Genetics study reveals how pneumococcus bacteria evolve to evade vaccines

January 29 2012

Genetics has provided surprising insights into why vaccines used in both the UK and US to combat serious childhood infections can eventually fail. The study, published today in *Nature Genetics*, which investigates how bacteria change their disguise to evade the vaccines, has implications for how future vaccines can be made more effective.

Pneumococcus (Streptococcus pneumoniae) causes potentially life-threatening diseases including pneumonia and meningitis. Pneumococcal infections are thought to kill around a million young children worldwide each year, though the success of vaccination programmes has led to a dramatic fall in the number of cases in countries such as the UK and US. These vaccines recognise the bacteria by its polysaccharide, the material found on the outside of the bacterial cell. There are over ninety different kinds – or 'serotypes' – of the bacteria, each with a different polysaccharide coating.

In 2000, the US introduced a pneumococcal vaccine which targeted seven of the ninety serotypes. This '7-valent' vaccine was extremely effective and had a dramatic effect on reducing disease amongst the age groups targeted. Remarkably, the vaccine has also prevented transmission from young children to adults, resulting in tens of thousands fewer cases of pneumococcal disease each year. The same vaccine was introduced in the UK in 2006 and was similarly successful.

In spite of the success of the vaccine programmes, some pneumococcal strains managed to continue to cause disease by camouflaging

themselves from the vaccine. In research funded by the Wellcome Trust, scientists at the University of Oxford and at the Centers for Disease Control and Prevention in Atlanta studied what happened after the introduction of this vaccine in the US. They used the latest genomic techniques combined with epidemiology to understand how different serotypes of the pneumococcus bacteria evolve to replace those targeted by the initial vaccine.

The researchers found bacteria that had evaded the vaccine by swapping the region of the genome responsible for making the polysaccharide coating with the same region from a different serotype, not targeted by the vaccine. This effectively disguised the bacteria, making it invisible to the vaccine. This exchange of genome regions occurred during a process known as recombination, whereby one of the bacteria replaces a piece of its own DNA with a piece from another bacterial type.

Dr Rory Bowden, from the University of Oxford, explains: "Imagine that each strain of the pneumococcus bacteria is a class of schoolchildren, all wearing the school uniform. If a boy steals from his corner shop, a policeman – in this case the vaccine – can easily identify which school he belongs to by looking at his uniform. But if the boy swaps his sweater with a friend from another school, the policemen will no longer be able to recognise him and he can escape. This is how the pneumococcus bacteria evade detection by the vaccine."

Dr Bowden and colleagues identified a number of recombined serotypes that had managed to evade the vaccine. One in particular grew in frequency and spread across the US from east to west over several years. They also showed that during recombination, the bacteria also traded a number of other parts of the genome at the same time, a phenomenon never before observed in natural populations of pneumococcus. This is of particular concern as recombination involving multiple fragments of DNA allows rapid simultaneous exchange of key regions of the genome

within the bug, potentially allowing it to quickly develop antibiotic resistance.

The original 7-valent vaccine in the US has now been replaced by a 13-valent vaccine, which targets thirteen different serotypes, including the particular type which had escaped the original vaccine. In the UK, the 7-valent vaccine resulted in a substantial drop in disease overall. This overall effect was a mixture of a large drop in frequency of the serotypes targeted by the vaccine with some growth in serotypes not targeted by the vaccine. The 13-valent vaccine was introduced in the UK in 2010.

Derrick Crook, Professor of Microbiology at the University of Oxford and Infection Control Doctor at the Oxford University Hospitals NHS Trust, adds: "Childhood vaccines are very effective at reducing disease and death at a stage in our lives when we are susceptible to serious infections. Understanding what makes a vaccine successful and what can cause it to fail is important. We should now be able to understand better what happens when a pneumococcal vaccine is introduced into a new population. Our work suggests that current strategies for developing new vaccines are largely effective but may not have long term effects that are as successful as hoped."

Dr Bernard Beall, a scientist at the Centers for Disease Control and Prevention commented: "The current vaccine strategy of targeting predominant pneumococcal serotypes is extremely effective, however our observations indicate that the organism will continue to adapt to this strategy with some measurable success."

The Wellcome Trust, which part-funded this research, views combating infectious disease and maximising the health benefits of genetic research as two of its strategic priorities. Dr Michael Dunn, Head of Molecular and Physiological Sciences at the Wellcome Trust commented: "New technologies allow us to rapidly sequence disease-causing organisms and

see how they evolve. Coupled with collaborations with epidemiologists, we can then track how they spread and monitor the potential impact this will have on vaccine efficiency. This will provide useful lessons for vaccine implementation strategies."

More information: Golubchik, T et al. Pneumococcal genome sequencing tracks a vaccine escape variant formed through a multi-fragment recombination event. *Nature Genetics*; e-pub Jan 29, 2012.

Provided by Wellcome Trust