Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Disease

journal homepage:www.elsevier.com/locate/apjtd

Document heading doi:10.1016/S2222-1808(11)60019-4

Study on the possible use of Vi polysaccharide typhoid fever vaccine to control endemic typhoid fever in Nepal

Surendra Karki[1], Kuldeep Kumar[2*]

[1]*The Alfred Centre, 99 Commercial Road, Melbourne VIC 3004, Australia*

[2]*Novartis Health Care Pvt Ltd, Hyderabad, India*

ARTICLE INFO

Article history:
Received 16 January 2011
Received in revised form 26 February 2011
Accepted 8 March 2011
Available online 28 March 2011

Keywords:
Vi polysaccharide typhoid fever vaccine
Typhoid fever
Vaccine
Nepal
Salmonella paratyphi
Enteric fever
Paratyphoid fever

ABSTRACT

This review of literature was conducted to explore the various aspects of typhoid fever in Nepal and to identify the factors concerned in the possible use of the Vi polysaccharide typhoid fever vaccine in Nepal as the tool for prevention and control. There are hotspots of Typhoid fever in developing countries, urban areas and slums, where poor conditions of safe drinking water and sanitation prevail. The use of currently available typhoid fever vaccines, especially the Vi polysaccharide vaccine has been recommended by World Health Organization to control typhoid fever in endemic areas. However, factors like, the burden and the changing epidemiological pattern of the disease, efficacy of the vaccines, ease for intervention, cost effectiveness, financing, and programmatic issues should be considered in local settings before the introduction of vaccines as a public health tool for prevention. We concluded that the possible use of currently available Vi polysaccharide vaccine to control endemic typhoid fever in Nepal might not have the same positive impact as reported in trials from different Asian countries. The major issues to be considered are emergence of *Salmonella Paratyphi* A as a major cause of enteric fever, no difference in prevalence of typhoid fever in preschool and school children, similar clinical profiles and severity of typhoid and paratyphoid fever. So, an ideal vaccine that can provide the protection both to typhoid and paratyphoid fever, and the vaccination programs that also includes preschool children would be the best option for Nepal.

1. Introduction

Typhoid fever is caused by *Salmonella enterica(S. enterica)* Serovar Typhi, a Gram-negative bacteria of family *Enterobacteriaceae*. *Salmonella paratyphi (S. paratyphi)* A and B can cause paratyphoid fever, which is a similar but somewhat less serious illness. The term enteric fever includes both typhoid fever and paratyphoid fever. There are hotspots of typhoid fever in developing countries, urban areas and slums, where poor conditions of safe drinking water and sanitation prevail. Prevention and control of typhoid fever in endemic areas can significantly reduce the morbidity, mortality, costs of hospitalization, treatment and other associated costs. The provision of safe drinking water, sanitation and use of preventive vaccines has been often discussed as effective prevention and control strategy for typhoid fever in endemic areas. The former two interventions require high political will, economic resources, and often take much longer period of time in resource poor countries. The use of currently available typhoid fever vaccines, especially the Vi polysaccharide vaccine has been recommended by World Health Organization to control typhoid fever in endemic areas. However, factors like the burden and the changing epidemiological pattern of the disease, efficacy of the vaccines, ease for intervention, cost effectiveness, financing, and programmatic issues should be considered in local settings before the introduction of vaccines as a public health tool for prevention. This paper discusses about the issues regarding the possible use of Vi polysaccharide typhoid fever vaccines in control of endemic typhoid fever in Nepal.

The global estimation of typhoid fever in 1986 showed a total of 16 million cases with 600 000 deaths each year[1]. Recently, Crump *et al*[2] estimated 21 million illnesses and 216 510 deaths in 2004 due to typhoid fever, and a total of 5.4 million cases of paratyphoid fever. Asia, particularly

*Corresponding author: Dr. Kuldeep Kumar, MBBS, MIH (Child Health), Novartis Health Care Pvt Ltd, Hyderabad, India.
E-mail: kuldeep.kumar.09@ucl.ac.uk

South Asia has been described as the hotspot of typhoid fever. A multicenter study including five Asian countries viz. China, India, Pakistan, Vietnam and Indonesia reported highest burden in Pakistan with the incidence of 451.7/100000 population/year and China had the lowest burden with incidence of 15.3/100 000 population/year[3].

2. Enteric fever in Nepal

Enteric fever is one of the major public health problems in Nepal and the incidence of typhoid fever is estimated to be more than 100/100 000 cases per year[2]. Murdoch *et al*[4] has reported enteric fever as one of the common causes for adults to visit health facilities in Nepal. Many outbreaks of enteric fever occur in urban areas, during rainy seasons, probably due to contamination of drinking water system with sewerage. A bacteriologic analysis of urban water supply of Kathmandu valley reported that 14% of samples from different sampling points were contaminated with *S. enterica*, of which *Salmonella typhi (S. typhi)* and *S. paratyphi* contributed to more than 50% isolates[5]. A massive outbreak of multi-drug resistant *S. typhi* with total cases of 5 963 within in a 7 weeks period was recorded during the summer of 2002, in Bharatpur, Nepal[6]. The emergence of multi-drug resistance in *S. typhi* as well as in *S. paratyphi* might be a big problem in the future, both in terms of case fatalities and cost for treatment, if effective prevention and control strategies are not implemented in a timely manner. There have been reports of complete resistance to Ciprofloxacin from Pakistan and India, otherwise previously considered as a very effective antibiotic[7]. In Nepal, Pokharel *et al*[8] reported 5% prevalence of MDR (resistance to two or more antibiotics) among isolates *S. enterica*. Similarly, the largest single point source outbreak of multi-drug resistant typhoid fever outbreak with crude attack rate of 64.9/1000 population has been described from Bharatpur[6], Nepal indicating toward a possible disastrous morbidity, and mortality from the outbreaks that might occur in future.

Studies from Nepal suggest a similar burden of typhoid fever in preschool children and school children, and a relatively higher proportion of *S. paratyphi* as a causative agent of enteric fever. Most importantly in Nepal, there is no difference in clinical symptoms as well as in severity of illness in typhoid and paratyphoid fever, and the proportion of patients with typhoid and paratyphoid fever is similar[9,10]. So, any of the program targeting only for typhoid fever would not be a real solution to the problem of enteric fever in Nepal. One of the largest studies conducted in a hospital of Kathmandu valley reported that among the total enteric fever cases, 70.7% were due to *S. typhi* and 29.3% were due to *S. paratyphi* A. The study also reported that the isolation rate of *S. typhi* and *S. paratyphi* A in the period of 2001-2003 was more than double compared to three years period earlier[11]. Similarly, a recent study from a Periurban area of Kathmandu reported that among the total cases of enteric fever, only 34.6% were caused by *S. typhi* and 65.4% caused by *S. paratyphi* A, with most of the cases in the age group of 1-15 years[12]. The global estimation of typhoid fever burden showed that children of age group 5-15 years were the mostly affected ones[2]. However, a hospital based study among children presenting with febrile illnesses in Kathmandu showed that there was no significant difference in occurrence of enteric fever in the age group of 1-5 and 6-10 years[13]. According to another hospital based study outside Kathmandu Valley, more than 50% of positive blood cultures from patients presenting with febrile illnesses were due to *S. typhi* and *S. paratyphi*[14]. It is very difficult to estimate the incidence of enteric fever from hospital based surveys in Nepal, as most of the febrile illnesses are treated as outpatients, and many of the patients get the antibiotics from the private pharmacies without any type of diagnosis. There is no representative population based and age stratified data describing the incidence of typhoid fever in Nepal. Most of the published papers related to epidemiology of typhoid fever do not provide reliable data to inform and guide the policy makers to plan effective interventions. However, most of the studies indicate towards a high burden of enteric fever in Nepal.

3. Vi polysaccharide typhoid fever vaccine

Currently, two types of typhoid vaccines have been licensed. One is capsular polysaccharide based subunit vaccine, the Vi vaccine, which is administered parenterally (intramuscular or subcutaneous) and another is live attenuated oral vaccine, the Ty21a vaccine, which is administered orally. The use of Ty21a vaccine for public health programs is not favored much, possibly because it should be administered in 3 doses every other day, as well as due to other programmatic issues. The inactivated whole cell vaccine against Typhoid fever is also available, but its usefulness is mainly limited by its high rate of reactogenicity[15].

The Vi polysaccharide vaccine is much studied and mostly advocated vaccine to control typhoid fever in endemic areas. The protection by Vi vaccine starts after 7th day of vaccination whereas the peak level of antibody protection rises on 28th day. The vaccine can only be given to individuals older than 2 years. Revaccination is essential in every three years to maintain the effectiveness[16]. The efficacy of Vi vaccine has been proved in various randomized trials. One of the earliest trials was conducted in Nepal among 6 907 individuals aged 5-44 years. The study showed 75% efficacy up to 17 months of follow up[17]. Similarly, another efficacy trial in South Africa showed that the protective efficacy was 64% in follow up period of first 21 months, which decreased to 55% after 3 years[18]. The public health impact of Vi polysaccharide vaccine has been demonstrated in China by a mass vaccination program. The program was implemented to vaccinate school aged children, student and food handlers in 1995, with repetition of vaccination in every 3 years and evaluated in 2006. After

10 years, there was tremendous decrease in incidence from prevaccination average of 47/100 000 in general population and 61/100 000 in students to 0.2-4.5/100 000 in all study groups[15]. The efficacy trials conducted earlier had focus only on the efficacy above the age group 5 years. However, a recent randomized control trial from the urban slum of Kolkata has demonstrated 80% protection in age group of 2-5 years, and has demonstrated herd immunity with 44% level of protection in spite of only 61% coverage. The study also reported an overall efficacy in all age groups and efficacy in all residents of the Vi vaccine cluster was found to be 57%[19]. However, the Vi vaccine has some important drawbacks. The Vi polysaccharide vaccine relies on T-cell independent production of antibodies which lacks the immunological memory, and the second dose of vaccine would not have booster effect, so should be repeated on every three years. However, the Vi conjugated vaccines with recombinant Pseudomonas aeruginosa Exotoxin A (rEPA) has potentiality to overcome the problem. The field trial of such conjugated Vi vaccine in Vietnam showed a more than 90% of efficacy in children aged 2-5 years[20]. However, the Vi vaccine can not induce the mucosal immunity, which means it can not target the pathogen early during the route of infection. The mass vaccination programs requires huge amount of needles and syringe, so safe disposal of large amount of biohazardous waste is another problem in resource poor settings like Nepal. The Vi vaccine does not show any cross protection against *S. paratyphi* related enteric fever as *S. paratyphi* lack the Vi antigen. So, in a country like Nepal where there is increasing trends of *S. paratyphi* related enteric fever, the possibility to use Vi vaccine as a tool for prevention and control of only typhoid fever should be judged critically.

4. Challenges

The implementation of mass vaccination programs for typhoid fever is challenging, since the vaccines do not fit in expanded program on immunization (EPI) schedule as well as the efficacy in clinical trials is not so higher. However, the diseases of most impoverished (DOMI) program funded by Gates foundation is conducting researches to provide sufficient information on epidemiology, and economic analysis to guide for the introduction of typhoid Vi vaccine in targeted Asian Countries[21]. A recently published Vi typhoid vaccine cost effectiveness study in four urban areas of Asia has shown that Vi vaccine is cost effective in vaccinating children in slums of Kolkata, Karachi and North Jakarta, according to the WHO definition of cost effectiveness, but not in Hue (Vietnam)[22]. The study also showed that the vaccination cost per children in Indian slum of Kolkata constitutes about one fourth of per capita total public investing in health[22]. So, for low income countries like Nepal the government has difficulty in managing sufficient resources to spend for the public programs in vaccinating with typhoid vaccines. The way of financing through the donor agencies, also remains unclear as the vaccine itself is not fitted to the EPI schedule, less duration of protection and there is need for revaccination. The need for introduction of an effective vaccine is more or less justified in the endemic area of Asian countries, as indicated by the higher incidence of disease, emergence of drug resistance. However, there is no clear cut plan for financing the program, neither from the national governments nor from the donor agencies. A contingent valuation survey from Kolkata, India has demonstrated the possibility of introducing user fees in typhoid vaccination programs and they anticipate sufficient private demands of the vaccine[23]. The Global Alliance for Vaccine and immunization (GAVI) on its working group meeting on vaccine investment strategy on 2008, decided that the currently licensed typhoid vaccines are not ideal to implement in GAVI eligible countries, mainly because of its small duration of protection and need for revaccination after three years. The working group showed preference to conjugated Vi vaccine, however it decided that it is not suitable for GAVI market as there is only a single producer of vaccine for the time being[24].

The target areas for the typhoid fever vaccination campaigns should be the high risk population of the high endemic areas[15]. A study from North Jakarta, Indonesia has demonstrated the feasibility of primary school based Vi typhoid fever vaccination program with coverage of 91%, however, the project used the already existing school based vaccination platform[25]. Another study in Hue city, central Vietnam has also reported the feasibility of school based Vi vaccination campaign in terms of safety, logistics, and coverage, however the coverage was only 57.5%[26]. Recently the Vi conjugate typhoid vaccine (Vi-rEPA), evaluated among infants has shown to be safe and able to elicit the protective levels of IgG[27]. Similarly, in an effort to develop an affordable and broadly protective vaccine against enteric fever, Novartis vaccine institute for global health has started its first program on developing a multivalent vaccine protecting against *S. Typhi* and *S.paratyphi* A[28]. In Nepal, the available data suggests that the urban areas with poor supply of unsafe drinking water, and sanitation have the high burden of typhoid fever, and should be the target area for prevention. However, there have been no recent research to discuss, the feasibility, acceptance, coverage, primary school based mass vaccination programs in the urban areas of Nepal, with high population density, as for example Kathmandu Valley.

In conclusion, the possible use of currently available Vi polysaccharide vaccine to control endemic typhoid fever in Nepal might not have the same positive impact as reported in trials from different Asian countries. The major issues to be considered are emergence of *S. paratyphi* A as a major cause of enteric fever, no difference in prevalence of enteric fever in preschool and school children, similar clinical profiles and severity of typhoid and paratyphoid fever. So, an ideal vaccine that can provide the protection both to typhoid and paratyphoid fever, and the vaccination programs that also includes preschool children would be the best option for Nepal. Further good quality researches

describing the epidemiology of enteric fever and economic analysis for interventions are essential to inform health policy makers and guide them for appropriate decision making in controlling endemic enteric fever in Nepal.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Edelman R, Levine MM. Summary of an international workshop on typhoid fever. *Rev Inf Dis* 1986; **8**: 329-349.

[2] Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bull World Health Organ* 2004; **82**(5): 346-353.

[3] Ochiai RL, Acosta CJ, Danovaro-Holliday MC, Baiqing D, Bhattacharya SK, Agtini MD, et al. A study of typhoid fever in five Asian countries: disease burden and implications for control. *Bull World Health Organ* 2008; **86**(4): 260-268.

[4] Murdoch DR, Woods CW, Zimmerman MD. The etiologyof febrile illness in adults presenting to Patan Hospital inKathmandu, Nepal. *Am J Trop Med Hyg* 2004; **706**: 670-675.

[5] Bhatta DR, Bangtrakulnonth A, Tishyadhigama P, Saroj SD, Bandekar JR, Hendriksen, et al. Serotyping, PCR, phage-typing and antibiotic sensitivity testing of *Salmonella serovars* isolated from urban drinking water supply systems of Nepal. *Lett Appl Microbiol* 2007; **44**(6): 588-594.

[6] Lewis MD, Serichantalergs O, Pitarangsi C, Chuanak N, Mason CJ, Regmi, et al. Typhoid fever: a massive, single-point source, multidrug-resistant outbreak in Nepal. *Clin Infect Dis* 2005; **40**(4): 554-561.

[7] Chau TT, Campbell JI, Galindo CM, Van Minh Hoang N, Diep TS, Nga TT, et al. Antimicrobial drug resistance of *Salmonella enterica* Serovar Typhi in Asia and molecular mechanism of reduced susceptibility to the fluoroquinolones. *Antimicrobial Agents Chemother* 2007; **51**(12): 4315-4323.

[8] Pokharel BM, Koirala J, Dahal RK, Mishra SK, Khadga PK, Tuladhar NR. Multidrug-resistant and extended-spectrum beta-lactamase (ESBL)-producing *Salmonella enterica* (serotypes Typhi and Paratyphi A) from blood isolates in Nepal: surveillance of resistance and a search for newer alternatives. *Int J Infect Dis* 2006; **10**(6): 434-438.

[9] Woods CW, Murdoch DR, Zimmerman MD, Glover WA, Basnyat B, Wolf L, et al. Emergence of *Salmonella enterica* serotype Paratyphi A as a major cause of enteric fever in Kathmandu, Nepal. *Trans R Soc Trop Med Hyg* 2006; **100**(11): 1063-1067.

[10] Maskey AP, Day JN, Phung QT, Thwaites GE, Campbell JI, Zimmerman M, et al. *Salmonella enterica* serovar Paratyphi A and *S. enterica* serovar Typhi cause indistinguishable clinical syndromes in Kathmandu, Nepal. *Clin Infect Dis* 2006; **42**(9): 1247-1253.

[11] Maskey AP, Basnyat B, Thwaites GE, Campbell JI, Farrar JJ, Zimmerman MD. Emerging trends in enteric fever in Nepal: 9124 cases confirmed by blood culture 1993-2003. *Trans R Soc Trop Med Hyg* 2008; **102**(1): 91-95.

[12] Pokharel P, Rai SK, Karki G, Katuwal A, Vitrakoti R, Shrestha SK. Study of enteric fever and antibiogram of *Salmonella* isolates at a Teaching Hospital in Kathmandu Valley. *Nepal Med Coll J* 2009; **11**(3):176-178.

[13] Prajapati B, Rai GK, Rai SK, Upreti HC, Thapa M, Singh G, et al. Prevalence of *Salmonella typhi* and paratyphi infection in children: a hospital based study. *Nepal Med Coll J* 2008; **10**(4): 238-241.

[14] Sharma NP, Peacock SJ, Phumratanaprapin W, Day N, White N, Pukrittayakamee S. A hospital-based study of bloodstream infections in febrile patients in Dhulikhel Hospital Kathmandu University Teaching Hospital, Nepal. *Southeast Asian J Trop Med Public Health* 2006; **37**(2): 351-356.

[15] World Health Organization. Typhod vaccine: WHO position paper. *Weekly Epidemiol Report* 2008; **83**: 49-60.

[16] Garmory HS, Brown KA, Titball RW. *Salmonella* vaccines for use in humans: present and future perspectives. *FEMS Microbiol Rev* 2002; **26**(4): 339-353.

[17] Acharya IL, Lowe CU, Thapa R, Gurubacharya VL, Shrestha MB, Cadoz M, et al. Prevention of Typhoid fever in Nepal with the Vi capsular polysaccharide of *Salmonella typhi*. A preliminary report. *N Engl J Med* 1987; **317**(18); 1101-1104.

[18] Klugman KP, Koornhof HJ, Robbins JB, Le Cam NN. Immunogenicity, efficacy and serological correlate of protection of *Salmonella typhi* Vi capsular polysaccharide vaccine three years after immunization. *Vaccine* 1996; **14**(5): 435-438.

[19] Sur D, Ochiai RL, Bhattacharya SK, Ganguly NK, Ali M, Manna B, et al. A cluster-randomized effectiveness trial of Vi typhoid vaccine in India. *N Engl J Med* 2009; **361**(4): 335-344.

[20] Lin FY, Ho VA, Khiem HB, Trach DD, Bay PV, Thanh TC, et al. The efficacy of a *Salmonella typhi* Vi conjugate vaccine in two-to-five-year-old children. *N Engl J Med* 2001; **344**(17): 1263-1269.

[21] International Vaccine Institute. Typhoid fever. 2010. [Online] Available from: http://www.ivi.int/program/tr_domi_Typhoid.html [Accessed 15th Feb 2010].

[22] Cook J, Jeuland M, Whittington D, Poulos C, Clemens J, Sur D, et al. The cost-effectiveness of typhoid Vi vaccination programs: calculations for four urban sites in four Asian countries. *Vaccine* 2008; **26**(50): 6305-6316.

[23] Whittington D, Sur D, Cook J, Chatterjee S, Maskery B, Lahiri M, et al. Rethinking cholera and typhoid vaccination policies for the poor: Private demand in Kolkata, India. *World Development* 2009; **37**(2): 399-409.

[24] Global Alliance for Vaccines and Immunization. Vaccine investment strategy. 2008 [Online] Available from: http://www.google.no/url?url=http://www.gavialliance.org/resources/WG_retreat_DC_29___30_Sept___FINAL_REPORT.pdf. [Accessed 15th Feb 2010].

[25] Agtini MD, Ochiai RL, Soeharno R, Lee HJ, Sundoro J, Hadinegoro SR, et al. Introducing Vi polysaccharide Typhoid fever vaccine to primary school children in North Jakarta, Indonesia, via an existent school-based vaccination platform. *Public Health* 2006; **120**(11): 1081-1087.

[26] Thiem VD, Danovaro-Holliday MC, Canh do G, Son ND, Hoa NT, Thuy DT, et al. The feasibility of a school-based VI polysaccharide vaccine mass immunization campaign in Hue City, central Vietnam: streamlining a Typhoid fever preventive strategy. *Southeast Asian J Trop Med Public Health* 2006; **37**(3): 515-522.

[27] Thiem VD, Lin FY, Canh DG, Son NH, Anh DD, Mao ND, et al. Vi conjugate typhoid vaccine (Vi-rEPA) is safe, elicits protective levels of IgG anti-Vi and is compatible with routine infant vaccines. *Clin Vaccine Immunol* 2011; Mar 16. [Epub ahead of print].

[28] Enteric fever caused by *Salmonella* infections. 2011 [Online] Available from: http://www.nibr.com/downloads/research/NVGH/Salmonella-Fact-Sheet.pdf.