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Understanding the host–pathogen interaction saves lives: lessons from vaccines and vaccinations

Julie R Garon and Walter A Orenstein

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.

Address
Emory University School of Medicine, 1462 Clifton Road, NE, Suite 446, Atlanta, GA 30322, United States

Corresponding author: Orenstein, Walter A (worenst@emory.edu)

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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

Figure 1

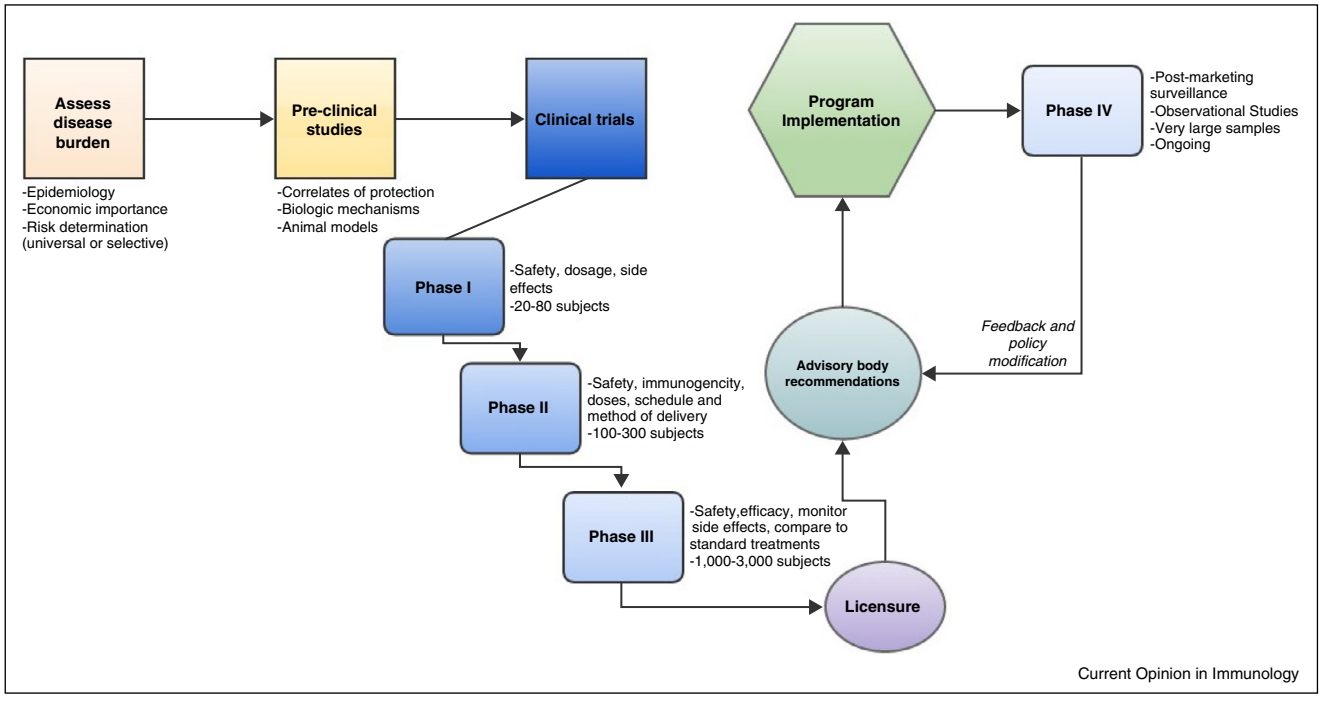

Diagram illustrating vaccine development process from risk assessment to program implementation.

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

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

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