research, Novato, CA, USA) grew mouse neuronal cells both with and without oxygen for up to 24 h. Cells deprived of oxygen produced higher levels of neuroglobin protein and mRNA than controls. In-vivo simulation of ischaemia by cerebral vascular occlusion for 90 min also resulted in higher expression of neuroglobin in rat cortex cells (*Proc Natl Acad Sci USA* 2001; 98: 15306–11).

Researchers also compared mouse cells that were engineered to either overexpress or underexpress neuroglobin, and found that increasing the expression of the protein lessened hypoxic injury—shown by reduced integrity of cell membranes—whereas reducing expression worsened the effects.

Greenberg is excited about the possible implications of the results. "Neuroglobin may serve to limit brain damage from stroke. If this is the case, searching for drugs that can increase neuroglobin expression might lead to new treatments for stroke", he told *The Lancet*.

However, the study is only a starting point for further work. "We are now focused on determining how hypoxia turns on neuroglobin expression, how neuroglobin protects neurons from hypoxia, and whether changes in neuroglobin expression modify outcome from stroke", states Greenberg.

Burmester and Hankeln agree that although the research represents an important step, more work is needed. "Clearly, however, a lot of genetic and physiological studies remain to be done in humans and in animal model systems to confirm and to extend their findings. In particular, the cellular function of neuroglobin, be it sensing or storage of oxygen, or even additional ones, such as binding nitric oxide, still remains unclear", they said.

Sarah Venis