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Delivery strategies to enhance oral vaccination against enteric infections ☆

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ABSTRACT

While the majority of human pathogens infect the body through mucosal sites, most licensed vaccines are injectable. In fact the only mucosal vaccine that has been widely used globally for infant and childhood vaccination programs is the oral polio vaccine (OPV) developed by Albert Sabin in the 1950s. While oral vaccines against Cholera, rotavirus and *Salmonella typhi* have also been licensed, the development of additional non-living oral vaccines against these and other enteric pathogens has been slow and challenging. Mucosal vaccines can elicit protective immunity at the gut mucosa, in part via antigen-specific secretory immunoglobulin A (SIgA). However, despite their advantages over the injectable route, oral vaccines face many hurdles. A key challenge lies in design of delivery strategies that can protect antigens from degradation in the stomach and intestine, incorporate appropriate immune-stimulatory adjuvants and control release at the appropriate gastrointestinal site. A number of systems including micro and nanoparticles, lipid-based *strategies* and enteric capsules have significant potential either alone or in advanced combined formulations to enhance intestinal immune responses. In this review we will outline the opportunities, challenges and potential delivery solutions to facilitate the development of improved oral vaccines for infectious enteric diseases.

Contents

Abbreviations: APC, antigen presenting cell; BCG, Bacillus Calmette–Guérin; cAMP, cyclic adenosine monophosphate; CDCA, chenodeoxycholic acid; CFA, colonisation factor antigen; CMCE, carboxymethylethylcellulose; CSR, class switch recombination; CT, cholera toxin; CTA, A subunit of CT; CTB, B subunit of CT; CTL, cytotoxic lymphocyte; DAMP, damage-associated molecular pattern; DCA, deoxycholic acid; DC, dendritic cell; DC-SIGN, DC-specific intercellular adhesion molecule 3-grabbing nonintegrin; dmLT, double mutant LT; ETEC, Enterotoxogenic *Escherichia coli*; FAE, follicle-associated epithelium; FDC, follicular dendritic cell; GALT, gut associated mucosal tissue; GC, germinal centre; GIT, gastrointestinal tract; GM1, monosialotetrahexosylganglioside; GP, glucan particles; GP2, glycoprotein 2; HepB, Hepatitis B; HIV, human immunodeficiency virus; HPV, human papillomavirus; IBD, inflammatory bowel disease; IEC, intestinal epithelial cell; IEL, intra-epithelial lymphocyte; ILF, isolated lymphoid follicle; Ig, immunoglobulin; IFNγ, interferon gamma; iNKT cell, invariant natural killer T cell; IPV, injectable polio vaccine; IRIV, immunopotentiating reconstituted influenza virosome; ISCOM, immune-stimulating complex; LP, lamina propria; LPS, lipopolysaccharide; LT, heat labile toxin from *Escherichia coli*; M cell, microfold cell; MAIT cell, mucosal-associated invariant T cell; MADCAM-1, mucosal addressin cell adhesion molecule-1; MHC, major histocompatibility complex; MLN, mesenteric lymph node; MNP, mononuclear phagocyte; OMV, outer membrane vesicle; OPV, oral polio vaccine; OVA, ovalbumin; PAMP, pathogen-associated molecular pattern; pIgR, polymeric Ig receptor; PLA, poly(lactic acid); PLGA, poly(lactic-co-glycolic acid); PP, Peyer's patch; PVA, polyvinyl alcohol; SC, stromal cell; SED, subepithelial dome; SIgA, secretory immunoglobulin A; SIV, simian immunodeficiency virus; TB, tuberculosis; TFH, follicular helper T; TLR, toll-like receptor; UEA-1, *Ulex europaeus* agglutinin-1; VLP, virus-like particles; WCK, whole cell killed; UN, United Nations

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1. Introduction

1.1. Enteric infections

Infectious diarrhoea is a significant global health challenge. Most diarrhoeal diseases are spread via the faecal oral route, primarily through contaminated water and food, resulting from poor sanitation. In the developed world, diarrhoeal diseases account for significant morbidity whereas in the developing world, where sanitation systems are often sub-optimal, it is associated with high levels of mortality [1], especially in children under 5 years of age who are most at risk at contracting and succumbing to such diseases [2]. Although oral rehydration therapy has reduced the overall number of fatalities caused by diarrhoeal disease, the long term damage resulting from disease episodes is a significant cause for concern [1]. During the first two years of life, infants undergo a significant period of brain development and physical growth. If, during this critical period, children suffer from diarrhoeal diseases, episodes of which can occur repeatedly and are accompanied by impaired nutrient absorption, there is a significant risk that long term developmental disabilities might occur. Stunted growth (often by up to 8 cm at age 7), lower levels of physical fitness, and impaired cognitive function adversely impacting on academic performance can have serious implications in both adolescent and adult life [3]. Diarrhoeal diseases caused by pathogenic *Escherichia coli*, *Vibrio cholerae* and rotavirus have a particularly large global impact. However, a number of other enteric pathogens including *Shigella dysenteriae*, *Salmonella enterica*, *Helicobacter pylori* and *Clostridium difficile* are major causes of morbidity and mortality globally [4] and the development of effective non-living oral vaccines for these would be very desirable.

Enterotoxogenic *Escherichia coli* (ETEC) infections cause acute watery diarrhoea and are spread through the consumption of contaminated food and water. The global disease burden of ETEC is estimated at over 210 million cases and 380,000 deaths annually, mostly in children. ETEC is also a leading cause of Traveller's Diarrhoea in visitors to endemic regions. Recently, oral vaccine efforts against ETEC have focused on the generation of whole cell killed (WCK) bacteria expressing colonisation factor antigens (CFAs), a family of molecules that mediate the attachment of ETEC bacteria to intestinal epithelial cells (IECs), an essential step in pathogenesis [5,6]. Cholera is a severe diarrhoeal infection that continues to pose a major challenge globally and for which oral vaccination to induce toxin and *lipopolysaccharide* (LPS) specific secretory Immunoglobulin A (*SIgA*) responses is seen as the most appropriate vaccine strategy [5]. The diarrhoea caused by cholera however, is much more severe than ETEC, causing between 3–5 million cases and resulting in over 100,000 deaths annually. Disease outbreaks are frequent in endemic regions and often follow in the wake of natural disasters and conflict. Additionally, changes in global climate patterns are leading to increased disease outbreaks as pathogens find new environmental niches to occupy. Recently a correlation between the rise in the global burden of cholera and global warming due to climate change was proposed, indicating that future outbreaks may be more prevalent and may occur in previously unaffected regions [7]. The devastation resulting from the introduction of a diarrhoeal pathogen is exemplified by Haiti which experienced a cholera outbreak in the wake of the 2010 earthquake that was introduced to the country by *United Nations* (UN) relief soldiers from Tibet [8]. In such situations, oral vaccination is a quickly implementable strategy allowing for the containment and even prevention of such outbreaks [9–11]. Owing to this, oral vaccines have also generated interest as a frontline tool in biodefence against possible terrorist or biological *weapon attack* [12].

1.2. Benefits of oral vaccines

Since the development of the first vaccine against smallpox in 1796 by Edward Jenner [13], vaccines have made an enormous contribution to public health, most notably the global eradication of small pox by 1979 [14]. One of the greatest success stories of modern vaccine discovery was the development of an injectable polio vaccine (IPV) by Jonas Salk. IPV reduced the number of cases of polio in the United States from 35,000 in 1953 to 161 cases in 1961, a mere 6 years after its launch in 1955. Concurrently with Salk's efforts, a group led by Albert Sabin developed a live-attenuated oral polio virus vaccine (OPV). These efforts culminated in large scale clinical trials conducted within the Soviet Union in the 1950s which proved the safety and effectiveness of the OPV concept. These results led to the licensing of Sabin's OPV in 1962. The National Institute of Health launched a large scale OPV campaign in the United States in 1963, which largely replaced Salk's IPV vaccine due to the lower cost and ease of administration of OPV. In fact, up to 20 doses of OPV can be applied to sugar cubes and administered to children in the time it takes to load and administer a single dose of IPV, while the discomfort of receiving the injection is also circumvented. This was the first large scale demonstration of the benefits of oral vaccines versus traditional injectable vaccines. Despite its efficacy, OPV has been largely replaced by IPV in western vaccination schedules and OPV will be phased out globally over coming years in the interest of achieving a polio-free World. Polio virus has been documented in the stool of vaccinated individuals, possibly spreading infectious material [15]. This is likely due to shedding of the virus after non-disease causing

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