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Systematic Review
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The Role of Vaccination in Prevention of Foodborne Disease in Children: A Systematic Review

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ABSTRACT

Background: Foodborne diseases pose a significant global health challenge, particularly for children in developing countries. Vaccination has emerged as a crucial strategy in controlling these diseases. This review examines the effectiveness and safety of foodborne disease vaccines in children based on recent literature.
Subjects and Method: This systematic review was conducted using Google Scholar, PubMed, and WHO websites with the keywords "vaccine" and "foodborne disease". Peer-reviewed articles from the past 10 years were analyzed using a narrative synthesis approach.
Results: This review identified significant developments in vaccines for rotavirus, cholera, typhoid, and candidate vaccines for Shigella, Enterotoxigenic Escherichia coli (ETEC), and norovirus. Rotavirus vaccines demonstrated positive impacts in reducing hospitalization rates and deaths due to diarrhea, although effectiveness varied across populations. Inactivated oral cholera vaccines showed protection rates of 52-62% over the first two years. Typhoid vaccines showed potential in reducing disease burden in endemic areas. Development of Shigella, ETEC, and norovirus vaccines is ongoing with promising initial results.
Conclusion: Significant progress has been made in developing foodborne disease vaccines, but efforts are needed to improve global vaccination efficacy and coverage. Further research is required to optimize vaccine formulation, delivery strategies, and long-term evaluation across various target populations.

Keywords: vaccine, foodborne disease

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BACKGROUND

Food contamination by pathogens such as bacteria, viruses, parasites, or chemical contaminants including heavy metals can cause more than 200 diseases. This phenomenon is a growing public health problem and has significant socio-economic impacts, including an increased burden on healthcare systems, decreased productivity, and negative effects on tourism and trade. These diseases contribute substantially to global morbidity and mortality. The etiology of foodborne diseases is closely related to contamination that can occur at any stage of

the food production, distribution, and consumption chain. This contamination can originate from various environmental factors, including water, soil, or air pollution, as well as food storage and processing practices that do not meet food safety standards (World Health Organization, 2022).

The clinical spectrum of foodborne diseases is broad, ranging from mild manifestations such as diarrhea to more serious conditions such as malignancies. Although the majority of cases manifest as gastrointestinal disorders, they can also cause neurological, gynecological, and immunological symptoms. Diarrheal diseases are a major problem worldwide, with a disproportionate burden in low- and middle-income countries and in populations of children under 5 years of age (World Health Organization, 2022).

Acute enteric infections (ACI) presenting as diarrhea and gastroenteritis are a global public health problem with significant mortality and morbidity, especially among pediatric populations in low- and lower-middle-income countries. Global data show that each year, approximately 500,000 children under 5 years of age die from severe diarrhea and dysentery resulting in dehydration, while millions more require hospitalization, with the majority of cases occurring in lower-middle-income countries (Riddle et al., 2018). Furthermore, growing scientific evidence indicates that children are also vulnerable to long-term physical and cognitive health consequences from repeated exposure to enteric infections (Nataro & Guerrant, 2017).

The acute consequences of enteric infections are of global significance that have prompted scientific and public health efforts to mitigate them, and there is growing scientific evidence indicating an association between these infections and a variety of chronic health manifestations involving the neurological, hematological, and rheumatologic systems. Furthermore, as with many other global infections, antimicrobial resistance in bacterial pathogens, particularly Salmonella and Shigella, has raised concerns about the potential for decreased efficacy of antibiotic therapy for these infections (Riddle et al., 2018).

A comprehensive and multidimensional approach, including improved sanitation and hygiene, clean water provision, food security, promotion of breastfeeding, and adequate nutrition, is needed to holistically address enteric disease. As an integral part of this approach, several enteric vaccines are available, and efforts are underway to expand their use during the development phase, which offer significant potential to improve the health status of at-risk populations in both high-income and lower-middle-income countries (Riddle et al., 2018).

In this review, we present the current status of the effectiveness and safety of foodborne disease vaccines in children for rotavirus, typhoid fever, and cholera, and describe new vaccines that are soon to be available and have entered advanced phases of clinical trials, including controlled human infection model studies or field trials in target populations.

SUBJECTS METHOD

1. Study Design

This study is a systematic literature review. Using a narrative synthesis approach for data analysis. Period of publication reviewed: the last 10 years.

2. Population and Sample

Population: All research articles related to vaccination in preventing foodborne disease in children. Sample: Peer-reviewed articles from Google Scholar, PubMed, and

WHO website databases that meet the inclusion criteria.

3. Inclusion criteria:

a. Peer-reviewed articles
b. Publications within the last 10 years
c. Relevant to the topic of foodborne disease vaccination in children
d. Available in designated databases Study Variables

The main variables studied:

a. Type of foodborne disease vaccine
b. Vaccine effectiveness
c. Vaccine safety profile
d. Target population (children)

4. Operational Definition of Variables

a. Foodborne disease vaccine: A biological product used to prevent foodborne diseases
b. Vaccine efficacy: The degree to which a vaccine is successful in preventing disease in the target population
c. Safety profile: Safety characteristics of a vaccine including side effects and contra-indications
d. Pediatric population: Age group below 18 years.

5. Study Instruments

a. Search databases: Google Scholar, PubMed, and WHO website
b. Search keywords: "vaccine" and "food-borne disease" and their variations in English
c. Article selection checklist based on inclusion criteria
d. Data extraction form to collect relevant information from selected articles

6. Data Analysis

a. Using a narrative synthesis approach
b. Analysis stages: a. Selection of articles based on title and abstract b. Full-text review of articles that passed the initial selection c. Data extraction from selected articles d. A narrative synthesis of findings based on main themes e. Preparation of systematic and structured reviews

RESULTS

Foodborne diseases are a major cause of morbidity and mortality worldwide, affecting one-third of the global human population each year (World Health Organization, 2005). Pathogenic agents contained in food, both microbiological (including viruses, bacteria, and parasites) and chemical (including toxins, heavy metals, pesticide residues, and veterinary drug residues), pose significant risks to human health. Global estimates show that each year, around 600 million individuals experience illness and 420,000 deaths occur due to consumption of unsafe food, resulting in the loss of 33 million healthy life years (Disability-Adjusted Life Years/DALYs). The population of children under 5 years of age is a particularly vulnerable group, with mortality rates reaching 125,000 cases per year due to foodborne diseases. It is important to note that most of this morbidity and mortality could actually be prevented through appropriate interventions. Unsafe food causes 1 in 10 people to fall ill each year worldwide. Foodborne diseases cause 33 million healthy life years lost each year. Children account for 1/3 of deaths from foodborne diseases (World Health Organization, 2024).

Literature studies have shown that strategies to combat foodborne pathogens include vaccines against norovirus and rotavirus, which provide hope that these vaccines will significantly reduce the burden of foodborne diseases caused by these viruses or other pathogens. Licensed vaccines currently available against rotavirus, cholera, and typhoid, as well as potential second and third generation vaccines against these pathogens, are currently under development (Riddle et al., 2004).

DISCUSSION

Rotavirus vaccine

Rotavirus remains one of the most significant pathogens associated with diarrheal mortality in the pediatric population, even in the era of vaccine availability. Current estimates suggest that rotavirus is still responsible for approximately 129,000 diarrheal deaths in infants and children globally, with more than 90% of cases occurring in countries in Africa and Asia. In addition to its impact on mortality, rotavirus infection also contributes significantly to morbidity, with an incidence of more than 258 million episodes of diarrhea and more than 1.5 million hospitalizations each year. Given the large burden of this disease, the World Health Organization (WHO) has recommended the integration of rotavirus vaccination into national immunization programs in all countries (GBD Diarrhoeal Diseases Collaborators, 2017).

Implementation of rotavirus vaccine has shown significant impact on child health in various areas of implementation, with substantial reductions in diarrhea-related hospitalization rates and diarrhea-related mortality observed post-vaccine introduction (Jonesteller et al., 2017; Burnett et al., 2017). However, despite the success of vaccination programs, rotavirus remains a major contributor to the burden of residual diarrheal disease, even among vaccinated populations (Mwenda, et al., 2017). Several factors postulated to cause suboptimal performance of current rotavirus vaccines include:

1. Presence of maternal antibodies
2. Inadequate nutritional status
3. Environmental enteropathy
4. Alterations in the composition of the intestinal microbiota
5. Micronutrient deficiencies
6. Exposure to other enteric pathogens

Cholera vaccine

Global estimates suggest that cholera is responsible for approximately 1.3 million cases and 21,000 deaths annually (Ali et al., 2015). However, it should be noted that these figures are likely to be a significant underestimation of the true burden of cholera, given the substantial negative impact on tourism and trade in reporting countries. Conditions such as conflict, political instability, or natural disasters that disrupt already fragile basic sanitation infrastructure and result in population displacement into crowded, unhygienic environments create an ecosystem conducive to cholera outbreaks. Vaccination strategies are therefore a crucial component of cholera control efforts. Parenteral cholera vaccines are no longer recommended and have been abandoned due to their less favorable reactogenicity profile and relatively short duration of protection. Currently, there are two main categories of oral cholera vaccines (OCVs) available globally (Riddle et al., 2018):

1. Inactivated vaccine (killed Oral Cholera Vaccine/kOCV)
2. Live attenuated Oral Cholera Vaccine/ OCV

These two types of vaccines offer different approaches to immunization against cholera, with each having specific characteristics, effectiveness, and safety considerations (Riddle et al., 2018).

Inactivated oral cholera vaccine (kOCV) has undergone a series of comprehensive efficacy and effectiveness evaluations. Based on systematic reviews, the estimated level of protection of this vaccine ranges from 52-62% during the first two years after vaccination (Sinclair et al., 2011). However, observations showed a gradual decline in the level of protection in the third and fourth years post-vaccination, to 39% and 26%, respectively (Bi, et al.,

2017). Furthermore, stratified analysis by age revealed that the level of protection provided to children under 5 years of age was relatively lower (30-38%) compared to older children and the adult population (Sinclair et al., 2011).

Given the logistical challenges associated with administering two doses of vaccine at a specific interval, a study on the efficacy of a single-dose regimen of kOCV was conducted. The results showed an overall efficacy of 40% at 6 months post-vaccination. However, further age-stratified analysis revealed that in the early childhood group (1-4 years), the level of protection conferred was only 16%. These findings underscore the complexity in developing and implementing an optimal cholera vaccination strategy, especially in the context of age-specific variations in immune responses and logistical considerations in vaccine administration (Qadri, et al., 2016).

Currently, oral cholera vaccines (OCVs) that have met the World Health Organization (WHO) qualification are limited to formulations consisting of inactivated whole cells, namely Dukoral, Shanchol, and Euvichol. Since July 2013, WHO has initiated the management of a global OCV stockpile for implementation in cholera control efforts. Observations show a significant increase in OCV utilization, especially in the context of humanitarian crises, with an exponential increasing trend each year between 2013 and 2017. As an illustration, there was an increase from 200,000 doses distributed in 2013 to 4.6 million doses in 2016. Consequently, the increase in OCV production by low-cost manufacturers has been considered a positive development in the face of escalating demand for cholera control. (Deployments from the oral cholera vaccine stockpile, 2017)

However, as with other oral vaccines, including rotavirus and poliovirus vaccines (Riddle et al., 2018), OCVs show suboptimal immunogenicity phenomena in developing countries compared to industrialized countries (Desai et al., 2014). Several etiologic factors have been hypothesized to contribute to reduced OCV efficacy including malnutrition, intestinal microbiota dysbiosis, and environmental enteropathy (Parker, et al., 2017).

Typhoid vaccine

A recent review found that approximately 17.8 million cases of typhoid fever occur annually in low- and middle-income countries, with a peak incidence identified in the child population aged 2 to 4 years (Antillón, et al., 2017). The geographic distribution of the disease shows significant regional variation, with the highest prevalence concentrated in South and Southeast Asia. In these regions, typhoid fever is endemic, and Salmonella Typhi is the predominant pathogen isolated from blood cultures (Obaro et al., 2017).

Typhoid fever also contributes significantly to the global public health burden, with increasing awareness of the high incidence of the disease in parts of Africa and its potential to manifest as an epidemic (Marks, et al., 2017). Outside the context of low-middle-income countries with a high burden of disease, typhoid fever remains a persistent threat to deployed military personnel and travelers who are frequently exposed to situations with limited access to safe food and water, and are at high risk for typhoid transmission (Dave & Sefton , 2015).

Recent Developments in Enteric Vaccines: Focus on Shigella, ETEC, and Norovirus Vaccines

In the contemporary enteric vaccinology landscape, there has been significant progress in the development of vaccines for

three major pathogens that cause diarrhea: Shigella, Enterotoxigenic Escherichia coli (ETEC), and Norovirus. Each of these pathogens contributes substantially to global morbidity and mortality, especially in developing countries and in vulnerable populations such as children.

1. **Shigella Vaccine**

Shigellosis is a major etiology of diarrheal disease globally, with a higher prevalence in low- and middle-income countries (Kotloff, 2018). The disease also remains a significant health problem for travelers visiting endemic areas (Riddle et al., 2018). Current estimates suggest a mortality rate of approximately 164,000, mainly among the pediatric population in low- and middle-income countries (Kotloff, 2018).

Shigella vaccine development remains a high priority on the global health agenda, based on several crucial factors:

1. Substantial burden of disease (Platts-Mills et al., 2015).
2. Increasing prevalence of antimicrobial resistance (Gu et al., 2015).
3. Increasing understanding of post-shigellosis infection sequelae, including stunting and cognitive deficits (O'Ryan et al., 2015).

Molecular epidemiology indicates that Shigella flexneri 2a, 3a, and 6, together with Shigella sonnei, are responsible for approximately 85% of shigellosis cases in low- and middle-income countries. This emphasizes the importance of developing a multivalent Shigella vaccine that includes these dominant serotypes (Livio et al., 2014).

1. Enterotoxigenic Escherichia coli (ETEC) Vaccine

Enterotoxigenic Escherichia coli (ETEC), one of the pathotypes of diarrheagenic E. coli, is an etiologic agent of secretory diarrhea with a spectrum of clinical manifestations ranging from mild discomfort to cholera-like disease. ETEC has been identified as a highly prevalent bacterial pathogen in pediatric diarrhea cases in low- and middle-income countries (LMICs) (Kotloff et al., 2017). Current estimates suggest that the infant mortality rate due to ETEC infection ranges from 7,000 to 76,000 cases per year (Hosangdi et al., 2019).

In addition to its significance in the context of public health in low- and middle-income countries, ETEC is also the predominant etiology of traveler's diarrhea, accounting for 30-50% of reported cases. The dual role of ETEC in global public health and medicina peregrinans (travel medicine) has been a catalyst in the development of a safe and effective ETEC vaccine (Riddle et al., 2018).

The complexity of ETEC epidemiology, including variability in strains and virulence factors, as well as differences in disease patterns between endemic and traveler populations, poses specific challenges in vaccine design and development. Current vaccinological approaches to ETEC focus on several strategies (Bourgeois et al., 2016):

1. Development of toxin-based vaccines, targeting heat-labile toxins (LT) and heat-stable toxins (ST)
2. Vaccines that target ETEC colonization factors

A combination approach that includes both toxin components and colonization factors

2. Norovirus vaccine

Noroviruses cause a significant global burden of disease, both in high-income and low- and middle-income countries (Hall et al., 2016). This virus has emerged as the predominant etiology of gastroenteritis and diarrhea in countries that have implemented rotavirus vaccination. In addition, norovirus is a major causal agent in food-

borne disease outbreaks in high-income countries and a significant cause of diarrhea in travelers (Riddle & Walker, 2016).

Epidemiological characteristics of norovirus include:

1. High infectivity: Very low infectious dose (<10-100 virions).
2. Acute clinical manifestations: Fever, nausea, emesis, abdominal cramps, malaise, and diarrhea lasting 2-5 days.
3. Prognosis: Generally self-limiting, but geriatric and immunocompromised populations are at risk for more severe manifestations and longer disease duration.
4. Immunity: Post-infection protection is transient and genotype-specific, resulting in susceptibility in all age groups.

Current management is limited to supportive therapy, primarily oral rehydration, with no specific therapy to mitigate disease severity. Development of a norovirus vaccine faces several significant challenges (Riddle & Walker, 2016):

1. Limitations of model systems for pathogenesis exploration and efficacy evaluation of vaccine candidates
2. Uncertainty regarding the duration of protective immunity
3. Complexity of virus cultivation at production scale
4. Intra-genogroup and inter-genogroup antigenic variability and genotypes

However, recent advances in vaccine technology, such as the use of virus-like particles (VLPs) and multivalent approaches, provide hope for the development of effective norovirus vaccines. Optimal vaccination strategies need to consider strain variability, target populations (including children, the elderly, and travelers), and effective delivery mechanisms to induce mucosal immunity (Riddle & Walker, 2016). There are various challenges in developing a norovirus vaccine, significant progress has been made through a recombinant approach based on virus-like particles (VLPs) that have the ability to self-assemble. This innovative strategy has demonstrated promising protective potential in two human challenge efficacy studies (Bernstein et al., 2015).

Norovirus virus-like particles (VLPs) are viral capsid structures that do not contain infectious genetic material, but retain antigenic and immunogenic characteristics similar to intact virions. The advantages of the VLP approach include (Bernstein et al., 2015):

1. Safety: The absence of viral genetic material eliminates the risk of replication and pathogenesis.
2. Immunogenicity: VLPs are able to induce robust humoral and cellular immune responses.
3. Flexibility: Allows genetic modification for optimization of immunogenicity or inclusion of multiple genotypes.

Results from two human challenge efficacy studies (Bernstein et al., 2015) showed that a norovirus VLP-based candidate vaccine could:

1. Induce significant antibody responses to norovirus antigens.
2. Provide partial protection against infection and/or symptomatic disease following challenge with a homologous norovirus strain.
3. Reduce the severity of symptoms in infected subjects post-vaccination.

These findings provide crucial proof of concept for the viability of a VLP-based vaccine approach for the prevention of norovirus infection. However, it should be noted that challenges remain, including:

1. Optimization of vaccine formulation to improve efficacy and duration of protection.

2. Development of multivalent vaccination strategies to address antigenic variability of norovirus.
3. Evaluation of vaccine efficacy in broader and more diverse populations, including children and the elderly.
4. Further investigation of immunological correlates of protection.

These promising early results stimulate further research and development of norovirus vaccines, with significant potential to reduce the global burden of disease caused by this pathogen. Further studies with larger scale and longer observation duration are needed to confirm and expand these findings, as well as to optimize future norovirus vaccination strategies (Bernstein et al., 2015).

The conclusions of this study are that while significant advances in vaccinology have been made, there is still an urgent need to expand the spectrum of available vaccines and increase global vaccination coverage. Collaborative efforts and continued investment in foodborne disease vaccine research and development have the potential to have a transformative impact on global health, substantially reducing morbidity and mortality associated with foodborne infections. Improved understanding of the long-term health sequelae associated with these infections, as well as the health threats posed by the escalation of antimicrobial resistance, underscores the urgency and critical value of preventive strategies, particularly vaccination.

AUTHORS CONTRIBUTION

The authors have made substantial contributions to the conception, literature survey, and preparation of the review.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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