

GENOME WATCH

The great escape

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This month's Genome Watch highlights how genomics has improved our understanding of how vaccines impact pathogen populations and their genomes.

Vaccines are arguably the most successful measure to protect against pathogens. Improving our ability to design vaccines and understanding their impact on bacteria is therefore of crucial importance. The diversity of bacterial genomes makes it challenging to target all variants of a bacterial species, and thus vaccines are often designed to target the main disease-causing types. The clearance of vaccine-target strains leaves an unoccupied niche that can be filled by strains that are not targeted by the vaccine.

One prominent example of a successful vaccine where the emergence of escape strains was addressed using large-scale genome sequence analyses is that which has been used to target *Bordetella pertussis*¹. Genomics was used to assess changes in the main antigens that are used in the vaccine; however, several other loci were also found to adapt, including genes that are involved in metabolism, indicating physiological adaptation by the pathogen. Interestingly, no substantial decrease in the number of different strains was observed after the introduction of a vaccine.

Many opportunistic pathogens have complex genomes due to their large accessory gene content, and recent studies have focused on the evolutionary dynamics of the entire complement of genes within a species (that is, the pan-genome). Although the total number of genes is relatively stable for bacterial species, the

proportion of core genes and variable genes differs widely. McInerney *et al.*² recently compared evolutionary models of horizontal gene transfer that could explain the differences between organisms that easily change between diverse habitats and organisms that are very restricted with respect to changing their niche. They concluded that the pan-genome is under adaptive rather than neutral evolution and that the easy transition between niches for organisms like *Escherichia coli*, and its large effective population size, favours a more dynamic gene pool.

A recent study that compared >600 *Streptococcus pneumoniae* genomes observed vaccine-induced metabolic shifts, where the clearance of lineages through vaccination opened metabolic niches, and advantageous genes were transferred from vaccine-targeted to non-vaccine-targeted lineages³. Corander *et al.*⁴ expanded analyses of the impact of vaccination on the metabolic and virulence profiles by using a collated data set of over 4,000 *S. pneumoniae* whole-genome sequences that were isolated from different geographical locations and from individuals that were either vaccinated or unvaccinated. The authors observed that a high number of intermediate frequency genes were specific for different lineages in the data sets. These genes were found to be under negative frequency-dependent selection (NFDS), meaning that the different alleles of these genes are rare in the population, giving the entire population better fitness. NFDS acted on genes that

enable competition for nutrient resources, such as metabolite transporters, thus providing access to different metabolic resources in the same niche. The other major group under NFDS were genes that encode proteins recognized by the host immune system; if a population has little variation at these loci, it is easily targeted by the host immune system; however, if many variant alleles exist at low frequency, the acquired immune response is less likely to recognize re-infection of a different strain. In addition, the abundance of different sequence types was not correlated between the different data sets; however, there was a correlation of distinct gene frequencies, which highlights the importance of maintaining a balance of intermediate-frequency genes in the population.

To summarize, the authors developed a new model to explain different rates of NFDS; simulations of the population dynamics could replicate the observed dynamics between serotype switching and lineage replacement, explaining how bacterial ecology can influence the impact of vaccine interventions.

With the rise of antimicrobial resistance, a better understanding of vaccine design and its impact on pathogen populations will be of crucial importance to reduce drug usage and thus the development of antimicrobial resistance.

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doi: [10.1038/nrmicro.2017.156](https://doi.org/10.1038/nrmicro.2017.156)

Published online 8 Dec 2017

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Competing interests statement

The author declares no competing interests.

