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## Vaccination-Induced Herd Immunity: Successes and Challenges

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The World Health Organization estimates that global vaccination programs save 2–3 million lives per year by priming the immune system to protect against pathogenic threats that pose significant global health and economic burdens<sup>1</sup>. Besides individual protection, vaccination programs also rely on population or “herd” immunity: the immunization of large portions of the population to protect the unvaccinated, immunocompromised, and immunologically naïve by reducing the number of susceptible hosts to a level below the threshold needed for transmission. For example, immunization of >80% of the global population against smallpox virus reduced transmission rates to uninfected individuals to a point low enough to achieve eradication of the virus<sup>2</sup>. Similarly, poliovirus is now targeted for eradication, with only Pakistan, Afghanistan, and Nigeria documenting endemic viral infections<sup>1</sup>.

Despite the success of select vaccination programs, societal and biological factors (Figure 1), including the inability of population groups to generate protective immunity in response to vaccination is a challenge for achieving herd immunity. The unvaccinated, including the very young, aged, and those who are immunocompromised due to infection, congenital conditions or medical history, must be protected by passive immunity. For example, unvaccinated females benefit from human papillomavirus (HPV) vaccination of their male partners<sup>3,4</sup>, as HPV strains 16 and 18 are linked to 70–80% of cases of cervical cancer<sup>4</sup>. While both males and females can be infected with HPV, females are more likely to experience detrimental oncogenic effects, including loss of reproductive capabilities. The vaccination of females and males in young populations with attenuated vaccines of the circulating HPV strains (6, 11, 16, and 18) has decreased transmission of these specific HPV viruses to young unvaccinated females in Scotland<sup>3</sup>. Thus, vaccination of the potential carriers within the population can promote disease prevention in the unvaccinated.

Immune senescence, immaturity, and imprinting limit human vaccine responses. These issues pose challenging obstacles to the development of vaccine-induced broadly protective long-lasting immunity. Immunosenescence refers to the progressive loss of responsiveness to a pathogen, resulting in decreased antibody titer or cellular responses, requiring booster vaccinations to restore immunity. In the late 20<sup>th</sup> century, measles was nearly eradicated in

China, Korea and the United States as the result of early-age vaccination and boosters with attenuated virus<sup>5,6</sup>. However, re-introduction of the wild-type virus into these localities has caused spikes of infection in immunized middle-aged adults and has been linked to the wild-type measles virus' capacity to overcome reduced antibody titers in these more aged populations<sup>5,6</sup>, indicating a prospective need for a tertiary booster in adults to bolster neutralization titers.

The breadth and length of duration of herd immunity are also dependent upon characteristics of the pathogen and its interactions with the immune system. Antigenic drift, antigenic shift, and recombination result in antigenic diversity within a pathogen pool, and a viral species can consist of multiple variants that are antigenically distinct from each other. The lack of a proof-reading function associated with most RNA polymerases makes RNA viruses particularly adept at generating strain diversity. For example, norovirus, the leading cause of acute gastroenteritis, has >30 genotypes. The GII.4 genotype evolves rapidly at surface epitopes that are key targets of protective immunity/neutralizing antibodies<sup>7</sup>. Despite maintaining 93.9% amino acid sequence homology between the earliest and most recent known pandemic strains, evolution at hypervariable epitopes correlates with pandemic bursts of disease approximately every 2–5 years. The immunocompromised, immunosenescent, and young children have been postulated to be norovirus reservoirs<sup>7</sup>. In these populations, a suppressed or naïve immune system may not fully neutralize every viral variant. Lower immune pressure on the virus, along with an error-prone RNA polymerase, allows for mutated variants to emerge and escape neutralization.

Pathogen-immune response interactions also shape Dengue and influenza virus immunity and subsequent vaccine design. Dengue circulates as four serotypes, (DENV1–4), which have roughly 70% sequence homology. Infection with one serotype induces production of both cross-reactive and serotype-specific neutralizing antibodies during initial infection<sup>8</sup>. Upon infection with a second serotype, the original memory immune response is preferentially stimulated. Due to antigenic differences between the primary and secondary viruses, pre-existing antibody is unable to effectively neutralize the second virus, allowing immune evasion through immune imprinting (original antigenic sin/antigenic seniority)<sup>8,9</sup>. Importantly, depending on the level and neutralization capacity of the cross-reactive pre-existing antibodies, a secondary infection can cause severe disease<sup>10</sup>. Similarly, the immune system preferentially recalls memory antibody responses to the earliest infecting strains of influenza A and norovirus and shows weaker consecutive responses to infection with subsequent serotypes, respectively<sup>11,13</sup>. As the herd is composed of individuals from many different age groups, and pandemic Influenza and norovirus strains change over time, effective vaccine development that induces broad protection is highly complicated by age and pre-exposure history. Conserved epitopes are potential vaccine targets for these and other pathogens that are susceptible to antigenic drift/shift and recombination<sup>7</sup>. While progress toward a universal influenza vaccine is being made, protection currently relies on regular vaccination with multiple attenuated circulating strains to reduce transmission and mitigate disease severity<sup>11</sup>. Despite a global surveillance network, predicting future flu epidemic strains for vaccine production is high risk, as evidence by influenza vaccine-contemporary strain mismatches in both 2014–2015 and 2017–2018<sup>14</sup>.

Norovirus, dengue, and influenza illustrate challenges in eliciting broad immunity through vaccination with a single serotype of attenuated virus. While vaccination would protect against the vaccinated serotype, it has the potential to increase the severity of a secondary infection by inducing a dampened response to later variants based on antigenic variation, imprinting, and timing between inoculation and secondary infection and/or immune enhancement which occurs in Dengue virus secondary infections. Research focusing on protective immunity correlates, particularly cross-reactive neutralizing antibody titers, and chimeric serotype attenuated-viruses to elicit broad immunity is underway<sup>7,8</sup>. Understanding and optimizing these factors may induce broad immunity across populations.

As vaccines that can overcome the challenges of poor immune responsiveness in hosts and antigenic diversity in pathogens are developed, public policy plays a critical role in achieving the high population vaccination rate needed to achieve herd immunity and freedom from disease. Universal access to affordable health care is of the highest priority, as individuals of lower socioeconomic status often forgo vaccinations due to accessibility reasons<sup>12</sup>, which can leave large pockets of non-vaccinated, susceptible people who not only may suffer disease themselves but can also facilitate transmission to others who are unable to get immunized, thus breaking the protective barrier herd immunity provides. The observed spike in incidents of pertussis and measles in children and adults in the United States<sup>15</sup>, indicates a need for effective public education to counter anti-vaccination proponents whose fear of vaccine side-effects form pockets of susceptibility and opportunity for spread of pathogens among those who are immunocompromised or unable to receive a vaccine due to age requirements. The more accessible we make vaccination through education programs, minute clinics, job-site resources, and lowered costs, the more effective vaccination programs will be<sup>12</sup>. To reach the goal of protection from disease and eradication of pathogens through vaccination, governments, scientists, and citizens will have to commit resources equivalent to the diversity and abundance of the pathogens we fight.

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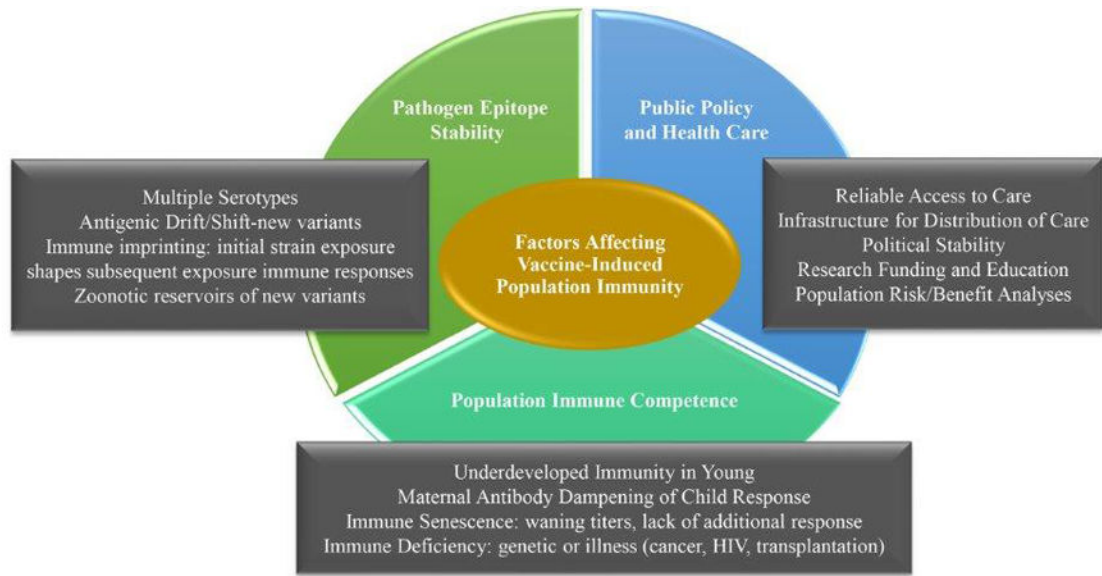
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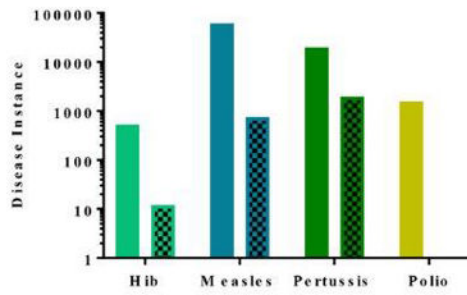
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B



**Figure 1.** Biological and societal factors affecting vaccine-induced population immunity.