



Vaccines against enteric infections : cholera, typhoid and shigellosis

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Typhoid vaccines: High disease burden of 21.6 million cases with 216,000 deaths, mounting drug resistance and difficulty in improving sanitation and safe drinking water make effective typhoid vaccines the only option in achieving immediate and effective control of typhoid fever in developing countries and for travelers to such countries.

Typhoid vaccines: Currently two typhoid vaccines are licensed for use i.e. Vi antigen injectable vaccine and oral Ty21a vaccine.

Vi antigen typhoid vaccine: Purified Vi antigen vaccine was developed by NIH, USA and is now licensed for persons > 2 years of age in more than 88 low and middle income countries.

Safety: Pooled estimates from trials done using Vi typhoid vaccine show that 1% of vaccinees develop fever and 3-4% develop swelling. Overall the side effects are mild and well tolerated.

Efficacy: Vi vaccines have been used in single dose given intramuscularly in 3 major field trials. Efficacy in these studies has been 72% (95% CI 41-87) at 17 mo follow up in Nepal, 55% (95% CI 30-71) at 3 year follow up in South Africa and 69% (95% CI 28-87) at 19 months follow up in China. Efficacy in South Africa was significant in the 1st and the 2nd year follow up but not in the third year. Recently a community based study done in Kolkata, India showed effectiveness of 82% (95% CI 58-92) in 2-4 year olds. Mass vaccination has been shown to be effective in Guangxi, China where the incidence of typhoid fell from 57/100,000 to 0.2-4.5/100,000 after vaccination.

Ty21A oral typhoid vaccine: Oral live typhoid vaccine was developed from Ty2 strain which contains galE4 mutation which makes the vaccine immunogenic but non-pathogenic. It has been

shown that liquid formulation and enteric capsules given as 3 or 4 doses at 2 days interval have the best efficacy. It was licensed in Europe in 1983 and then in USA in 1989.

Efficacy: Trials have shown efficacy of 96% (95% CI 67-99) at 3 years follow up with liquid formulation in Egypt, 67% (95% CI 37-88) at 3 years follow up with enteric capsule formulation in Chile, and 42% (95% CI 21-58) at 30 months follow up with capsule formulation and 53% (95% CI 34-67) with liquid formulation in Indonesia. Meta-analysis of Ty21a vaccine studies estimates efficacy of 47% (95% CI 33-58) for enteric capsule formulation and 74% (95% CI 38-89) for liquid formulation. Recent data suggests that Ty21a vaccine is significantly protective even against paratyphi A (Chile) and paratyphi B (Israel).

Vi conjugate vaccines: Vi-rEPA conjugate vaccine was studied in 2-5 year old children in Vietnam given as 2 doses at 6 weeks interval. The efficacy at 27 months of active surveillance was 91.5% (95% CI 77.1-96.6) and 82.4% (95% CI 22.3-99.1) at 46 months.

Newer typhoid vaccines: Newer live attenuated typhoid vaccines are being evolved like CVD908, CVD 909, Ty800, ZH9 etc, including new Vi conjugate vaccines like Vi-CRM and Vi-DT vaccines.

Cholera vaccines: High disease burden of 3-5 million cases and 100,000-130,000 deaths, emergence of more virulent O1 El tor variant, increasing drug resistance and difficulty in improving sanitation and safe drinkable water make cholera vaccines desirable for control of cholera.

Cholera vaccines: Only 2 cholera vaccines are at present available for use. They include oral monovalent whole cell killed cholera vaccine with recombinant cholera toxin subunit B (WC-rBS - Dukoral) and oral and oral bivalent killed cholera vaccine without B subunit of cholera toxin (Shanchol/mOCR/VVAX).

WC-rBS (Dukoral): This vaccine developed and licensed in Sweden in 1991 and is now licensed in more than 90 countries. It contains formalin and heat killed whole cells of O1 strain of cholera (both classic and El tor and Inaba and Ogawa) plus recombinant B subunit of cholera toxin. It is not licensed for < 2 years old.

Safety: The vaccine is very safe and side effects are mild GI disturbance. In a trial involving 240,000 participants the side effects in vaccinees were no more than in controls.

Efficacy: Trial done in Matlab, Bangladesh in 2-15 year old children and women > 16 years of age showed efficacy of 85% at 4-6 months, 62% during 1st year, 58% at during 2nd year which fell to 18% during 3rd year with overall efficacy of 51% over 3 years of follow up. Efficacy in 2-5 years old was 100% at 4-6 months, 38% in 1st year, 47% in 2nd year and 0% in 3rd year. Subsequent studies in Peru showed 86% protection against El tor cholera in 16-45 years old military recruits. Later case control trail done in Mozambique showed 84% effectiveness at 1-6 months following vaccination with 2 doses and 78% with one or two doses. It also shows cross protection of 67% against ETEC diarrhea and 86% against severe ETEC diarrhea.

Shanchol/mORCVAX: Bivalent oral vaccine containing heat and formalin killed whole cells of O1 and O 139 strains of cholera without cholera B subunit are developed by International Vaccine Institute (IVI) with funding from Gates foundation and are now available as Shanchol in India and mORCVAX in Vietnam.

Efficacy: The new bivalent vaccine has been studied in a placebo controlled trial involving 100 adults and 100 children in Kolkata, India. The results of the study showed that the vaccine was safe and immunogenic in vaccinees with 53% of adult vaccinees and 80% of children 1-5 years old showing seroconversion to O1 strain. A double blind placebo controlled cluster study is ongoing in Kolkata, India using Shanchol involving 107774 subjects > 1 year old. Interim analysis showed effectiveness of 67% at 2 years follow up. The study will continue for 5 years.

Herd effect with cholera vaccines: Reanalysis of WC and WC-rBS vaccines studies done in Bangladesh showed herd effect seen with both the vaccines. It is estimated that at 50% coverage of the population the vaccine is likely to result in 93% reduction in cholera cases due to direct and herd effects of the vaccine.

Shigella vaccines: High disease burden of 90 million episodes with 500,000 deaths, emerging drug resistance coupled with difficulties in improving the standards of hygiene make Shigella vaccine the only alternative to control Shigella disease burden. Many vaccines have reached advanced stage of development, yet ideal Shigella vaccine is still eluding mankind.

Shigella vaccines: Except for a Chinese vaccine, no other Shigella vaccine is at present commercially available. Conjugate Shigella vaccines, live attenuated Shigella vaccines and invasion complex Shigella vaccines (Invaplex) are in various stages of development.

Live invasive Shigella vaccines: Currently Center for Vaccine Development (CVD) at University of Maryland, USA and Walter Reed Army Institute of Research (WRAIR), USA are perusing these vaccines. CVD 1204 vaccine contains *guaBA* mutation, CVD 1205 has *guaBA* and *virG* mutations and CVD 1207/1208 has *guaBA*, *virG*, and *set* and *sen* mutations. Comparative trial of CVD 1204 and 1208 using 3 doses of either vaccine in human volunteers showed that both the vaccines were highly immunogenic. Further field trials with CVD 1208 will confirm safety and immunogenicity and CVD is working on similar vaccines using other Shigella serotypes. SC 602 vaccine using *S. flexneri* 2a strain with mutation of *virG* gene was found to be safe and immunogenic in adult volunteers in USA. However subsequent study done in Bangladesh failed to show immunogenicity. This proves that one needs different dose of vaccine in endemic areas as compared to naïve population. Similar *virG* mutation based *S. sonnei* vaccine WRSS1 and *S. dysenteriae* 1 vaccines WRSd1 are being developed.

Conjugate Shigella vaccines: O-SP antigen has been conjugated to rEPA or CRM9 carriers. An earlier double blind vaccine controlled randomized study tested *S. sonnei*-rEPA conjugate vaccine containing 25 µg of O-specific polysaccharide showed efficacy of 47% (28-100) against *S. sonnei* infection. A recent study used *S. sonnei* and *S. flexneri* vaccines conjugated with rEPA in 1-4 years old Israeli children. Efficacy was found to be 71% in 3-4 years old children. Further studies need to be conducted before this vaccine can be considered for commercial use.

Shigella invasin complex (Invaplex) vaccines: This vaccine developed by WRAIR contains LPS and invasive plasmid antigens Ipa B, IpaD and Ipa C and is called Invaplex 50. Phase 1 study done in human volunteers used Invalex-50 as 3 doses given intranasally divided between two nostrils at 0, 14, 28 days. Vaccine was found to be safe and immunogenic. Further studies are planned using this vaccine in field.

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