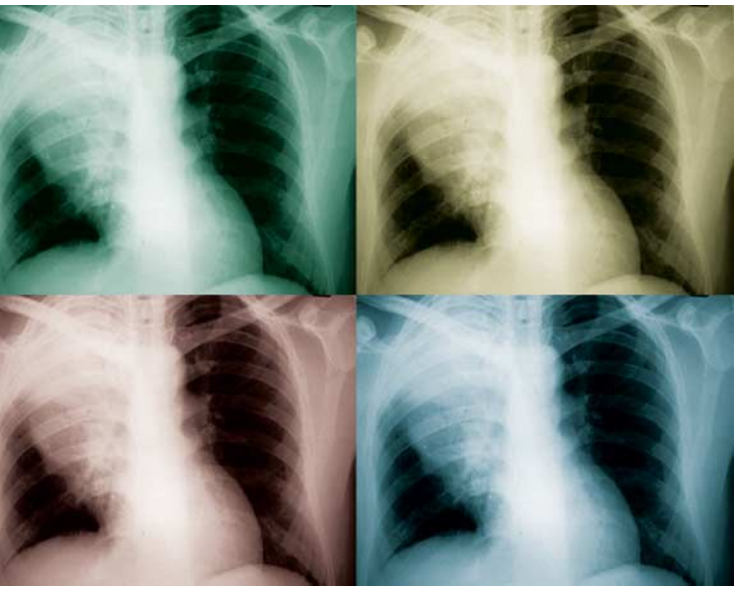
INFECTIOUS DISEASE

Partners in crime



Chest X-ray of a man with *Streptococcus pneumoniae* pneumonia.

Analysis of a clinical trial just published in *Nature Medicine* suggests that bacterial and viral cases of pneumonia might not be as independent as previously believed.

Acute respiratory infections kill more than two million children each year and are the leading cause of death in children under five years of age. Although *Streptococcus pneumoniae* remains the most common bacterial cause of lower-respiratory illness in children, viral pathogens also dominate as a common cause of these infections. From previous analysis of a clinical trial to evaluate the efficacy of a 9-valent pneumococcal conjugate vaccine, it was shown that this vaccine reduced the incidence of radiologically confirmed pneumonia and also reduced the incidence of vaccine-serotype and antibiotic-resistant invasive pneumococcal disease among children. In this study, Keith Klugman and colleagues addressed the question of whether the vaccine had any effect on virus-associated pneumonia. Although earlier studies had demonstrated temporal associations between viral infections and bacterial pneumonia, the hypothesis that viruses and pathogens were co-pathogens in the disease had not been studied in the context of a randomized clinical trial.

To investigate the link between pneumonia caused by the bacterial pathogen and cases of the disease with a viral aetiology, the authors extended their analysis of the clinical trial data to show that the conjugate vaccine prevented 31% of pneumonias associated with any of seven respiratory viruses including influenza A and respiratory syncytial virus. By contrast, no differences were found in the frequency of all-cause or virus-specific bronchiolitis between children who received the vaccine and those who received the placebo. These data clearly demonstrate that the conjugate vaccine reduces pneumonia associated with respiratory viral infections, indicating that *S. pneumoniae* has an important role

BACTERIAL PATHOGENICITY

A sticky situation

A report in *Science* presents evidence that the functional adaptation of a bacterial adhesin in response to changes in the predominant blood groups in the local human population contributes to the success of *Helicobacter pylori* as a gastric pathogen.

H. pylori persistently colonizes the gastric mucosa, and is present in more than 50% of the global population. *H. pylori* infection is a risk factor for the development of gastritis, peptic ulcers and gastric adenocarcinoma. Several *H. pylori* adhesins have been identified that help the bacterium stick to the surface of gastric epithelial cells. Now, researchers from the United States and Sweden have undertaken a large-scale study of the variations in binding of one particular adhesin, BabA.

In humans, a combination of cell-surface protein, glycoprotein and glycolipid antigens determines an individual's blood type, with two of the most common systems being the ABO and Lewis antigens, which are highly expressed in the gastric epithelium. Previously, *H. pylori* BabA had been shown to bind to the H antigen and its associated Lewis antigen, Lewis b (Leb), which correspond to blood group O.

Initially, Aspholm-Hurtig *et al.* studied variation in Lewis antigen binding capacity in a small group of *H. pylori* strains and found that the strains tested fell into two distinct categories — generalists, which bind blood group A, B and O Lewis antigens, and specialists, which only bind Leb, the blood group O Lewis antigen. When the analysis was extended to 377 different *H. pylori* isolates from a variety of geographical locations the authors noticed that geography seemed to influence binding: 95% of isolates from Sweden, Germany, Spain, Japan and Alaska were generalists, whereas 40% of Amerindian isolates examined (from Peru, Venezuela and Columbia) were specialists. The preponderance of specialists in the South American isolates examined is in line with the fact that, unusually, the Amerindian populations in this region are almost all blood group O.

The affinity of BabA for Leb is higher than it is for the other Lewis antigens, and the authors speculate this could increase the strength of binding of *H. pylori* to the gastric epithelium in individuals who are blood group O. There is no further differentiation in affinity for Leb between specialists and generalists however, indicating that for generalists, the key to successful long-term survival within a host population is a flexible binding capacity.

Evolutionary analysis revealed that BabA has been subject to heterogeneous selection pressure, as well as evidence for diversifying selection for amino acid changes. The authors conclude this study by proposing that the binding specificity of BabA can evolve rapidly during cycles of selection for adherence during infection and transmission, and this rapid adaptation of BabA has contributed to the success of *H. pylori* as a pathogen.

Sheilagh Clarkson

References and links

ORIGINAL RESEARCH PAPER Aspholm-Hurtig, A. *et al.* Functional adaptation of BabA, the *H. pylori* ABO blood group antigen-binding adhesin. *Science* **305**, 519–522 (2004)

in the development of pneumonia associated with viruses and that these viruses contribute to the pathogenesis of bacterial pneumonia.

In conclusion, this study establishes that a significant proportion of viral pneumonia is attributable to bacterial co-infection and is preventable by a bacterial vaccine. Because immunization of children has been shown to reduce invasive *S. pneumoniae* disease, these data also raise the exciting possibility that infant immunization with pneumococcal vaccines might also reduce morbidity and mortality associated with viral pneumonias in children and adults.

David O'Connell

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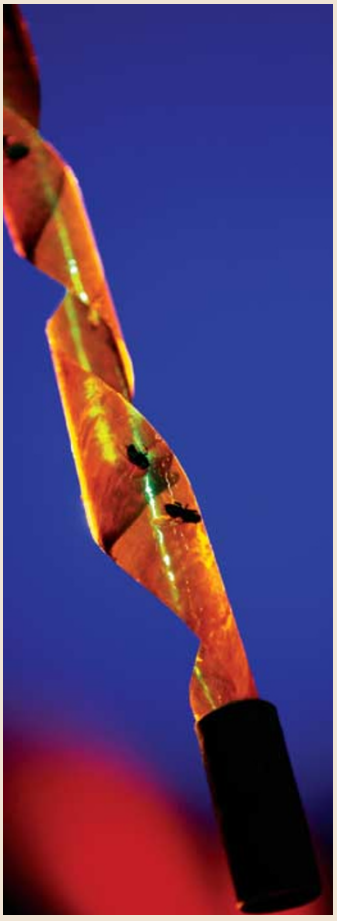
FURTHER READING Klugman, K. P. *et al.* A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N. Engl. J. Med.* **349**, 1341–1348 (2003)

WEB SITE

Keith Klugman's laboratory: http://www.sph.emory.edu/ih/kklugman.html



MALARIA

Joint attack on malaria

An international group of scientists, drawn from both academia and industry, has developed a new antimalarial drug candidate that will move into human clinical trials later this year.

The multidisciplinary team, which brought together researchers from the University of Nebraska, USA, Monash University, Australia, The Swiss Tropical Institute, Switzerland, and Hoffman-La Roche, Switzerland, describe in a recent issue of *Nature* how the early determination of the essential characteristics for a new antimalarial drug guided the discovery process, and ultimately enabled the selection of a new synthetic peroxide drug candidate with an improved therapeutic and pharmaceutical profile compared with artemisinin.

Malaria is caused by unicellular parasites of the *Plasmodium* genus, which can be transmitted to human blood by the bite of the *Anopheles* mosquito. Artemisinin contains a crucial peroxide bond that is believed to enable the formation of unstable free radicals of the drug, which poison the *Plasmodium* parasite by alkylating one or more of its essential proteins. Although artemisinin itself and several semisynthetic derivatives are in use today, concerns exist about their high cost of production, low oral activity and the length of treatment required.

The group's goal was to identify a new synthetic peroxide antimalarial with improved oral potency, shorter treatment requirements, low toxicity, and which is cheaper and easier to produce. With these aims in mind, the team developed a clearly defined product profile that guided the lead-optimization process.

First, they established a number of required molecular properties of the compound to ensure adequate oral absorption, such as lipophilicity, polar surface area and solubility. They then selected suitable intermediate compounds, to which functional groups could be added using simple chemical transformations to create candidate compounds having these desired properties. The antimalarial activity of a single dose of each candidate was assessed *in vivo* using mice infected with *Plasmodium berghei*, and the rate at which active compounds were broken down was assessed *in vitro* using microsome preparations containing metabolizing enzymes.

Candidates with good oral bioavailability, high activity and an acceptable half-life were then subjected to more rigorous secondary screens, in which they were compared with currently used malaria treatments, including artemisinin derivatives. Antimalarial activity was assessed *in vitro* against *Plasmodium falciparum*, the main cause of severe clinical malaria and death in humans. The *P. berghei* mouse model was also used to assess how quickly the compounds reduced disease symptoms, whether symptoms recurred and whether the compounds could protect against disease when administered before infection. Candidates were also assessed for their susceptibility to metabolism by cytochrome P450 enzymes, in addition to being subjected to standard toxicity tests.

A candidate has been selected on the basis of these tests that will undergo clinical testing in humans later this year. If successful, it will not only improve treatment for the millions of people in developing countries who contract malaria each year, but will also highlight the value of establishing strict selection criteria early on in the drug discovery process to guide lead optimization. Success would also demonstrate the potential for fruitful collaborations between academia and industry.

Clare Ellis, Associate Editor,
Nature Reviews Drug Discovery

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