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Current state and challenges in developing oral vaccines☆

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ABSTRACT

While vaccination remains the most cost effective strategy for disease prevention, communicable diseases persist as the second leading cause of death worldwide. There is a need to design safe, novel vaccine delivery methods to protect against unaddressed and emerging diseases. Development of vaccines administered orally is preferable to traditional injection-based formulations for numerous reasons including improved safety and compliance, and easier manufacturing and administration. Additionally, the oral route enables stimulation of humoral and cellular immune responses at both systemic and mucosal sites to establish broader and long-lasting protection. However, oral delivery is challenging, requiring formulations to overcome the harsh gastrointestinal (GI) environment and avoid tolerance induction to achieve effective protection. Here we address the rationale for oral vaccines, including key biological and physicochemical considerations for next-generation oral vaccine design.

Contents

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1. Introduction

Vaccines have substantially reduced the burden of infectious disease, second only to clean drinking water in reducing mortality worldwide [1]. Immunization is a cost effective strategy that protects not only the vaccinated individuals, but can indirectly protect the surrounding community through the generation of herd immunity [2].

Development of vaccines against a variety of diseases, including diphtheria, tetanus, polio, measles, mumps, rubella, hepatitis B, and meningitis, have reduced the associated mortality by 97–99% [3]. However, even with multiple successful vaccination campaigns, infectious diseases remain the second leading cause of death worldwide, disproportionately affecting children under the age of 5 and people in low income countries [4]. In fact, five of the top ten leading causes of death in low income countries are caused by infectious agents: lower respiratory infections (e.g. pneumonia), HIV/AIDS, diarrheal disease, malaria, and tuberculosis. While some of these pathogens currently lack a vaccine necessary for disease control, an estimated 20% of these deaths result from vaccine-preventable diseases, indicating the need for substantial improvement in vaccine technology and administration [4–6].

The majority of infections occur after crossing one of the body's numerous protective mucosal barriers [5,7,8]. For example, potentially fatal diarrheal diseases are often caused by enteropathogens crossing the mucosal barrier of the GI tract after ingestion of contaminated water [9]. The formation of an immunologically strong mucosal barrier would be an effective strategy to prevent infection at the point of contact between microbes and the host. However, the current standards of vaccine technology typically only address pathogens that have already surpassed a mucosal barrier. The majority of licensed vaccines are administered either by subcutaneous or intramuscular injection. The resulting immune response is generally limited to systemic humoral immunity (*e.g.* antibody production) against the pathogen or toxin, with limited cellular immunity (*e.g.* T cell-mediated), and only weak protection generated at the mucosal surfaces [10,11]. In contrast, vaccination at mucosal surfaces successfully induces mucosal antibodies (IgA) and cell-mediated immune responses, while still producing a systemic antibody response (IgG) [12–15].

The largest mucosal surface, the GI tract, is readily accessible via oral administration. The oral delivery of therapeutic drugs represents the current gold standard of therapeutic drug administration due to the opportunity for self-administration, improved patient compliance, and the ease of distribution compared to injection-based therapies [16–19]. Vaccine efficacy is highly correlated to its regional coverage, which is affected by the accessibility, stability, and distribution of the formulation [2,20]. Consideration of these parameters is important in the development of next-generation vaccines.

Unfortunately, despite the numerous immunological and practical advantages associated with oral delivery, only a limited number of oral vaccines are available [21,22]. Herein, we present a systematic analysis of the barriers associated with the gastrointestinal delivery of vaccines, currently available oral vaccines, and design strategies for novel delivery vehicles and next-generation oral vaccine development.

2. Oral administration

Oral delivery is the most desirable and patient-accepted route of administration, with over 60% of commercialized small molecule drug products using the oral route [23,24]. Despite this, only a small fraction of currently licensed vaccines are oral formulations due to the inherent obstacles presented by the gastrointestinal system. The induction of a robust protective immune response by oral immunization requires: (i) successful delivery of the intact and active antigen to the intestine, (ii) transport across the mucosal barrier, and (iii) subsequent activation of antigen-presenting cells [14,23,25]. However, the GI tract poses difficulties to each step, including degradation of fragile antigens through the harsh environment in the stomach and requirement of adequate doses to generate immunity instead of tolerance [21,26]. Each challenge within the GI tract poses a unique engineering problem that requires careful consideration to achieve efficacious vaccine design.

2.1. Advantages of oral administration

Vaccine efficacy is dependent on both the degree of protection conferred to individuals as well as the total coverage, accessibility, and costs associated with administering the formulation [2]. Vaccine distribution represents one of the main limiting factors in the impact of these prophylactic systems, particularly in developing nations with limited resources [27,28]. Oral vaccines have the capacity to improve distribution compared to traditional injections due to their ease of administration, allowing for the self-administration of oral formulations. Self-administration is ideal for the widespread and rapid distribution of vaccines as it minimizes the need for trained healthcare personnel [16,29,30]. This could further reduce cost of vaccine programs, since training and mobilization of health care workers can account for up to 25% of the cost of introducing a new vaccine [31]. Additionally, needle-free administration would eliminate occupational needle-stick injuries, which occur in approximately 5% of health-care workers each year, exposing them to blood-borne infectious diseases such as HIV/AIDS and Hepatitis [32].

From a regulation standpoint, oral vaccines could enable more cost-effective production since they do not require the extensive purification necessary for injected formulations. Parenteral injections require a) aseptic technique during synthesis and manufacturing, b) equipment and training of the healthcare personnel for optimal delivery, and c) appropriate use of sterile needles [33]. Moreover, use of these traditional techniques generates a huge amount of biohazardous waste [34], which the majority of developing countries simply do not have the infrastructure to handle properly. All of these factors increase the cost of immunizations, which can significantly affect their access in emergent regions.

Oral immunization has the potential to improve vaccine efficacy simply by increasing accessibility and coverage, however the oral route also provides the additional advantage of stimulating mucosal immunity. The mucosal epithelium covers the largest surface area in the body and constitutes the first line of defense against external pathogens [8,26,35]. These mucosal surfaces involve physicochemical and