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Review

A brief review on the immunological scenario and recent developmental status of vaccines against enteric fever

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ABSTRACT

Enteric fever has been one of the leading causes of severe illness and deaths worldwide. *S.* Typhi and *S.* Paratyphi A, B and C are important enteric fever-causing organisms globally. This infection causes about 21 million cases among which 222,000 typhoid related deaths occurred in 2015. These estimates do not reflect the ultimate and real status of the disease due to the lack of unified diagnostic and proper reporting system from typhoid endemic and other regions. Current control strategies have become increasingly ineffective due to the emergence of multi-drug resistance among the strains. This situation worsens the disease-burden in developing as well as in developed countries. Moreover the emergence of *S.* Paratyphi A as a major enteric fever-causing organism in several Asian countries, demands a prophylactic measure at this hour. Other than two licensed vaccines of *S.* Typhi, there are no exsisting vaccines for *S.* Paratyphi A. Moreover, travelers returning from endemic regions are becoming more susceptible to have these infections. In this situation, a need for bivalent approach is required where a single immunogen (consisting from each organism) will be effective against the disease. In this review, we have focused on the general information about typhoidal fever, its spread and epidemiology in brief and the present status of typhoidal vaccines and its future. This review highlights existing gaps in the typhoidal salmonellae research with a special emphasis on the status of present typhoidal salmonellae vaccine research.

Contents

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1. Introduction

1.1. Prevalence of enteric disease – S. Typhi and S. Paratyphi A.

Enteric fever caused by *Salmonella enterica* serovar Typhi (*S.* Typhi) and *Salmonella enterica* serovar Paratyphi A, B and C (*S.* Paratyphi A, B and C) is an important etiological agent of enteric fever causing global morbidity and mortality [1–3]. The estimates of the infection may not always indicate the real status of the disease due to the lack of suitable diagnostics and insufficient systemic data collection. Developing countries with poor surveillance are more affected with enteric infections, but the surveillance information remains very less. Increasing antibiotic resistance in the circulating serovars of the typhoidal salmonellae is a challenge to establish an effective treatment of enteric fever [4]. Reporting of *S.* Paratyphi B and C is very rare, if present, but on the other hand, *S.* Paratyphi A is found to be the major enteric fever causing bacteria in the Asian as well as other developing countries [5]. Due to the absence of a market available paratyphoid vaccine and rise in infection, research should be done on it with utmost priority [1].

The burden of the disease varies between countries [1]. The spread of the disease depends on several factors, such as, the personal hygiene, quality of the sanitation system, socio-economic status, emergence of drug resistant strains in epidemic and endemic regions etc. [1,6]. Outbreaks are most likely to occur due to poor quality of water and foods [1,7].

Travelers returning from endemic regions of the world are more prone to develop the disease and they are likely the carriers and responsible for transmission of the disease. Traveling to rural areas with poor sanitation are considered to be associated with cases of enteric fever. The risk even increases when the precautions for food and water hygiene are not being followed up properly [7]. The infection transmits itself via fecal-oral route and humans acts as the sole reservoir of the infection [8]. Although the major sources for outbreak are related to food and water, but an increasing number of incidence in recent years have been associated with foreign travelers [7,9]. Chronic carries of the disease also act as a threat to the healthy population. Chronic carriage occurs as a result of incomplete or no antibiotic treatment following the infection. About 2–5% cases of acute typhoidal infections, become chronic in nature. They persistently shed the bacilli in stool as a result of the infected gall bladder acting as the reservoir organ [1].

1.2. Background of present typhoidal vaccine research

Unlike other gastrointestinal disorders, the prevalence of *S.* Typhi does not occur early in life, but it occurs in the age group of 5–12 years or pre-high school children. The reason for less number of cases in less than 5 years of age-group could be the underdeveloped reticulo-endothelial system [10]. Globally, two licensed typhoidal vaccines are available in market. One is Ty21a (a live attenuated *galE* mutant of Ty2) and the other one is Vi polysaccharide vaccine. In India, several other licensed vaccines are available. Among them, a Vi polysaccharide recombinant vaccine (rEPA, Vi polysaccharide conjugated with *Pseudomonas aeruginosa* exotoxin A) and two Vi polysaccharide vaccines conjugated with tetanus toxoid are promising to become a vaccine of choice [1]. Although the orally administered Ty21a provides protection for seven long years, but its only protective for 50–70% of the population. The purified Vi antigen is for persons aged two years and above, whereas the live attenuated oral Ty21a vaccine in capsule formulation for those over five years of age. [1].

In this review, we have focused on typhoidal salmonellae research, treatment, the basic concepts of typhoidal salmonellae vaccine and the present status of globally as well as locally available typhoidal salmonellae vaccines. We have also pointed out the lacunae of typhoidal salmonellae vaccine research and what could be the cure for them.

2. Current epidemiological situation in different countries

As stated above, the majority of enteric fever related infections occurs by *S* Typhi and *S.* Paratyphi A. In the 19th century, enteric fever was common in USA and European countries, but in recent times, enteric fever is one of the major health issues in developing countries. It is endemic in Africa, Asia and persists in the Middle East, a few Southern and Eastern European countries and central and South America as well [11]. The most un-characterized data was obtained from sub-Saharan countries, but in these countries, non-typhoidal infections predominate. Nonetheless, reports of enteric fever emerges [12] time to time. Isolation of various *Salmonella* spp. from sewage water intended to use as agriculture use has increased the fear of the organism being spread in the population [13–15].

In Asian countries on the other hand, a large number of enteric fever incidences occurs in China, India, Pakistan, Indonesia and Vietnam, making this region one of the majorly affected enteric fever region [16]. Moreover, as told before, a rise in the *S.* Paratyphi A infection is occurring at an alarming rate and sometimes more than 50% bloodstream isolates are *S.* Paratyphi A [12,5,8]. During the last pandemic of cholera in Latin American countries, strict water and sanitation measures were introduced and this has caused a decline in the rate of endemic enteric fever infection. In this area, the enteric fever infection rate was found to be lowered with economic stability [12]. Thus the picture clearly shows that control measures are necessary to eradicate the infection. Common control measures of enteric fever include both non-vaccine measures and the use of vaccines.

3. Importance of seroprevalence of typhoid infection

Seroprevalence data is an important measure of having an idea about an infection, its spread into the population and potential for outbreak in the future [17]. It owns its importance in its applications in epidemiology where the data shows the proportion of a specific population having been infected before or having the immunity against a specific infectious agent. Seroprevalence data on enteric fever could open up new avenues stating the obvious needs for the population (e.g. vaccination) and its importance.

In terms of its nature and symptoms of infection, enteric fever is very similar to that of the malaria infection(s). A study from Cameroon compared typhoidal infection with malaria and showed that the prevalence of enteric fever is much less than it was expected before [18]. The study had also helped the physicians to carry out simple, cost effective methods of detecting positive cases for enteric fever. A regression model was also formulated using the adult's

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