Interrupting the transmission of infectious agents by introducing new vaccines into a population and creating herd immunity has proven to be a remarkable hidden genie for vaccine effectiveness. For example, one- to two-thirds of the effectiveness of the bacterial conjugate vaccines is linked to protection of the unvaccinated. However, the mechanisms of herd immunity are often not well understood, it is poorly predicted and/or considered in licensure or implementation strategies for new vaccines, and the long-term consequences of preventing natural exposure to agents covered by vaccine are not known. Defining, quantifying, and monitoring the impact of herd immunity is becoming increasingly important for analyses of vaccine effectiveness and cost effectiveness and for decisions about vaccine introduction and use. In this issue of the Journal, Maiden et al. [1] report on the

impact of meningococcal serogroup C polysaccharide conjugate vaccines on the prevalence of meningococcal carriage, herd immunity, and meningococcal disease in the United Kingdom. In one of the largest multicenter meningococcal carriage studies ever performed, 48,309 samples from students were obtained during a 2-year period after vaccine was introduced (2000 and 2001). A total of 8599 meningococcal isolates were recovered and characterized by genotyping andphenotyping. A significant and specific reduction in the prevalence of serogroup C meningococcal carriage was noted that lasted at least during the 2 years of the study, without evidence of new meningococcal serogroup replacement. Vaccine efficacy against serogroup C carriage was at least 75%, with a high impact on the virulent clonal complex of serogroup C meningococci associated with invasive meningococcal disease. The decreases in the prevalence of carriage correlated with reductions in serogroup C meningococcal disease in unvaccinated individuals; at least 50% of the effectiveness of the meningococcal serogroup C conjugate vaccines is due to herd immunity [2], and the impact of herd immunity against this serogroup has lasted for years [3].

Herd immunity has long been recognized as an important benefit of vaccines. Vaccines against diphtheria poliovirus, varicella, rubella, measles, hepatitis B virus, Bordetella pertussis, and a variety of veterinary pathogens have important herd immunity effects, and herd immunity is being emphasized as an important strategy against influenza [4]. Largely unanticipated at the time of vaccine introduction, the herd immunity effect of the bacterial polysaccharide conjugate vaccines has been a major contributor to the successful control of invasive and noninvasive disease due to Haemophilus influenzae type b (Hib), major serotypes of Streptococcus pneumoniae, and Neisseria meningitidis serogroup C. The dramatic herd immunity impact of the Hib conjugate vaccines (accounting for one-third of the >95% reduction in invasive Hib disease [5]) and the meningococcal serogroup C conjugate vaccines has been established. Other important examples include the effect on the incidence of invasive pneumococcal disease in unvaccinated children and adults that results from administering the heptavalent pneumococcal conjugate vaccine to infants and young children (69% of cases prevented through indirect effects [6]) and the role of the pneumococcal conjugate vaccines in reducing influenza-associated morbidity [7].

The study by Maiden et al. [1] and other recent studies [3, 5, 8–11, 12, 13] provide additional lessons about how herd immunity and bacterial polysaccharide conjugate vaccines work together, as well as information about the limitations of herd immunity. However, many questions remain to be answered. How should these vaccines be introduced to maximize and maintain effectiveness through individual and herd immunity (e.g., should...
we use an infant or toddler strategy, other limited cohorts, catch-up campaigns, or focus on individuals with highest carriage and transmission dynamics? How is agent acquisition, and thus transmission, prevented? How will these vaccines alter microbial biology, which can have short-term or long-term influences on vaccine effectiveness and/or population susceptibility? Does each bacterial conjugate vaccine have similar herd immunity effects? How can herd immunity be maintained? What is the role of herd immunity in the protection of populations with waning individual protection?

The meningococcal serogroup C polysaccharide-protein conjugate vaccines were introduced in the United Kingdom as a broad catch-up campaign that first targeted children and adolescents up to 19 years of age, followed by infants, and included the population (i.e., adolescents) with the highest rates of meningococcal carriage and transmission. A toddler-to-young adult vaccination strategy for serogroup C meningococcal polysaccharide conjugate vaccines demonstrated equally dramatic herd immunity when used in The Netherlands [9]. In the case of the heptavalent pneumococcal conjugate vaccine, rapid herd immunity effects in the unvaccinated population >5 years of age were seen with 1-3 doses of an infant vaccine and a limited toddler catch-up strategy in the United States. Again, this approach targeted the population with highest rates of pneumococcal carriage and transmission [9]. Thus, campaigns that rapidly target the populations important in transmission and acquisition are predicted to induce the highest levels of herd immunity and vaccine effectiveness, which can last for years. Plans to use a new meningococcal polysaccharide serogroup A polysaccharide conjugate vaccine in sub-Saharan Africa are focused on generation of herd immunity to maximize vaccine effectiveness. New acellular pertussis vaccination programs that target adolescents and young adults are predicted to decrease the spread of B. pertussis to infants, the population in which mortality is highest [14]. Strategies that provide a gradual introduction of vaccine or do not continue to target populations with the highest rates of transmission are predicted to have much less impact [3, 12].

Although no significant change in the overall prevalence of meningococcal carriage and no evidence for the emergence of new meningococcal serogroups or replacement by other serogroups was noted during the 2 years following the introduction of vaccination in the Maiden et al. study [1], the meningococcal C conjugate vaccines did have an effect on meningococcal biology. The proportion of serogroup C ST-11 meningococcal strains that did not express capsule was significantly increased. Thus, the vaccines selectively reduced serogroup C transmission and carriage and selected for noncapsule-expressing variants of the virulent phenotype, which may have the capacity to revert. Also, the vaccine’s particular success against ST-11 clones may be related in part to the high levels of capsule they express. Thus, the large herd immunity effect on ST-11 serogroup C strains might not be seen with other meningococcal serogroups, with all meningococcal conjugate vaccines, or against encapsulated bacteria in general. In support of this concept, the herd immunity impact of the pneumococcal conjugate vaccine may be influenced by serotype [8].

Replacement of one virulent microbial population with another remains a concern with respect to altering microbial transmission dynamics. In general, the Hib conjugate vaccines have not led to significant replacement disease due to other serotypes or nontypeable Hae- mophilus species. Although cases of invasive disease due to H. influenzae serotypes a and f have been associated with increased carriage, these serotypes appear not to have the same capacity for causing invasive disease, even if replacement occurs. For the heptavalent pneumococcal conjugate vaccine, replacement and replacement disease have become a concern. Although the serotypes contained in the vaccine continue to decline in most vaccinated and unvaccinated age groups, significant serotype replacement (e.g., serotype 19A) and selection for capsule-switching variants has been observed. Replacement has not lessened the tremendous impact of this vaccine, but continued surveillance and expanded serotype coverage in new vaccines is essential.

Another benefit of herd immunity is the protection of individuals whose immunity is waning. The original infant schedule in the United Kingdom of 3 doses of the meningococcal conjugate vaccines at 2, 3, and 4 months did not provide long-term individual protection and was subsequently modified to include a booster. For N. meningitidis and Hib, where rapid onset of disease can follow acquisition, individual protection appears not to be conferred by the generation of immunological priming or memory responses alone [13]. However, in the United Kingdom, the number of serogroup C meningococcal cases in children remained small due to the persistence of herd immunity to serogroup C [3]. The waning of both herd immunity and individual immunity can lead to a resurgence of disease, as was seen with Hib disease in the United Kingdom [13]. The introduction of a Hib conjugate vaccine in 1992 in the United Kingdom for infants at 2, 3, and 4 months and an initial catch-up campaign for children ≤4 years old resulted in a rapid decline in the incidence of invasive Hib disease in all age groups, including adults. Toddlers have the highest rates of pharyngeal carriage of Hib, and most of the Hib conjugate vaccines dramatically reduced transmission and carriage. The infant schedule was maintained, but Hib disease had increased in all age groups by 1999, and as was seen historically, the increases were most marked in children <5 years old. Resurgence was the result of a decline in herd immunity, waning individual immune protection among children who were vaccinated in infancy, a change to a less immunogenic Hib vaccine combination for young infants [13], and a larger pool of susceptible adults. A Hib-booster cam-

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ppaign in 2003 for toddlers, the reservoir for Hib, reestablished herd immunity and was followed by a rapid reduction in the number of cases reported among older children and adults. In countries that maintained a Hib conjugate booster for toddlers, the disease has remained at low levels in all age groups.

The effects of eliminating natural immunity created by colonization and natural boosting through carriage also may affect vaccine effectiveness. As Hib vaccine protection and herd immunity waned in the late 1990s among UK children, the number of cases of Hib disease in adults rose to levels higher than those during the prevaccine era. Vaccines that have a broader impact on colonizing microbial flora (such as large populations of *Neisseria* species [e.g., *N. lactamica*], *Haemophilus* species, or pneumococci), much like antibiotic selection, could result in significant selection and replacement and decreased levels of natural immunity. Targeting transmission of a specific, virulent microbial population may be the best strategy.

The immune basis for herd immunity is not well defined. The bacterial polysaccharide-protein conjugate vaccines produce higher levels of mucosal IgG antibody, presumably due to transudation of IgG from serum and possibly higher-avidity antibodies [15]. It has been proposed that this mechanism prevents acquisition of new strains, thus limiting new colonization and transmission, but may have little effect on established colonization. Hib conjugate vaccines that produce lower antibody levels have less of an impact on transmission dynamics and herd immunity. However, much more needs to be known about the immunological basis of herd immunity and mucosal responses to bacterial conjugate vaccines. Herd immunity also may vary in different populations. Despite high levels of vaccine coverage in children, Hib transmission and disease has continued to occur in the indigenous populations of Alaska [10, 11]. Some of this persistence appears to be related to the use of a less immunogenic vaccine, but transmission dynamics and the burden of carriage (e.g., a large adult reservoir) may influence herd immunity in different populations.

Protecting the unvaccinated through herd immunity is a remarkable and very powerful effect of vaccines and should be an important consideration in strategies for vaccine introduction, implementation, evaluation, and monitoring, rather than an afterthought. A better understanding of the dynamics of herd immunity and the length of protection it provides, as well as the impact of herd immunity on microbial biology, the mechanisms of microbial replacement, and natural immunity and biology are clearly needed to use this genie wisely.

References


