Summary of Key Points

WHO Position Paper on Typhoid Vaccines, February 2018

World Health Organization

Introduction

- This position paper replaces the WHO position paper on typhoid vaccines published in 2008
- It re-emphasizes the importance of vaccination to control typhoid fever and presents the WHO recommendations on the use of a new generation of typhoid conjugate vaccine.

Background

- Typhoid fever is an acute generalized infection, caused by an enteric bacterium, *Salmonella enterica* serovar Typhi, generally termed *Salmonella* Typhi (*S.* Typhi).
- Global estimates of typhoid fever burden range between 11 and 21 million cases and approximately 128 000 to 161 000 deaths annually.
- Children are disproportionately affected by typhoid fever, with peak incidence known to occur in individuals aged 5 to <15 years of age.

Background

- If the circulating *S*. Typhi strains are susceptible, acute typhoid fever and chronic carriage of *S.* Typhi can be effectively treated with antibiotics.

- The emergence of multidrug resistant[1] (MDR) strains of *S.* Typhi over the past few decades and recent outbreak of ceftriaxone-resistant typhoid in Pakistan demonstrates the importance of understanding local resistance patterns to enable the selection of appropriate antibiotics.

1 Resistance to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole

Vaccines

- Currently three types of typhoid vaccines are licensed for use:
  1. Parenteral typhoid conjugate vaccine (TCV)
  2. Parenteral unconjugated Vi polysaccharide (ViPS)
  3. Oral live attenuated Ty21a vaccines
- The second and third types have been recommended for programmatic use by WHO since 2008.
- Recommendations on use of the more recently licensed conjugate vaccine are provided in this position paper.

Vaccine Efficacy & Effectiveness

- Typhoid conjugate vaccine
  - Evidence review limited to one Vi-TT conjugate vaccine
  - In infants 6–11 mos and children 12–23 mos, a single dose elicited high titres of IgG anti-Vi antibody (1937.4 [95% CI: 1785.0–2102.9]) that persisted up to 5 years in 84% of children[1]
  - Efficacy of 87% [95% CI: 47.2–96.9] was demonstrated in human challenge studies with a licensed in adult volunteers[2]

1 Mohan VK et al. Safety and immunogenicity of a Vi polysaccharide-tetanus toxoid conjugate vaccine (Typbar-TCV) in healthy infants, children, and adults in typhoid endemic areas: a multicenter, 2-cohort, open-label, double-blind, randomized controlled phase 3 study. Clin Infect Dis. 2015;61:393-402.
2 Jin C et al. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. Lancet. 2017;390:2472–2480.

Vaccine Efficacy & Effectiveness

- **Vi polysaccharide vaccine**
  - Vaccine efficacy (VE) in pre-licensure trials ranged from 64% [95% CI: 36–79] to 72% [95% CI: 42–86] over variable periods of follow up.[1, 2, 3]
  - In post-licensure cluster randomized trials, VE was demonstrated as follows:
    - In Kolkata, India, VE of 56% [95% CI: 18–77] among children aged 5–14 years, and 80% [95% CI: 53–91] in children aged 2–4 years[4]
    - In Karachi, Pakistan, VE of 57% [95% CI: 6–81] among children aged 5–16 years, and there was no protection for the 2–4 year age group (Ref here is Khan et al) [5]

1 Klugman K et al. Protective activity of Vi polysaccharide vaccine against typhoid fever. Lancet. 1987;2:1165-1169.
2 Plotkin SA et al. A new typhoid vaccine composed of the Vi capsular polysaccharide. Arch Intern Med. 1995;155:2293-2299.
3 Yang HH et al. Efficacy trial of Vi polysaccharide vaccine against typhoid fever in south-western China. Bull World Health Organ. 2001;79:625-631.
4 Sur D et al. A cluster-randomized effectiveness trial of Vi typhoid vaccine in India. N Eng J Med. 2009;361:335-344.
5 Khan MI et al. Effectiveness of Vi capsular polysaccharide typhoid vaccine among children: a cluster randomized trial in Karachi, Pakistan. Vaccine. 2012;30:5389-5395.

Vaccine Efficacy & Effectiveness

- **Ty21a vaccine**
  - Three doses of Ty21a in enteric-coated capsules, taken orally every second day, conferred 67% [95% CI: 47–79] protection over 3 years[1] and 62% protection over 7 years[2] of follow-up in a cluster randomized placebo-controlled field trial of efficacy.
  - Vaccine efficacy increased with age and was 59% in children aged 5–9 years, 67% in those aged 10–14 years and 85% in persons aged ≥15 years[3]

1 Levine MM et al. Large-scale field trial of Ty21a live oral typhoid vaccine in enteric-coated capsule formulation. Lancet. 1987;1:1049-1052.
2 Levine MM et al. Duration of efficacy of Ty21a, attenuated salmonella typhi live oral vaccine. Vaccine. 1999;17:S22-S27.
3 Levine MM et al. Ty21a live oral typhoid vaccine and prevention of paratyphoid fever caused by Salmonella enterica Serovar Paratyphi B. Clin Infect Dis. 2007;45:S24-S28.

Vaccine Safety

- Typhoid conjugate vaccine
  - No safety signals were identified for Typbar-TCV based on the evaluation and safety data [1]
  - Fever, pain and swelling were reported in approximately 1–10% of vaccinees
- Vi polysaccharide vaccine
  - No serious adverse events and a minimum of local adverse events[2]
  - proved to be well tolerated and safe when co-administered with routine childhood vaccines
- Ty21a vaccine
  - well tolerated and is associated with low rates of adverse events

1 See No. 2, 2017 pp. 13–20.
2 Plotkin SA et al. A new typhoid vaccine composed of the Vi capsular polysaccharide. Arch Intern Med. 1995;155:2293–2299.

WHO Position

- WHO recommends programmatic use of typhoid vaccines for the control of typhoid fever
  - Programmes should be implemented in the context of other efforts
- TCV[1] is preferred at all ages in view of its improved immunological properties, use in younger children and longer duration of protection.
- TCV should be prioritized in countries with high burden of disease or antimicrobial resistance.
- Countries may also consider the routine use of ViPS vaccine in those ≥ 2 years, and Ty21a vaccine for those > 6 years.

1 Only one of the two licensed products was assessed in the review.

WHO Position

- Typhoid conjugate vaccine
  - a 0.5 mL single dose of TCV in children from 6 months and in adults up to 45 years in endemic regions is recommended
  - Administration is encouraged at the same time as other vaccines, at 9 months or in the second year of life
- Vi polysaccharide vaccine
  - a single dose of the vaccine should be administered intramuscularly or subcutaneously from 2 years
- Ty21a vaccine
  - a 3-dose oral immunization schedule, administering the vaccine every second day, is recommended above 6 years
- Catch-up vaccination with TCV up to 15 years of age is recommended when feasible and supported by epidemiologic data

WHO Position

- WHO recommends vaccination in response to confirmed outbreaks of typhoid fever and in humanitarian emergencies depending on the risk assessment in the particular setting
- The potential need for revaccination with TCV is currently unclear
- Revaccination is recommended every 3 years for ViPS, and every 3 to 7 years in most endemic settings for Ty21a or every 1 to 7 years for travelers from non-endemic to endemic areas, depending on national policies.

WHO Position

Vaccination of special populations, contraindications and precautions

- TCV and ViPS vaccines are contraindicated for individuals with known hypersensitivity to any component of the vaccine
- Ty21a should not be administered to persons taking antibiotics
- Certain antimalarials (mefloquine), may suppress the Ty21a antibody response and should not be given from 3 days before until 3 days after giving the Ty21a vaccine.

WHO Position

- Vaccination is recommended for food handlers in endemic areas, travelers going to endemic areas and clinical microbiology laboratory staff with exposure risk
- There are no theoretical safety concerns for ViPS and TCV, though data are lacking
  - Use of the live attenuated Ty21a vaccine during pregnancy should be avoided
- Immunocompromised and HIV-infected persons should receive TCV or VIPS. Ty21a can be administered to HIV-infected, immunologically stable individuals[1]

1 Individuals with a CD4 percent >25% for children aged <5 years or CD4 count ≥200 cells/mm^3 if aged ≥5 years

Future Research Needs

- WHO recommends:
  1. Post-licensure monitoring of effectiveness and safety of TCV especially in special population groups
  2. Use of Brighton Collaboration case definitions
  3. Analysis of non-specific effects of vaccination
  4. Endemic countries strengthen the surveillance of typhoid fever in all age groups, and monitor antimicrobial resistant strains before and after introduction of vaccines

For more information on the WHO position paper on typhoid vaccines, please visit the WHO website:

www.who.int/immunization/documents/positionpapers

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