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Editorial

The evolutionary consequences of vaccination

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Vaccination is a primary tool for controlling and eradicating infectious diseases. Although research on vaccines has traditionally been the purview of medical scientists and virologists, evolutionary biologists have, in recent years, made significant empirical and theoretical contributions to this field. Many of these contributions have stemmed from a growing realization that evolutionary biology can offer important insights into a variety of issues related to human health and disease [1,2].

Pathogens often have the potential to evolve very rapidly, because of their short generation times, large population sizes and high rates of mutation. It is now commonly believed that the use of vaccines will typically result in novel selective pressure on pathogen populations, often resulting in the emergence of resistant genotypes. The purpose of this Special Supplement is to evaluate the current state of knowledge of vaccine-driven evolution, and to consider important potential areas of future research on this topic. The research reported in this Special Supplement originated from a workshop on the Evolutionary Considerations of Vaccine Use held at Rutgers University's Center for Discrete Mathematics and Theoretical Computer Science (DIMACS) in June 2005.

The contrasting evolutionary outcomes of vaccination for measles versus influenza demonstrate that developing a thorough understanding of the evolutionary consequences of vaccination is crucial for designing successful vaccination programs. Influenza displays a well-characterized pattern of continual antigenic evolution (see articles by Boni and by Gog, in this Special Supplement), whereas measles undergoes relatively little evolutionary change in this regard. As a result, influenza vaccines must be continually updated to maintain their effectiveness, while measles vaccines do not. This makes vaccination a more effective control strategy for measles than for influenza, because influenza can, in effect, evolve to circumvent this control measure. Similar differences in evolutionary outcomes have also been identified and analyzed for other pathogens ([3]; see articles by Gandon and Day and by Poolman et al., this Special Supplement).

These simple comparisons highlight a clear need for the development of a predictive evolutionary framework, based on the use of quantitative models, to help in the design of optimal vaccination strategies. While some progress towards this goal is being made (as evidenced by the contributions to this Supplement), many important issues still remain to be explored. These include:

(i) *Conflicts between epidemiology and evolution*. Vaccination strategies that are optimal from an evolutionary standpoint need not be optimal from an epidemiological standpoint. For example, perhaps the strategy that is most likely to be successful in the absence of evolutionary change is also the one that is most likely to lead to adverse evolutionary outcomes. Can we predict when conflicts between evolutionary and epidemiological processes are likely? If there are conflicts for vaccination strategies, how can we weight the relative importance of evolutionary and epidemiological issues in order to make informed decisions? The optimal balance between epidemiological and evolutionary outcomes depends on the timescales over which these outcomes occur, and the level of discounting of the future relative to present. Evolutionary processes generally occur over a much shorter time scale than epidemiological processes. Consequently, the lower the discounting of the future relative to the present, the more important the evolutionary repercussions.

(ii) *Vaccination and virulence*. What is the expected relationship between vaccine use and the evolution of pathogen virulence, and how do different vaccination strategies affect the expected virulence of a pathogen? Examples of virulence include the prevalence of non-toxigenic diphtheria in highly vaccinated populations and the classical example of myoxma virus/rabbit studies of Australia. To date, most work on the evolutionary effects of vaccination has focused on escape mutants, but recent innovative research has addressed virulence evolution as well (see articles by Gimeno and by Mackinnon et al., this issue).

(iii) *Modes of vaccine action*. Vaccines work in different ways. Some block transmission, some reduce pathogen replication, while others might slow the progression of disease (see article by Mackinnon et al., this Special Supplement). Each of these modes has its own epidemiological advantage, but how does the mode of vaccine action affect the evolutionary response

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in the pathogen population? Are some types of vaccine more apt to result in evolutionary change than others? For example, are escape mutants more likely to occur, and to be evolutionary successful, in individuals that are vaccinated with transmission-blocking vaccines or replication-inhibiting vaccines? Are some types of vaccine more likely to result in beneficial evolutionary responses than others in terms of disease control? For example, some vaccines may select for increased virulence while others may select for reduced virulence [4,5]. Furthermore, for live vaccines, what conditions could promote reversion to the virulent strain of the pathogen?

(iv) *Multiple levels of natural selection*. Evolutionary change in pathogen populations takes place on at least two distinct scales [6]. First, evolutionary change in pathogen sub-populations within a host can occur. This within-host level of selection is exemplified by HIV, which rapidly evolves resistance against antiviral drugs. Second, evolutionary change in the pathogen population can also occur at the community level if some strains are more effective at being transmitted from person-to-person than others. This between-host level of selection is exemplified by influenza, which evolves over the course of an epidemic season. These different levels of selection are reflected in the phylogenetic trees of antigenic evolution in these pathogens. Evolutionary biologists have long been interested in such phylogenetic patterns and "levels of selection". It is clearly important that these issues be incorporated into any theory that deals with the evolutionary consequences of vaccination. How do different types of vaccines and/or vaccination strategies affect evolutionary change at these two levels? Is evolutionary change at one level often expected to oppose evolutionary change at the other? For example, does vaccination tend to result in the evolution of escape mutants within vaccinated individuals, but these escape mutants are nevertheless selected against at the population level because they do not transmit well? If so, when might we expect there to be sufficient time for compensatory evolution to occur within an individual that allows for efficient transmission between hosts? Are there vaccination protocols that minimize the probability of such detrimental outcomes?

(v) *Mechanisms of vaccine delivery*. Modern vaccines are comprised of purified, inactivated microorganisms typically administered by a sterile injection. Today's vaccines generally introduce a weakened version of an antigen that stimulates the production of specific antibodies. In a new and promising approach, DNA vaccination, genes encoding an antigen are delivered to cells that then produce the antigen and display it on their surface. New drive systems are at the heart of the new delivery mechanisms. They can include, among others, genetic vaccination using plasmid DNA, microparticle-based DNA delivery (in which the genes are encapsulated within or immobilized on a spherical polymer particle), and live attenuated transgene vectors. The new delivery mechanisms can improve vaccine potency by targeting the genes to appropriate cells of the immune system, and by allowing for the expression of antigens in synchrony with the life cycle of white blood cells and pathogen life-cycle stages. As of yet, however, very little is known about how such novel vaccination approaches are likely to affect the evolution of pathogen populations.

(vi) *Epidemiologic and surveillance methods for the study of the evolutionary repercussions of vaccination*. Many ecological and evolutionary consequences of long-term vaccination programs in populations will become obvious only on time scales longer than those of vaccine trials. The formalism of epidemiologic methods, which have proved useful in identifying risk factors in chronic and infectious diseases as well, still require further developments in order to address key questions in this context. It is expected that large-scale use of vaccines will alter the number and virulence of pathogen genotypes, either by reducing the force of infection or by directly altering the population dynamics of subsets of the circulating genotypes. Therefore, the licensing of new vaccines as well as the surveillance of new and current vaccines already in use must take into account the possible consequences of this for public health. Analogously to current vaccine trials that provide the necessary empirical background to assess the efficacy of a vaccine, informed public health decisions in this area must rely on study designs, sampling mechanisms and epidemiologic parameters specifically conceived with this end in mind.

The objective of this Special Supplement is to assemble leading experts who are working on the aforementioned problems. To date, most work has concentrated on the issues raised in (i)–(iii) and has resulted in two largely separate bodies of research [7,8]. The first focuses on so-called 'escape' mutants, and is directed towards understanding how vaccination and natural host immunity select for antigenic evolution resulting in strains that are able to evade the protective effects of the vaccine [7,9–13]. The second focuses on so-called 'virulence' or 'life-history' mutants, and is directed towards understanding how vaccination causes evolutionary change in the extent to which a parasite harms its host (i.e., evolutionary changes in its virulence; [4,7,14–16]). Recent work has also begun to draw these two areas into a single, comprehensive theory [17] but this division is still useful for categorizing much current research. As such, this volume is organized along these lines.

In the first article, Gandon and Day review both epidemiological and experimental evidence for vaccine-driven evolution in a variety of pathogens, including both escape mutant evolution, subtype replacement and virulence evolution. They present evidence that vaccination can increase the virulence of diseases, such as malaria, as well decrease virulence in other cases, for example diphtheria. Gandon and Day highlight the need for more empirical quantification of the costs of vaccine escape mutants in order to more accurately predict the evolutionary consequences of vaccination.

The next three articles focus on escape mutants and antigenic evolution. Boni analyzes data on the relationship between vaccination and antigenic evolution in influenza, explaining how intermediate levels of vaccination may generate the most antigenic influenza of pathogens. Gog presents a modeling framework that takes into account functional constraints that may limit antigenic evolution, and she applies this to explain patterns of antigenic evolution in influenza. Poolman et al. then present a novel theoretical framework for understanding and predicting antigenic evolution in Human Papilloma virus. They demonstrate that, depending on the degree of cross-immunity elicited by the vaccine, vaccination may either expand or contract the niche of HPV, but that the latter is more likely.

The last two articles focus on vaccine-driven virulence evolution. Gimeno presents a review of the extremely interesting case of vaccine-driven evolution in the infectivity and virulence of Marek's Disease Virus in chickens. MacKinnon et al. review and analyze the fascinating empirical research that has been done on virulence evolution and vaccination in malaria.

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