Title: “Understanding the host-pathogen interaction saves lives: lessons from vaccines and vaccinations”

Short Title: “Vaccines Don’t Save Lives, Vaccinations Save Lives”

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Abstract

Vaccines are one of the most successful and cost-effective public health tools employed to date, yet these benefits are only realized when the life-saving intervention reaches each and every targeted individual. Vaccine development is prioritized based on a number of factors such as health burden, feasibility, and determination of potential target populations. But only through an arduous process of pre-clinical development and progressive clinical trials does a vaccine become licensed and recommended for use. Once used in a wider and more diverse population safety issues, long-term impact and other unintended outcomes may become apparent, influencing policy modification. This commentary explores the role host-pathogen interaction plays in vaccine development and the operational and policy considerations that may impact vaccine success post-licensure.

Introduction

The ability to achieve disease reduction among human populations through vaccination depends on many factors. This starts with an assessment of the health and economic burden of a potential vaccine-preventable disease and whether the disease is of universal risk or limited to certain risk groups. Disease burden influences decisions to invest in vaccine development, public acceptance of vaccines, and potential recommendations for use. Should there be interest in vaccine development, there is a need for pre-clinical studies to determine what constitutes a protective immune response and an understanding of the biological mechanisms to induce it. Clinical trials must then be undertaken to establish both safety and efficacy. There are three major phases of clinical trials with the pivotal trial for licensure in the third phase. The results of those clinical trials along with information on product manufacture are presented to regulatory authorities who make the decision regarding whether to license the vaccines and on content of product labeling regarding indications, contraindications, and precautions. Once vaccines are licensed, immunization advisory bodies make recommendations for use. This is followed by program implementation, assuring persons for whom vaccine is recommended have access to vaccines and are actually vaccinated. Post-licensure surveillance for vaccine safety and effectiveness can lead to modifications in policy for vaccine use. The full process from the beginning stages of vaccine development to program implementation and use can be seen in Figure 1. This commentary will examine these factors as they relate to vaccine development and explore how vaccine technology, surveillance and policy changes may shape the disease prevention landscape of the future.

The ‘Ideal’ Vaccine: Prioritizing Development

Vaccine development, vaccine policy and other interventions for infectious disease control depend upon much more than the technical capabilities of the tool itself. The epidemiological landscape including disease burden and modes of transmission play an important role.

Incidence, economic burden, and severity of disease can lead to ranking development of a vaccine against that disease as a higher priority than diseases of more limited burden. The Institute of Medicine (IOM) has developed a tool to determine vaccine development priorities called the Strategic Multi-Attribute Ranking Tool for Vaccines (SMART Vaccines).[1] The tool is based on a multi-attribute utility model blending quantitative and qualitative vaccine attributes input by the user. These inputs include variables such as premature deaths averted per year, cost-effectiveness, cold-chain requirements, demographic considerations and other user-defined attributes. These attributes are then weighted to produce a “SMART Score” leading to a priority list of vaccines for development consideration. In addition to issues of health and economic burden, other factors can be considered such as public concern. For example, public concern about the recent Ebola outbreak in West Africa, a disease with rapid onset, a high case fatality rate and considerable media interest, has made development of an Ebola vaccine a top priority. Other vaccines, such as measles and varicella, were developed not so much for public fear, but because the health burdens were substantial. Trying to eradicate a disease may be a special situation. For example, in the instance of polio, only a few hundred cases remain in localized corners of the world making disease burden low, compared to an estimated 350,000 cases of paralysis in 1988, the year the eradication effort began. Concerns about the safety and effectiveness of the existing vaccines is leading to support for development of potential new vaccines, even at this late stage of the eradication program.[2]

There are several factors to consider when developing policy recommendations for new vaccines and these considerations should be taken into account early in the vaccine development process. Vaccines are evaluated based on immunogenicity, clinical efficacy, safety, duration of protection and potential for community protection through induction of mucosal immunity. Operational issues such as thermostability, route of delivery, number of doses required and multi-dose vial policies also play a role. Finally, cost and safe and

sustainable production, even for low income countries are important considerations for vaccine policy. A list of ideal vaccine characteristics can be seen in Box 1. Policy recommendations are made through the Advisory Committee on Immunization Practices (ACIP) in the U.S. and the Strategic Advisory Group of Experts (SAGE) globally. Economic analyses evaluating the economic benefits of vaccines, such as the cost per quality adjusted life year gained, are an essential part of deliberations as to whether to recommend a vaccine or not.[3]

Host-Pathogen-Vaccine Considerations

The most successful vaccines to date have been those against diseases for which the natural immune response against the pathogen itself leads to universal and long term immunity against that pathogen. In essence, natural infection becomes a model to emulate when trying to induce an immune response through vaccination. For example, natural infection with measles virus leads to lifelong immunity. Thus, the vaccine to be developed simply had to induce an immune response similar to natural infection without the pathogenicity of the natural virus. Measles antibody has been found to persist in the vast majority of vaccinees for more than 10 years following a second dose.[4] Waning immunity to measles vaccine, while documented, is rare and does not appear to play a role in sustaining measles transmission.[5] A vaccine ideally suited for disease reduction would induce an immune response in the host similar to natural infection with the pathogen and infer lifelong protection against disease with a single dose.

Less successful or unsuccessful response to vaccines occurs when the natural immune response of the host is suboptimal. For example, the dominant immune response to influenza is directed against a variable region of the globular head of the hemagglutinin rather than against more conserved regions.[6] This region is not vital for the influenza virus to replicate and changes in that region allow escape mutants to emerge that evade immunity induced by prior infections. Thus, the challenge for vaccine development is to induce immunity that is better than

that induced by natural infection and focus the immune response toward more conserved regions. While there is hope that this can be achieved, no “universal influenza vaccines” currently exist.[7] Thus, annual changes in vaccines to anticipate the antigenic variants that might circulate during the following season are required.

Although the bacille Calmette-Guérin (BCG) vaccine is effective at protecting children against severe tuberculosis, immunity wanes over time and developing a better, long lasting, more protective vaccine against TB requires induction of a strong T-cell immune response. However, reliable biomarkers are still lacking.[8] Challenges with development of an effective HIV vaccine include not only the global variability of the virus but also the lack of validated animal models and correlates of protection, integration of the HIV viral genome into the host, and destruction of the hosts immune cells by the HIV virus.[9]

The ability of a vaccine to not only induce protection against disease but also to induce protection against infection and spread of the pathogen plays a critical role in achievement of herd immunity and subsequent reduction of transmission in the community, important policy considerations. Pneumococcal conjugate vaccine has had a marked impact on vaccine serotype-specific nasopharyngeal carriage thus preventing transmission of vaccine type causes of disease.[10,11] Oral polio vaccine (OPV) is able to induce actual community immunity through passive spread of vaccine virus.[12] Conversely, inactivated polio vaccine (IPV) effectively protects recipients from paralysis but is less effective in inducing intestinal immunity and reducing transmission in communities, where fecal-oral spread of poliovirus is thought to be the major means of spread. [13] The strengths and weaknesses of the two available polio vaccines and their impact on individuals and communities have important implications for the polio endgame.[14]

Operational Considerations

Vaccine Safety

Before licensure, vaccines are tested in thousands of healthy individuals through clinical trials yet once in actual use most vaccines are widely used in the general population, where underlying conditions not addressed in clinical trials may be present. Further, there may be a desire to use vaccine in age groups not covered in the clinical trials for initial licensure. Thus, there is a need for post-licensure monitoring of both safety and effectiveness. While clinical trials may have tens of thousands of persons evaluated, they may not be capable of detecting rare causally related adverse events, such as those that occur on the order of 1 per 10,000 or less. In the U.S., a major post-licensure vaccine safety monitoring system is the Vaccine Adverse Event Reporting System (VAERS), managed jointly by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). This system encourages physicians, patients and manufacturers to make reports of significant adverse events following immunization. VAERS cannot usually ascertain whether or not a specific adverse event is definitely caused by a vaccine versus a coincidental event because there is no control group of unvaccinated persons. However, ongoing data analysis monitors for any unexpected patterns or specific events of interest. Findings can lead to further investigation and in some cases policy modification. Observational studies can be carried out using large linked databases such as the Vaccine Safety Datalink (VSD), an association of eight managed care organizations.[15] The VSD allows for comparing the incidence rate of a given adverse event in vaccinees versus non-vaccinees, which if significantly higher in vaccinees would support a role for vaccine in causation. Further, VSD can compare the incidence of a given adverse event in a specified interval following vaccination with the incidence in other intervals which allows participants in VSD to serve as their own controls.

Rotavirus is one of the leading causes of severe gastroenteritis in infants. In prelicensure trials in the U.S. a rhesus derived rotavirus vaccine (RotaShield) was over 80% effective in preventing severe disease.[16–18] In August of 1998, RotaShield was licensed by the FDA and distributed. Shortly thereafter reports emerged involving cases of intussusception, a rare bowel condition in which a portion of the intestine “telescopes” into itself causing blockages, perforation and infection. Only 5 cases of intussusception were seen in 27 clinical trials in which over 10,000 infants were vaccinated[19], yet only when the vaccine was fully licensed and used in a broader population (1.5 million doses were estimated to be administered), 98 cases of intussusception occurring within one week of vaccination were reported.[20] An excess risk of approximately 1-2 cases per 10,000 vaccine recipients was found to be associated with RotaShield vaccination and the vaccine was ultimately withdrawn until a safer formulation could be made.[21,22] In a similar event, an increased risk of fever was found to be associated with simultaneous vaccination with trivalent inactivated influenza vaccine and 13-valent pneumococcal vaccine, an effect seen only through post-licensure monitoring when vaccines were used in large populations according to recommended schedules.[23]

Sometimes, changes are made to vaccines due to perceived safety issues that turn out to create unanticipated problems. Soon after the diphtheria, tetanus toxoid and whole-cell pertussis vaccine (DTwP) was licensed in the U.S., reports of neurological events following immunization prompted further studies, stimulating public concern about potential permanent brain damage associated with DTwP.[15] Although no causal relationship was determined and the relationship between DTwP and brain damage was never proven, studies supported a rare outcome of acute encephalopathy associated with DTwP. This finding prompted development and subsequent use of acellular pertussis vaccines, shown to have comparable rates of protection and a better profile with regard to adverse events in the immediate post-vaccination period than DTwP.[15] However, there has been a major resurgence of pertussis in countries

like the United States, which appears primarily due to substantially greater waning immunity with the acellular vaccines compared to the whole cell vaccines.

To address the potential for rare causally related vaccine induced adverse events, The National Vaccine Injury Compensation Program (NVICP) was created in 1988. The NVICP was designed to compensate individuals injured by vaccines. It is funded by a vaccine excise tax on vaccines covered by the program (\$0.75 per dose per disease protected against in a given vaccine).[24] The NVICP recognizes the fact that when someone is vaccinated they are doing it not just for their individual protection but also for community protection (i.e., herd immunity). Thus, society has an obligation to compensate those who are truly injured by vaccines.

Policy Recommendations

The duration of vaccine-induced immunity as well as the schedules needed to induce immunity contributes to the level of coverage that can be achieved in a given population. For example, a one dose schedule is easier to implement and achieve than a five dose schedule. Further, vaccines that can be administered within an existing infrastructure are more likely to get used than vaccines which require a whole new healthcare contact for persons who do not normally have such contacts. In the United States, for example, the typical schedule in the first year of life includes visits at birth, 2, 4, and 6 months of age. In much of the developing world, the visits in the first year of life are at 6, 10, and 14 weeks and 9 months. Vaccines which fit within these schedules can be more easily implemented than having to institute a new visit (e.g. 7 months).

Some vaccines are recommended universally in which high coverage is easier to achieve. Others may target a specific population, a scenario when high coverage may be more difficult to achieve. In 2008 the ACIP expanded influenza vaccine recommendations to all children (up to 18 years of age) and then to all adults (persons aged 6 months or older) in 2010 to reduce disease burden, improve coverage and increase production capacity for pandemic

preparedness[25–27]. In addition, multiple studies have reported indirect effects of vaccination among unvaccinated contacts utilizing the concept of herd immunity to further decrease disease transmission.[28,29] A 2011 economic analysis strongly supported universal mass vaccination in terms of improved health outcomes and reduced overall costs, with a net benefit estimated of over \$2 billion.[27]

Policy Modifications: Vaccine Failure vs. Failure to Vaccinate

With implementation, there is a need to monitor remaining morbidity and determine if cases that continue to occur are the result of vaccine failure or failure to vaccinate. Problems with the latter require solutions to improve uptake of the vaccine. For example, in the United States, between 1989 and 1991, there was a major resurgence of measles during which there was more than 55,000 cases, more than 11,000 hospitalizations, and 123 deaths.[30,31] The major cause for the resurgence was failure to vaccinate young children, particularly those of racial/ethnic minorities living in inner cities. This led to a Presidential Childhood Immunization Initiative (CII), which among other things established a government purchase program, entitled the Vaccines for Children program (VFC) to remove vaccine cost as a barrier to vaccine access. The VFC also empowered a Federal Advisory Committee, the ACIP, to see its recommendations automatically funded if the committee voted a particular vaccine and its recommended use into the program. The Affordable Care Act (ACA), now requires insurers to provide coverage for vaccines and their administration without co-pays for ACIP recommended vaccines, if administered by an in-network provider.

With the number of total antigens available increasing in recent years, childhood vaccination schedules have become more complex and public acceptance plays a critical role in achieving desired vaccine coverage. Understandably, parents' confidence in the value of vaccines (that is that vaccines are important and vaccination is the right thing to do) was the best predictor of

parents vaccine decisions.[32] When it comes to children receiving several injections during one visit, providers often overestimate parents' concerns of their child experiencing pain, potential side effects, or uncertainty about vaccine effectiveness.[33] Health care providers are key advocates for vaccination and are often the main resource parents rely on for knowledge of vaccine preventable diseases, side effects and benefits of vaccination. Combination vaccines, which decrease the number of injections required, if as effective as the original products and as safe, may assure both parents and providers and contribute to higher levels of vaccine coverage.

Sometimes vaccine failure is the major cause of morbidity. For example, outbreaks of measles were not infrequently reported among school-aged populations in which high coverage with a single dose of measles vaccine was not adequate to prevent the outbreak. The measles virus was simply too contagious and could spread among the few people (~7%) not protected by a first dose. Thus, a second dose was recommended and with that second dose, as well as improved coverage with the first dose, indigenous transmission of measles virus in the United States was eliminated in 2000.

Conclusion

Ability for infectious disease control and reduction relies on continued understanding of complex host-pathogen interactions through a population perspective. Basic science advances, surveillance improvements and a deeper understanding of infectious disease population dynamics will further inform delivery of current vaccines in variable settings and guide the development of new tools. The ability of a vaccine to have an impact on overall disease reduction in humans depends on the larger context beyond the individual pathogen-host interaction including the socioeconomic landscape, disease epidemiology and operational issues associated with vaccine delivery.

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Figure 1: Diagram illustrating vaccine development process from risk assessment to program implementation.

Box 1: Characteristics of an ideal vaccine for consideration in vaccine development.

Figure 1

Characteristics	'Ideal Vaccine'
Protection against clinical disease and its complications	Complete
Route of administration	Non-injection
Thermostability	Heat and freeze stable
Humoral immunogenicity	Good
Prevention of Transmission	Effective
Cost	Minimal
Safe production	Widespread and no risk
Safety	No safety Issues
Schedule/duration of protection	1-dose
Method of administration	Routine and campaigns
Waste management	No risk
Cold storage space	Little or none